Neuropsychiatric Disease and Treatment

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REVIEW

Genetic Markers Associated with Postpartum Depression: A Review

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Abstract: Postpartum depression (PPD) is a common illness in mothers after childbirth. PPD negatively affect the mother's quality of life and the bond with the infant, which can interfere with the infant's emotional, social, and cognitive development. PPD is caused by various biological and psychosocial factors. The aim of this review is to summarize the latest evidence of the associations between genetic polymorphisms and PPD. PubMed and Scopus were used as the literature search databases for this review. The keywords used were postpartum depression, postnatal depression, genetic, and polymorphism. Twenty-seven articles were reviewed after screening and applying the inclusion criteria. As results, the serotonin gene (*5-HTTLPR*) and oxytocin genes (*OXTR*) have the most significant associations with PPD among other genes. Further research on PPD biomarkers should be conducted to diagnose and treat PPD patients.

Keywords: postpartum depression, biomarkers, genetic polymorphism, *5-HTTLPR*, *OXTR*

Introduction

The first 6 weeks after a mother gives birth is the postpartum period, during which her reproductive organs return to their pre-pregnancy state.[1] This period is also known as the fourth trimester or puerperium.[1] Depression is a mood disorder that begins with the emergence of frustration due to unresolved stress symptoms.[2] This condition is characterized by feelings of sadness, loneliness, despair, regret, and so on.[2] Postpartum depression (PPD) is a psychological problem commonly experienced by a mother after childbirth. PPD is typically marked by feelings of sadness, significant weight changes, fatigue, and decreased mood.[3]

Anokye[4] reported that the prevalence of PPD is difficult to determine due to various factors. However, PPD is a common occurrence in women within 12 months following childbirth.[4] Zhao and Zhang[5] showed that the risk factors for PPD are violence and abuse, gestational diabetes, immigrant status, cesarean section, vitamin D deficiency, lack of social support, multiple births, history of depression, and obesity.

Genetic polymorphisms and epigenetic modifications have been proposed to be potential PPD biomarkers.[6] Genetic biomarkers would allow for early detection to prevent the long-term effects of PPD and potentially develop specific therapies for patients.[6] In this review, original research from the past 10 years is examined to explore the relationship between PPD and genetic polymorphisms, aiming to summarize the latest evidence and determine which genetic polymorphisms significantly affect the PPD condition.

Methods

Data Sources and Search Strategy

PubMed and Scopus were used as the literature search databases for this review. To answer the question "Which genetic polymorphism has the most significant effect on the occurrence of postpartum depression"? The keywords used were

Received: 6 August 2023
Accepted: 24 January 2024
Published: 15 February 2024

(((postpartum depression) AND (postnatal depression)) AND (genetic)) AND (polymorphism). The publication date was limited to the last 10 years.

Inclusion Criteria

The literature included in this review met the following criteria: 1. reported original research; 2. investigated genetic polymorphisms; 3. either depression or an increase of PPD symptoms were measured; 4. studies were conducted in humans, and 5. English was used. Figure 1 shows the PRISMA flowchart for the literature search.

Results and Discussion

Studies on Genetic Polymorphisms Associated with PPD

Table 1 shows the 27 selected original articles that investigated the association between genetic polymorphisms and PPD. The articles primarily used the Edinburgh postnatal depression scale (EPDS) to assess PPD disorder, whereas others used instruments, such as the Beck depression inventory (BDI), the Los Angeles symptoms checklist (LASC), and the patient health questionnaire (PHQ), among others. The number of participants ranged from 71 to 1983 for a total of 13,125. The participants were from Asia, Europe, and the USA.

Serotonin

The serotonin transporter (*5-HTT*) acts as a key mediator and therapeutic target for various diseases associated with mental disorders.[34] Serotonin transporters inhibit serotonin transmission to the synaptic cleft through reuptake.[34] One of the polymorphisms studied in the context of PPD is the 5 HTT-linked polymorphic region (*5-HTTLPR*).[35] The incidence of low serotonin expression and transcriptional efficiency is associated with the short allele of *5-HTTLPR*. Carriers of this *5-HTTLPR* short allele are at high risk of developing a PPD disorder.[35]

