Meta-Analyses of Genome-Wide Association Studies for Postpartum Depression

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Objective: Postpartum depression (PPD) is a common subtype of major depressive disorder (MDD) that is more heritable, yet is understudied in psychiatric genetics. The authors conducted meta-analyses of genome-wide association studies (GWASs) to investigate the genetic architecture of PPD.

Method: Meta-analyses were conducted on 18 cohorts of European ancestry (17,339 PPD cases and 53,426 controls), one cohort of East Asian ancestry (975 cases and 3,780 controls), and one cohort of African ancestry (456 cases and 1,255 controls), totaling 18,770 PPD cases and 58,461 controls. Post-GWAS analyses included 1) single-nucleotide polymorphism (SNP)–based heritability (h^2_{SNP}), 2) genetic correlations between PPD and other phenotypes, and 3) enrichment of the PPD GWAS findings in 27 human tissues and 265 cell types from the mouse central and peripheral nervous system.

Results: No SNP achieved genome-wide significance in the European or the trans-ancestry meta-analyses. The h^2_{SNP} of PPD was 0.14 (SE=0.02). Significant genetic correlations were estimated for PPD with MDD, bipolar disorder, anxiety disorders, posttraumatic stress disorder, insomnia, age at menarche, and polycystic ovary syndrome. Cell-type enrichment analyses implicate inhibitory neurons in the thalamus and cholinergic neurons within septal nuclei of the hypothalamus, a pattern that differs from MDD.

Conclusions: While more samples are needed to reach genome-wide levels of significance, the results presented confirm PPD as a polygenic and heritable phenotype. There is also evidence that despite a high correlation with MDD, PPD may have unique genetic components. Cell enrichment results suggest GABAergic neurons, which converge on a common mechanism with the only medication approved by the U.S. Food and Drug Administration for PPD (brexanolone).

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Postpartum depression (PPD) is a perinatal form of major depressive disorder (MDD) with a global prevalence of 17% (1–3). PPD is one of the most frequent complications of childbirth (4–7) and is associated with many adverse outcomes, including maternal morbidity and mortality (1, 2), increased risk for infanticide (8), poorer maternal-infant attachment, and impaired parenting behaviors (6, 9). Despite these negative impacts, PPD is understudied in

psychiatric genomics, and its genetic risk factors are largely unknown. Smaller GWASs have been performed (10, 11), but no large GWAS meta-analyses have been done.

PPD is a strong candidate for genomic studies. PPD is a more homogeneous form of MDD: only females affected, reproductive age–banded, and with exposure to the same biopsychosocial event. Moreover, the twin heritability of PPD (54%) is higher than that of MDD (32%) (12). As sample sizes increase in number and diversity, clinically relevant results can begin to be uncovered and the genomic basis for PPD will become better understood. Not only could successful genomic analyses of PPD allow stratification of a specific presentation of MDD, but they may also allow delineation of the role genetic risk plays in the presentation of PPD features (i.e., onset, duration, symptom severity, recurrence), which could guide more effective treatment selection. This is critical given that there is currently only one medication approved by the U.S. Food and Drug Administration (FDA) with a specific indication for PPD, namely, brexanolone (13–15).

Discerning the biological basis of psychiatric disorders has been difficult. Most likely PPD is impacted by many genetic loci, each with small effects (16), similar to other psychiatric disorders (17–19). Although early GWASs for MDD were negative (20, 21), increases in sample size have yielded considerable progress (22, 23). The major lesson from MDD and other psychiatric GWASs is that progress is possible, but genetic approaches for higher-prevalence, lower-heritability diseases like PPD and MDD are challenging and require large sample sizes.

Therefore, we conducted the first large GWAS meta-analyses for PPD across 20 international cohorts (18 European ancestry, one East Asian, and one African). The results from these meta-analyses enabled us 1) to estimate the single-nucleotide polymorphism (SNP)–based heritability (h^2_{SNP}) of PPD; 2) to calculate genetic correlations (r_g) to identify potentially pleiotropic relationships between PPD and other psychiatric disorders, medical diseases, and biomedical traits; and 3) to identify specific cell types that may underlie PPD etiology.

METHODS

Study Participants

In total, we included 18,770 women with a history of PPD and 58,461 control participants across 20 cohorts collected internationally. Table S1 in the online supplement summarizes the source and genetic data for cases and controls for each sample, and full details for each cohort are provided in the main supplement file. Overall, case definition required a lifetime diagnosis of PPD within 1 year of childbirth and was identified via review of electronic medical records (three cohorts), the Edinburgh Postnatal Depression Scale (EPDS) (11 cohorts), structured clinical interview (three cohorts), or other self-report (three cohorts). For individuals identified using structured methodological review of medical records and population registries, diagnoses were required to meet international consensus criteria (DSM-IV, ICD-9, ICD-10). In addition, the EPDS, a widely used PPD screening instrument (24–27), was used to screen participants. The EPDS is a 10-item self-report assessment, focused on current symptoms, and it minimizes confounding of somatic symptoms of PPD with the demands inherent to parenting an infant (e.g., insomnia) (24). We also screened using the modified version of the EPDS that is capable of screening for a lifetime history of PPD (28). For both the standard and lifetime versions of the EPDS, PPD symptoms are rated on a scale of 0–30, with higher scores indicating greater symptom severity. When we used the EPDS, cases were defined as having scores ≥13, which is consistent with PPD (29). In a majority of cases (in 19 of the 20 cohorts), control participants were screened for the absence of lifetime MDD and were required to have a least one live term birth (≥36 weeks' gestation).