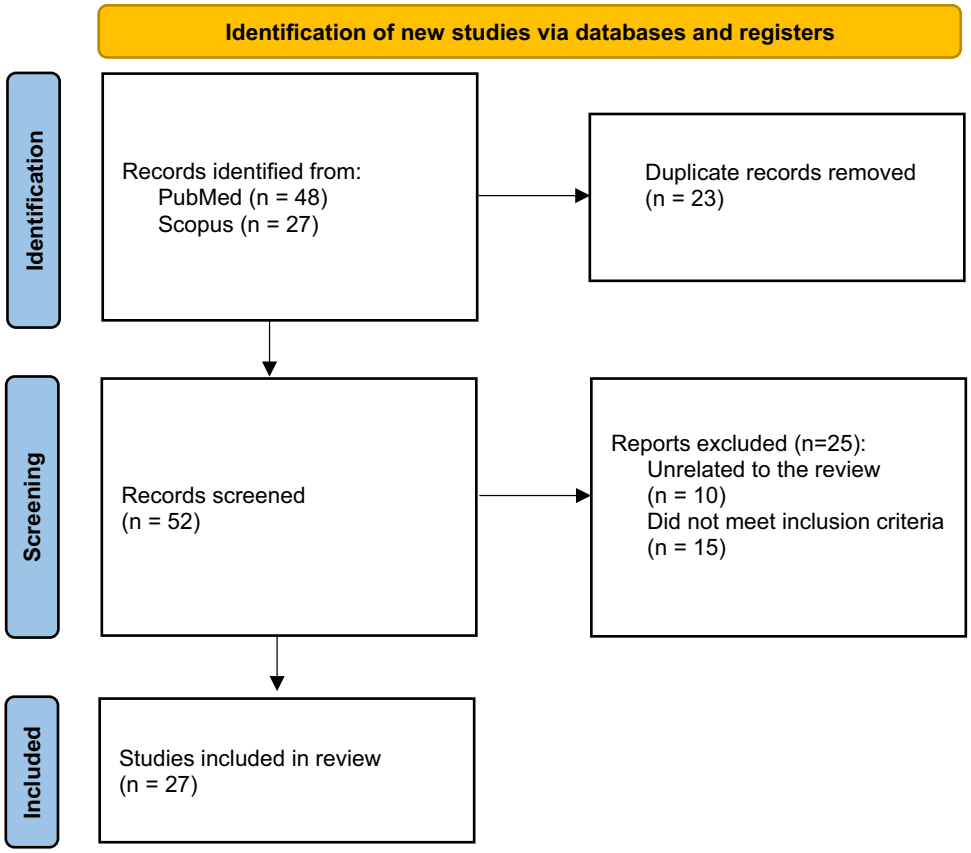

Figure 1 PRISMA flowchart for the literature search.

Table 1 List of Articles

No	Author	Type of Study	Year	Country	Gene	Participants	Number of Participants	Assessment Tool
1	Landoni[7]	Longitudinal design study on serotonin genes	2022	Italy	*5-HTTLPR*	Caucasian women	n = 155	BDI, EPDS, LASC, PHQ
2	Hu[8]	Cohort study on serotonin genes	2019	China	*5-HTTLPR*	Postpartum women	n = 437	EPDS and SRDS
3	Pinheiro[9]	Cross-sectional study nested within a cohort study on serotonin genes	2013	Brazil	*5-HTTLPR*	Postpartum women	n = 276	EPDS
4	El-Ibiary[10]	Case control and prospective study on serotonin genes	2013	USA	*HTR2A*	Postpartum women	n = 71 (24 controls and 24 cases)	EPDS
5	Khabour[11]	Cross-sectional study on tryptophan and serotonin genes	2013	Jordan	*SLC6A4, TPH1*, and *TPH2*	Postpartum women	n = 370 (240 controls and 130 cases)	EPDS
6	Comasco[12]	Longitudinal study on catechol-O-methyltransferase (*COMT*) and oxytocin receptor (*OXTR*) genes	2016	Sweden	*COMT* and *OXTR*	Swedish women	n = 217 (166 controls and 51 cases)	EPDS
7	Schneider[13]	Prospective cohort study on estrogen receptor gene, progesterone receptor gene, and COMT	2023	Germany	*COMT, ESR1, PGR*, and *CYP19A1*	Pregnant women	n = 361	EPDS
8	Zou[14]	Case control study on estrogen receptor gene	2016	China	*ERα*	Postpartum women	n = 90 (45 controls and 45 cases)	EPDS
9	Pinsonneault[15]	Cohort study on estrogen receptor gene	2013	Canada	*ESR1*	Postpartum women	n = 257 (32 controls and 225 cases)	EPDS and MADRS
10	Tan[16]	Case-control study on estrogen receptor gene	2018	Singapore	*ESR1* and *ESR2*	Chinese descent	n = 713 (554 controls and 159 cases)	EPDS
11	Jonas[17]	Longitudinal study on oxytocin genes	2013	Canada	*OXT* and *OXTR*	Canadian women	n = 431	CES-D scale and CTQ scale
12	Asherin[18]	Association study on oxytocin receptor genes	2020	USA	*OXTR*	Postpartum women	n = 104	BDI-II
13	Bhatti[19]	Association study on oxytocin gene	2019	USA	*OXTR*	Perinatal mothers	n = 220	EPDS
14	Apter-Levy[20]	Cohort study on oxytocin gene	2013	Israel and Singapore	*OXTR*	Women	n = 1983	BDI
15	Tan[21]	Case-control study on glucocorticoids and CRH	2015	Singapore	*CRHR1* and *GR*	Chinese descent	n = 725 (549 controls and 147 cases)	EPDS

(*Continued*)

https://doi.org/10.2147/NDT.S434165 DovePress

Table 1 (Continued).

No	Author	Type of Study	Year	Country	Gene	Participants	Number of Participants	Assessment Tool
16	Engineer[22]	Prospective cohort study on glucocorticoids and CRH	2013	UK	*CRHR1* and *GR*	Caucasian women	n = 140	EPDS
17	Schneider[23]	Prospective cohort study on glucocorticoids and CRH	2014	Germany	*CRHR1, NR3C1*, and *FKBP5*	Pregnant women	n = 361	EPDS
18	Iliadis[24]	Longitudinal population-based study on Hydroxysteroid dehydrogenase genes	2017	Sweden	*HSD11B1*	Women	n = 769	EPDS
19	Skalkidou[25]	Longitudinal population- based study on Hydroxysteroid dehydrogenase and serpin genes	2019	Sweden	*HSD11B1* and *SERPINA6*	Postpartum women	n = 635	EPDS
20	Duan[26]	Association study on Alpha-2A Adrenergic Receptor genes	2021	China	*α2AAR*	Parturients	n = 568 (465 controls and 103 cases)	EPDS
21	Luo[27]	Cohort study on Sirtuin genes	2020	China	*SIRT1, SIRT2*, and *SIRT6*	Chinese women	n = 363 (295 controls and 68 cases)	EPDS
22	Wang[28]	Association study on kynurenine-3-monooxygenase genes	2017	China	*KMO*	Chinese women	n = 710	EPDS
23	Pillai[29]	Cross-sectional study on Vitamin D Binding Protein genes	2022	India	*VDBP*	Indian women	n = 660 (330 controls and 330 cases)	EPDS
24	Duan[30]	Association study on indoleamine-2,3-dioxygenase genes	2019	China	*IDO*	Chinese women	n = 96 (48 controls and 48 cases)	EPDS
25	Quan[31]	Cross-sectional study on kynurenic aminotransferase genes	2020	China	*KAT*	Chinese women	n = 360	EPDS
26	Ping[32]	Prospective cohort study on glutamate receptor gene	2023	China	*GRIN2B, GRIN3A*	Parturients	n = 362	EPDS
27	Tan[33]	Case-control study on retinoic acid induced 1 gene	2014	Singapore	*RAI1*	Chinese women	n = 679 (540 controls and 139 cases)	EPDS

Abbreviations: *5-HTTLPR*, serotonin-transporter-linked promoter region; *HTR2A*, 5-hydroxytryptamine receptor 2A; *SLC6A4*, solute carrier family 6 member 4; *TPH1* and *TPH2*, tryptophan hydroxylase 1 and tryptophan hydroxylase 2; *COMT*, catechol-O-methyltransferase; *OXT*, oxytocin; *OXTR*, oxytocin receptor; *ESR1/ERα*, estrogen receptor alpha; *ESR2*, estrogen receptor beta; *PGR*, progesterone receptor; *CYP19A1*, aromatase; *CRHR1*, corticotropin-releasing hormone receptor 1; *GR/NR3C1*, glucocorticoid receptor; *FKBP5, FKBP* prolyl isomerase 5; *HSD11B1*, 11β-hydroxysteroid dehydrogenase type 1; *SERPINA6*, serpin family A member 6; *α2AAR*, α2A-adrenergic receptor; *SIRT1/SIRT2/SIRT6*, sirtuin 1/sirtuin 2/sirtuin 6; *KMO*, kynurenine 3-monooxygenase; *VDBP*, vitamin D binding protein; *IDO*, indoleamine 2.3-dioxygenase; *KAT*, lysine acetyltransferase; *GRIN2B*, glutamate receptor subunit epsilon-2; *GRIN3A*, glutamate receptor subunit 3A; *RAI1*, retinoic acid induced 1; EPDS, Edinburgh Postnatal Depression Scale; LASC, Los Angeles Symptom Checklist; PHQ, Patient Health Questionnaire; SRDS, Self-Rating Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; CES-D, Center for Epidemiological Studies Depression Scale; CTQ, Childhood Trauma Questionnaire; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II.

Table 2 Studies on Serotonin Genes

No	Author	Gene	Polymorphism	Assessment Tool	Results
1	Landoni[7]	*5-HTTLPR*	*5-HTTLPR* polymorphism	BDI, EPDS, LASC, PHQ	There is an association between serotonin transporter gene polymorphism (SS genotype) and PPD (p=0.001).
2	Hu[8]	*5-HTTLPR*	*5-HTTLPR* fragment length polymorphism	EPDS and SRDS	There is no significant association between the *5-HTTLPR* genotype (SS genotype) and PPD at both the early (p=0.236) and late (p=0.181) postpartum periods.
3	Pinheiro[9]	*5-HTTLPR*	*5-HTTLPR* S and L polymorphism	EPDS	There is an association of *5-HTTLPR* genetic polymorphism (LL and SS genotype) and PPD depending on the type of allele it carries (p=0.07).
4	El-Ibiary[10]	*HTR2A*	*HTR2A* (rs6311, rs2070040, rs6314)	EPDS	There is an association between *HTR2A* polymorphisms (rs6311) with PPD (p=0.002).
5	Khabour[11]	*SLC6A4*	*SLC6A4* S and L polymorphisms	EPDS	There is no association between *SLC6A4* polymorphisms (L and S alleles) and PPD (p=0.480).

Abbreviations: *5-HTTLPR*, serotonin-transporter-linked promoter region; *HTR2A*, 5-hydroxytryptamine receptor 2A; *SLC6A4*, solute carrier family 6 member 4; BDI, Beck Depression Inventory; EPDS, Edinburgh Postnatal Depression Scale; LASC, Los Angeles Symptom Checklist; PHQ, Patient Health Questionnaire; SRDS, Self-Rating Depression Scale; PPD, postpartum depression.

Table 2 shows the studies conducted on the serotonin genes suspected to be associated with PPD in several countries including Italy, China, Brazil, USA, and Jordan. Of the five studies, three conducted research on the *5-HTTLPR* gene. In these studies, an association was observed between gene polymorphisms and PPD based on each individual's S and L alleles. Landoni reported that the SS genotype has the greatest effect on PPD, as it moderates PPD symptoms 2–4 months postpartum.[7] It is suspected that this genotype is directly or indirectly related to aspects of PPD.[7] Consistent with these findings, Hu showed that the *5-HTTLPR* gene is not directly associated with PPD.[8] However, the interaction between the *5-HTTLPR* gene polymorphism and changes in 17β-estradiol levels has a significant effect on the risk of PPD.[8] Women with the SS genotype experience a larger decrease in 17β-estradiol levels after childbirth, indirectly increasing the risk of PPD during the early and late postpartum period.[8]

Pinheiro indicated that the LL genotype has a more significant effect on PPD.[9] The prevalence of PPD is higher in women with the LL genotype who experience stressful life events during pregnancy, while the SS genotype tends to be associated with PPD in postpartum women who have received psychiatric therapy.[9] This may be related to the indirect influence of the SS genotype on PPD, which is associated with 17β-estradiol.[9]

Besides the *5-HTTLPR* genotype, El-Ibiary reported that *HTR2A* single-nucleotide polymorphisms (SNPs) were most associated with PPD.[10] The most significant SNP is rs6311, where the T allele is protective and is found in PPD at a frequency of 0.19, compared to 0.49 in controls. Two other *HTR2A* SNPs are nominally associated with PPD, where the allele of the intronic SNP rs2070040 confers risk for PPD, while the allele of the non-synonymous SNP rs6314 protects PPD.[10] In contrast, no significant association is detected between the genotypes of the *SLC6A4* polymorphism with the L and S alleles and PPD ($p > 0.05$).[11]

The varied results of the five studies indicate that not all serotonin genes are significantly associated with postpartum depression. Research on the 5-HTTLPR gene by Landoni, Hu, and Pinheiro at different times and locations showed contradictory results.[7–9] The blood samples were taken around 6 weeks after delivery, but using different cell types and DNA extraction methods may have led to the differing results. Landoni and Pinheiro reported an association between *5-HTTLPR* and PPD,[7,9] while Hu's study showed different results.[8] Hu extracted and sequenced the genomic DNA using a phenol-chloroform method and PCR, respectively,[8] whereas Pinheiro extracted the DNA using a salting-out procedure and sequenced them using electrophoresis.[7]

COMT and MAO-A

Catechol-O-methyltransferase (*COMT*) and monoamine oxidase A (*MAO-A*) degrade neurotransmitters, such as dopamine, adrenaline, and noradrenaline, as well as catechol estrogens and external catechols, within the brain.[12] The

Val158Met polymorphism, which is a variation of the *COMT* and *MAO-A* genes, has been widely studied concerning the pathogenesis of PPD.[36,37]

The *COMT* Val158Met functional polymorphism is a genetic marker that may be associated with the corticolimbic monoaminergic neuroanatomical and neurochemical basis of prepulse inhibition (PPI). PPI is a neurophysiological measure of sensorimotor gating, where a weak stimulus (prepulse) suppresses the startle response to a stronger startle stimulus. It is believed to be linked to the dysfunction in the sensorimotor gating mechanism and is associated with various psychiatric and neurological disorders.[12] Comasco reported that pregnant women displayed more marked effect of *COMT* genotype on PPI, which is associated with PPD. However, there was no significant association between the *COMT* genotype and postpartum depression, thus a future research on this gene should be conducted.[12]

Table 3 presents these two studies on the relationship between the *COMT* gene and PPD, in which one of them was conducted in Sweden over a period of three years with pregnant and non-pregnant women as participants. The results of cohort and longitudinal studies indicate no significant relationship between the EPDS score and the rs4680 *COMT* polymorphism.[12,13]

Estrogen Receptor

Estrogen contributes to PPD disorders by affecting serotonin transmission.[16] The Nurses Health Study demonstrated that the *ESR1* and *ESR2* genotypes are linked to the risk of depression, and the association was affected by the use of post-menopausal hormone therapy.[16] Additionally, a higher occurrence of major PPD disorder was observed among individuals with these genotypes.[16,35]

Table 4 presents studies on the association between the estrogen receptor (*ER*) genes and PPD in China and Canada, with the majority of participants being of Caucasian and Chinese ethnicities. Among the four studies, there were

Table 3 Studies on *COMT* and *MAO-A* Genes

No	Author	Gene	Polymorphism	Assessment Tool	Results
6	Comasco[12]	*COMT*	*COMT* (rs4680)	EPDS	There is no association between COMT (rs4680) with PPD (p>0.05).
7	Schneider[13]	*COMT*	*COMT* (rs4680)	EPDS	There is no association between COMT (rs4680) and PPD (p>0.05).

Abbreviations: *COMT*, catechol-O-methyltransferase; EPDS, Edinburgh Postnatal Depression Scale; PPD, postpartum depression.

Table 4 Studies on Estrogen Receptor Genes

No	Author	Gene	Polymorphism	Assessment Tool	Results
8	Zou[14]	*Pvu II* and *Xba I* on Estrogen Receptor-α (*ERα*)	*Pvu II* gene polymorphism	EPDS	There is an association between ERα polymorphism (Pvu II gene) and PPD (p=0.019).
9	Pinsonneault[15]	*ESR1*	TA-repeat, rs2077647, rs988328, rs1801132, rs1884051, rs3020327, rs9340958, rs3020434, rs3798577	EPDS and MADRS	There is an association between ESR1 gene polymorphism (TA-repeat and rs2077647) with PPD (p=0.007 and p=0.03).
10	Tan[16]	*ESR1* and *ESR2*	*ESR1* (rs2077647, rs2234693, and rs9340799; and *ESR2* rs4986938)	EPDS	There is no association between ESR1 (rs2077647, rs2234693, rs9340799), and ESR2 (rs4986938) with PPD (p=0.714, p=0.374, p=0.411 and p=0.183)
17	Schneider[13]	*ESR1*	*ESR1* (rs488133)	EPDS	There is no association between ESR1 polymorphism (rs488133) and PPD (p>0.05).

Abbreviations: *ESR1*/*ERα*, estrogen receptor alpha; *ESR2*, estrogen receptor beta; EPDS, Edinburgh Postnatal Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; PPD, postpartum depression.

variations in the types of gene polymorphisms examined, including the *Pvu II* gene and SNPs from *ESR1* and *ESR2*. The *ERα Pvu II* gene polymorphism is correlated with the incidence of PPD. These results strengthen the evidence for the etiology of PPD as a modulation of serotonin signaling.[14]

Pinsonneault reported an association between TA-repeats and the *ESR1* polymorphism (rs2077647) with PPD (p=0.007 and p=0.03).[31] However, in another study on the rs2077647, Tan's study, gene polymorphism indicated a very low risk for PPD.[16] This discrepancy likely arises from differences in study design, as Tan only included participants with EPDS scores < 7 in the control group, making the likelihood of experiencing PPD very low.[16] Additionally, in Tan's study, all patient diagnoses were handled by psychiatrists.[16] In contrast, Pinsonneault utilized an unselected population of postpartum women and employed the Montgomery–Asberg Depression Rating Scale to assess PPD without psychiatric diagnoses.[15] Differences in race and environmental factors could account for the different findings in these studies. Schneider researched the rs488133 SNP from *ESR1*.[13] No association was found between the *ESR1* rs488133 polymorphism and PPD.[13]

Oxytocin

Studies on the oxytocin (*OXT*) system concerning PPD have become a focus. The oxytocin receptor (*OXTR*) has a vital function in regulating anxiety and stress and could be affected by various hormonal fluctuations and psychosocial factors associated with reproduction,[6] making the *OXTR* a promising area of study for PPD pathophysiologies.[6]

Table 5 shows five studies on *OXTR* gene polymorphisms, with participants predominantly of Caucasian, Latina, and Chinese ethnicities. Of the five studies, three indicated a relationship between the *OXTR* gene polymorphism and PPD, while the remaining two did not. Jonas et al examined two distinct groups of mothers from the Maternal Adversity, Vulnerability, and Neurodevelopment trial conducted in Hamilton and Montreal, Canada.[17] In the Hamilton dataset, a significant correlation was found between *OXT* rs2740210 and the Childhood Trauma Questionnaire, which measures the level of abusive behavior by mothers toward their children and a manifestation of PPD, indicating an impact on depression (p≤0.002).[17] Moreover, mothers with the CC genotype displayed higher levels of depression than mothers with at least one A allele. The Montreal dataset yielded similar results, in which depression was observed in women with the CC genotype of *OXT* rs2740210 but not in women with at least one A allele.[17] Asherin et al conducted a study involving 104 postpartum women in the USA.[18] Their results also indicated that mothers with the GG genotype exhibited significantly higher average BDI-II scores compared to mothers with the AG/AA genotype (p=0.02).[18] Furthermore, the average BDI-II scores of mothers with GG infants were significantly higher than those with AG/AA infants (p=0.01).[18]

Table 5 Studies on Oxytocin Genes

No	Author	Genes	Polymorphism	Assessment Tool	Results
11	Jonas[17]	*OXT* and *OXTR*	*OXT* (rs4813627; rs2740210) and *OXTR* (*OXTR* rs237885)	CES-D scale and CTQ scale	There were associations between *OXT* polymorphism (rs2740210) and PPD in both Hamilton and Montreal (p=0.002).
6	Comasco[38]	*OXTR*	*OXTR* polymorphism (rs237885 and rs53576)	EPDS	No association between *OXTR* polymorphism (rs237885, rs53576) and PPD (p=0.3 and p=1.0)
12	Asherin[18]	*OXTR*	*OXTR* (rs53576)	BDI-II	There was an association between *OXTR* polymorphism (rs53576) and BDI-II scores (p=0.01).
13	Bhatti[19]	*OXTR*	rs53576	EPDS	No significant association between *OXTR* polymorphism (rs53576) and PPD (p=0.366).
14	Apter-Levy[20]	*OXTR*	rs2254298	BDI	There was an association between *OXTR* polymorphism (rs2254298) and depressed mother (p=0.009).

Abbreviations: *OXT*, oxytocin; *OXTR*, oxytocin receptor; CES-D, Center for Epidemiologic Studies Depression Scale; CTQ, Childhood Trauma Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; PPD, postpartum depression.

Apter-Levy et al also reported the effect of the GG genotype, in which depressed mothers had a higher likelihood of possessing the GG risk genotype for *OXTR* rs2254298 than undepressed mothers (p=0.001).[20]

The remaining two studies conducted by Bhatti (USA)[19] and Comasco (Sweden) reported negative results.[38] The research conducted by Bhatti et al offered intriguing insight. Genetic variations in the *OXTR* system have been linked to differences in social functioning.[19] This research investigated whether rs53576 affects the relationship between low social support and symptoms of PPD. The interaction between the composite support measure (including support from the mother, father, and family) and *OXTR* rs53576 was not significant (p=0.07). However, the association between overall support and PPD symptoms was significantly stronger in the GG group than in the AA group (the same result as above regarding how possessing the GG genotype affects the occurrence of PPD; p=0.019). The participants' rs2268498 genotype did not moderate the effect of social support on PPD symptoms (p=0.366).[19] The second study conducted by Comasco et al on 170 Swedish women showed that neither *OXTR* rs237885 nor *OXTR* rs53576 had any significant association with postpartum mood in this particular group (p<0.05 and p=1.0, respectively).[38]

Mothers with the GG genotype exhibit significantly more PPD symptoms than mothers with the AG/AA genotype. Additionally, despite having the same gene studied, the differences in the results may be attributed to the use of different assessment tools. Using the EPDS resulted in no significant association between the *OXTR* polymorphism and PPD,[19,38] while assessments with the CES-D and BDI indicated the opposite.[17,18,20]

Glucocorticoids and CRH

This hypothesis suggests that after giving birth, the normal functioning of the hypothalamic-pituitary (HPA) axis fails to fully recover in women experiencing symptoms of PPD.[22] This is supported by the observation of diminished adrenocorticotropic hormone (ACTH) responses to corticotropin-releasing hormone (CRH) 6 and 12 weeks after childbirth, indicating prolonged suppression of the HPA axis.[22] The impaired signaling of molecules within the HPA axis, such as *GR* and *CRH-R1*, has been implicated in the development of various PPD disorders, including PPD.[22]

Table 6 explains three studies on gene polymorphisms, glucocorticoids, and CRH and their relationship with PPD with most of the participants were Caucasian and Chinese ethnicities. Significant associations were identified between the *CRHR1(2)* and BCll SNPs (p=0.003 and p=0.011, respectively), with allele frequencies that were higher in PPD patients at high risk.[22] Nevertheless, no indication was detected for a connection between the risk of PPD and the allele frequencies of the *CRHR1(1), CRHR1(3)*, or *ER22/23EK* SNPs.[22]

Table 6 Studies on Glucocorticoid and CRH Genes

No	Author	Genes	Polymorphism	Assessment Tool	Results
15	Tan[21]	*CRHR1* and *GR*	*CRHR1* (rs242939, rs1876828, rs242941, rs110402 and rs7209436) and *GR* (rs41423247, rs6190, rs853180, rs10482704, rs6195 and rs10482605)	EPDS	No significant association between *CRHR1* (rs242941) and *GR* (rs41423247) with PPD (p=0.905 and p=0.611)
16	Engineer[22]	*CRHR1* and *GR*	*CRHR1* (rs1876828, rs242939 and rs242941) and *GR* (BclI and ER22/23EK)	EPDS	There was an association between *CRHR1* polymorphism (rs242939, p<0.001) and PPD. In contrast, *GR* polymorphism (BclI, p=0.011) did not show any association with PPD.
17	Schneider[23]	*CRHR1, NR3C1*, and *FKBP5*	*CRHR1* (rs7209436, rs110402), *NR3C1* (rs41423247, rs6195, rs10482605) and *FKBP5* (rs1360780, rs9296158, rs3800373, rs9470080)	EPDS	The analysis of haplotypes did not yield any statistically significant results when subjected to the likelihood ratio test (*NR3C1*, p=0.78; *FKBP5*, p=0.45; *CRHR1*, p=0.61).

Abbreviations: *CRHR1*, corticotropin-releasing hormone receptor 1; *GR/NR3C1*, glucocorticoid receptor; *FKBP5*, FKBP prolyl isomerase 5; EPDS, Edinburgh Postnatal Depression Scale; PPD, postpartum depression.

However, two of the three studies conducted on the polymorphisms did not establish any association with PPD. Specifically, no significant association was observed between *GR* rs41423247 (BclI), and *CRHR1* rs242941 and the occurrence of PPD based on statistical analysis.[21] Furthermore, none of the examined haplotypes yielded significant results on the likelihood ratio test (*NR3C1*, p=0.78; *FKBP5*, p=0.45; *CRHR1*, p=0.61).[13]

Hydroxysteroid Dehydrogenase

Recent studies have implicated the involvement of 11β-hydroxysteroid dehydrogenase 1 (*11β-HSD1*) in the development of perinatal depression and the subsequent behavior of offspring.[23] This enzyme is responsible for converting inactive cortisone into active cortisol, thus contributing to the underlying mechanisms of these conditions.[23] One study detected a correlation between high evening salivary cortisol levels, a specific genetic variation in *HSD11B1*, and depression,[39] suggesting that *11β-HSD1* regulates the HPA axis and may contribute to susceptibility to depression.[39]

Two studies conducted in Sweden (Table 7) followed the initial hypothesis. Iliadis et al detected a positive correlation between the GG genotype and the presence of PPD symptoms (p=0.01).[24] Skalkidou et al demonstrated an association between *HSD11B1* SNPs and the EPDS scores at postpartum week 6 and month 6[33]. The rs12565406 SNP was significantly related to the EPDS score in postpartum week 6 and month 6 (p=0.0015 and p=0.029, respectively), rs10863782 was significantly related to the EPDS score in postpartum month 6 (p=0.034), and rs4844488 was significantly related to the EPDS score in postpartum week 6 (p=0.024). However, other SNPs that were also tested, including rs846908, rs701950, rs11119328, rs10863785, and rs3753519 showed a significant threshold of p>0.05.[25] These results indicate no significant association between these SNPs and PPD.[25]

Others

Table 8 shows that several studies have been conducted on other genes that are suspected to have significant associations with PPD. Duan[26] indicated that the *α2AAR* rs13316046 polymorphism is associated with PPD. That study reported that women with the *α2AAR* rs13316046AA genotype have a significantly greater risk of PPD than women with the AG and GG genotypes.[26] The observed effect of the A > G polymorphism may be attributed to changes in the binding capacity of miR-646, which affects the transcription levels of *α2AAR*.[26] PPD symptoms are significantly associated with specific *SIRT2* and *SIRT6* polymorphisms. The *SIRT2* polymorphisms at rs2873703 (TT genotype) and rs4801933 (TT genotype), as well as the *SIRT6* polymorphisms at rs350846 (CC genotype) and rs107251 (TT genotype), are correlated with PPD symptoms ($p < 0.05$).[27] Sirtuins are involved in histone deacetylation, relying on NAD+ as a cofactor. Sirtuins deacetylate proteins other than histones.[27]

Skalkidou[25] observed an association between PPD and polymorphisms in the *SERPINA6* gene, specifically SNP rs8022616. This particular SNP was correlated with PPD symptoms during gestational week 17 and at 6 weeks

Table 7 Studies on Hydroxysteroid Dehydrogenase Genes

No	Author	Genes	Polymorphism	Assessment Tool	Results
18	Iliadis[24]	*HSD11B1*	*HSD11B1* polymorphism (rs12565406)	EPDS	There was an association between *HSD11B1* polymorphism (rs12565406) and PPD (p=0.01).
19	Skalkidou[25]	*HSD11B1*	*HSD11B1* (rs846908, rs701950, rs12565406, rs10863782, rs11119328, rs4844488, rs10863785, rs3753519)	EPDS	Some *HSD11B1* polymorphisms were associated with PPD in week 6 (rs12565406, p= 0.0015 and rs4844488, p=0.024) and month 6 of postpartum (rs12565406, p=0.029 and rs10863782, p=0.034), whereas the other polymorphisms were not associated with PPD in both time-points (rs846908, rs701950, rs11119328, rs10863785, and rs3753519 with p>0.05)

Abbreviations: *HSD11B1*, 11β-hydroxysteroid dehydrogenase type 1; EPDS, Edinburgh Postnatal Depression Scale; PPD, Postpartum depression.

https://doi.org/10.2147/NDT.S434165 DovePress

Table 8 Studies on Other Genes

No	Author	Genes	Polymorphism	Assessment Tool	Results
20	Duan[26]	*α2AAR*	*α2AAR* polymorphism (rs13306146 and rs521674)	EPDS	There is an association between *α2AAR* (rs13316046) polymorphism and PPD (p=0.006).
21	Luo[27]	*SIRT1, SIRT2*, and *SIRT6*	*SIRT2* (rs2873703 and rs4801933), *SIRT6* (rs350846 and rs107251)	EPDS	There is an association between *SIRT2* (rs2873703, p=0.009 and and rs4801933, p=0.025) *SIRT6* (rs350846, p=0.021 and rs107251, p=0.032) polymorphisms with PPD.
19	Skalkidou[25]	*SERPINA6*	*SERPINA6* (rs941601, rs8022616, rs11627241, rs1998056)	EPDS	There is an association between *SERPINA6* (rs8022616) genes with PPD (p=0.0007) in week 6 postpartum.
22	Wang[28]	*KMO*	*KMO* polymorphism (rs3819976, rs1053221, rs669290, rs1053230, rs6429280, rs640718)	EPDS	There is an association between *KMO* polymorphism (rs1053221, p=0.008 and rs1053230, p=2.42x10^{-4}) and PPD.
23	Pillai[29]	*VDBP*	*VDBP* polymorphism (rs4588, rs7041)	EPDS	There is no association between *VDBP* polymorphisms (rs4588, p=0.76 and rs7041, p=0.69) with PPD.
24	Duan[30]	*IDO*	*IDO1* polymorphism (rs10108662, rs4503083)	EPDS	There was a significant correlation between the genetic polymorphism of the *IDO1* (rs10108662, p=0.006 and rs4503083, p=0.012) gene and the occurrence of PPD.
25	Quan[31]	*KAT*	*KAT* polymorphism (rs7046797, rs2279267, rs3738055, rs4145964, rs17711677, rs11804245, rs12729558, rs14490)	EPDS	There was no significant association between KAT polymorphisms (rs7046797, rs2279267, rs3738055, rs4145964, rs17711677, rs11804245, rs12729558, rs14490) and PPD (p>0.05).
7	Schneider[13]	*PGR, CYP19A1*	*PGR* (rs10895068, rs1042838), *CYP19A1* (rs4646, rs10046)	EPDS	No significant association between the EPDS values and the *PGR* (rs10895068, rs1042838) and *CYP19A1* (rs4646, rs10046) SNPs.
26	Ping[32]	*GRIN2B, GRIN3A*	*GRIN2B* (rs1805476, rs4522263, rs3026174), *GRIN3A* (rs3739722, rs1983812, rs2050639, rs10989563, rs2050641)	EPDS	Polymorphisms in the *GRIN2B* gene (rs1805476, p=0.014; rs4522263, p=0.022; and rs3026174, p=0.010) were associated with PPD. Nevertheless, the *GRIN3A* alleles (rs3739722, p=0.789; rs1983812, p=0.477; rs2050639, p=0.434; rs10989563, p=0.500; and rs2050641, p=0.967) were not associated with PPD.
27	Tan[33]	*RAI1*	CAG/CAA repeat and 14-repeat alleles	EPDS	There was a significant relationship between *RA1* gene (14-repeat alleles) and postpartum depression (p=0.016)
5	Khabour[11]	*TPH1* and *TPH2*	*TPH1* (A218C) and *TPH2* (G1463A) polymorphisms	EPDS	There was no statistically significant relation between *TPH1* (A218C) and incidence of PPD (p=0.661). Whereas the A allele was not detected in TPH2 polymorphism, therefore no analysis was performed.

Abbreviations: *SERPINA6*, serpin family A member 6; *α2AAR*, α2A-adrenergic receptor; *SIRT1*/*SIRT2*/*SIRT6*, sirtuin 1/sirtuin 2/sirtuin 6; *KMO*, kynurenine 3-monooxygenase; *VDBP*, vitamin D binding protein; *IDO*, indoleamine 2.3-dioxygenase; *KAT*, lysine acetyltransferase; *PGR*, progesterone receptor; *CYP19A1*, aromatase; *GRIN2B*, glutamate receptor subunit epsilon-2; *GRIN3A*, glutamate receptor subunit 3A; *RAI1*, retinoic acid induced 1; *TPH1* and *TPH2*, tryptophan hydroxylase 1 and tryptophan hydroxylase 2; EPDS, Edinburgh Postnatal Depression Scale; PPD, postpartum depression; SNPs, single-nucleotide polymorphism.

postpartum.[25] The results of a study on kynurenine-3-monooxygenase (*KMO*) showed that the incidence of PPD symptoms was 7.3% in the Chinese population.[28] Individuals with PPD symptoms exhibited higher levels of serum 3-HK and the 3-HK/KYN ratio compared to postpartum women without PPD symptoms ($p<0.05$).[35] Additionally, the presence of a specific *KMO* rs1053230 polymorphism was associated with the occurrence of PPD symptoms ($p<0.05$).[28]

Duan et al revealed that the prevalence of PPD symptoms was 6.9% in the Chinese population, due to increasing indoleamine 2.3-dioxygenase activity ($p<0.05$), compared with women without PPD symptoms.[30] That study also revealed that the occurrence of PPD was significantly linked to the *IDO1* rs10108662 variant ($p<0.05$).[30] Quan et al conducted a study on eight different SNPs on *KAT* polymorphisms and reported that there was no significant association between women with PPD and any of the SNPs.[31]

Tan et al found a significant difference in the genotypic distribution between subjects and the *RA1* gene CAG/CAA repeat ($p=0.031$).[33] Additionally, a correlation was observed between the 14-repeat allele and PPD ($p=0.016$).[33] Univariate analysis conducted by Ping et al showed that polymorphisms in the *GRIN2B* genes rs3026174, rs1805476, and rs4522263 were associated with PPD symptoms ($p<0.05$). The *GRIN2B* gene rs4522263 was associated with the idea of self-harm by the mother.[32] The *GRIN3A* allele is not associated with PPD symptoms.[32]

Three studies reported that specific gene polymorphisms did not correlate significantly with PPD. Pillai[29] demonstrated the potential association between genetic variants (rs7041 and rs4588) in the vitamin D binding protein (*VDBP*) and susceptibility to PPD, alongside their potential association with serum vitamin D and *VDBP* levels in Indian women with PPD. These findings indicate that the *VDBP* polymorphisms rs4588 and rs7041 and their haplotypes do not exhibit any significant association with PPD susceptibility in the South Indian population.[29] Three haplotypes were created by reconstructing SNPs in the *PGR* and *CYP19A1* genes (the most common haplotypes were GG and TC, respectively).[13] No significant correlation was found between the EPDS and the two SNPs.[13] No significant relationship was observed between *TPH1* (*A218C*) in the studied population and the incidence of PPD ($p>0.05$).[11]

Future Directions

Genes that are associated with PPD could potentially be used as biomarkers for diagnosis to ensure that patients receive appropriate treatment based on their specific gene polymorphisms. We suggest that further research be conducted with standardized methods for all genes, including in participant selection, DNA extraction, genotyping, and the use of the same assessment tools, particularly the serotonin (*5-HTTLPR*) and oxytocin genes (*OXTR*), which have major effects on PPD. In addition, conducting future research with a larger sample size than necessary will better represent the population and provide more accurate results.

Conclusion

Research conducted over the past few years has shown correlations between gene polymorphisms and depression experienced by postpartum women. Particular SNPs have a significant effect on PPD, while others lack any association with PPD. Based on the 27 reviewed articles, it is known that the gene polymorphisms that have the most significant effect on PPD are those in the serotonin (*5-HTTLPR*) and oxytocin genes (*OXTR*).

Funding

This study is supported by the Academic Leadership Grant from Universitas Padjadjaran, Indonesia, Grant Number 1549/UN6.3.1/PT.00/2023.

Disclosure

The authors report no conflicts of interest in this work.

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