All sites had documented permission from local ethics committees, and all participants provided informed consent for studies done in settings and countries where this was required.

Genotyping and Quality Control

Genotyping procedures can be found in the primary reports for each cohort (see Table S1 and main supplement file in the online supplement). Individual genotype data for each cohort were processed by the collaborating research teams using comparable procedures. SNPs were imputed using the Haplotype Reference Consortium reference panel (30) for samples of European Ancestry (EUR), the TOPMed (31) reference panel for samples of African ancestry (AFR), and the 1000 Genomes Asian (32) reference panel for samples of East Asian ancestry (EAS). More detailed information on sample quality control and association testing for each cohort is provided in the online supplement.

GWAS Meta-Analyses

Two meta-analyses for PPD case-control status were performed for European ancestry and trans-ancestry. A fixed-effects meta-analysis was conducted on EUR cohorts using the inverse variance method in METAL (33). A conventional random-effects meta-analysis was conducted on all cohorts (EUR, AFR, and EAS) using the inverse-variance method in METASOFT (34). For both meta-analyses, heterogeneity was assessed with Cochran's I^2 statistic. Test statistic inflation (λ) was calculated for each individual GWAS (see Figures S2 and S12 in the online supplement) and for the overall meta-analyses (Figures 1B and 1D) using all SNPs with minor allele frequency (MAF) >0.01 to identify residual population stratification or systematic technical artifact. EUR GWAS summary statistics were subjected to linkage disequilibrium score regression (LDSC) analyses on high-quality common SNPs (INFO score >0.9 and MAF >0.01) to examine the LDSC intercept as a more specific measure of inflation of the GWAS test statistic (35) due to residual artifact or stratification (see Table S2 in the online

supplement). The genome-wide significance threshold was set at a p value of 5.0×10^{-8}.

Heritability Estimation and Genetic Correlations

LDSC was used to estimate h^2_{SNP} from EUR and EAS genome-wide association summary statistics. Estimates of h^2_{SNP} on the liability scale depend on the assumed lifetime prevalence of PPD in the population (K), and we assumed a conservative K of 0.10 but also evaluated a range of estimates of K to explore sensitivity, including 95% confidence intervals for the EUR meta-analysis (see Figure S3 in the online supplement). For EUR and EAS heritability estimates, precomputed linkage disequilibrium (LD) score references provided by LDSC were used.

To estimate h^2_{SNP} from AFR samples, we used GCTA (36, 37). The direct estimation of heritability from genome-wide common variant data was possible given access to genotype-level data included in AFR mega-analysis.

We used LDSC to estimate r_g between PPD and a range of other disorders, diseases, and human traits. The intent of these comparisons was to evaluate the extent of shared common variant genetic architectures to suggest hypotheses about the fundamental genetic basis of PPD. The full list of summary statistics used can be found in Table S4 in the online supplement. All summary statistics were standardized to human genome build hg19 (using liftOver), with all rsIDs annotated to Ensembl GRCh37, release 92 (38). Summary statistics were processed using LDSC, using default parameters and precomputed LD score references provided by LDSC.

Tissue and Cell-Type Enrichment Analysis

We performed tissue and cell-type enrichment analysis aiming to identify relevant tissues and cell types underlying PPD. First, we analyzed GTEx gene expression data (version 8) (39) in 27 human tissues after excluding tissues with fewer than 100 donors, non-natural tissues (such as cell lines), and testis tissues (40). Second, for the cell type–specific analysis, we used single-cell RNA sequencing data with over 160K high-quality cells sampled from 19 regions in the entire mouse central and peripheral nervous system (41). We analyzed these data at the cell-type level, including 39 broad cell types (referred to as "level 4" for cell-type clustering in the Zeisel et al. data set [41]) and 251 refined cell types ("level 5" in the Zeisel et al. data set [41], after filtering five cell types with fewer than 20 cells). We considered only protein-coding genes with 1:1 orthology between human and mouse for the calculation of expression specificity. For both expression data sets, we calculated a metric of gene expression specificity as previously described (40); it measures, for each gene, its expression in a specific tissue or cell type relative to its total expression across all tissues or cell types. As in previous studies (40, 42), we utilized the genes with the top 10% specificity values in each tissue or cell type for the enrichment analyses.

We used partitioned LD score regression (pLDSC) (43) to test the enrichment of tissues and cell types in the EUR PPD GWAS results. Our analyses using pLDSC evaluated whether the SNPs within 100-kb regions of the top 10% of specifically expressed genes were enriched for SNP-based heritability. For each tissue or cell type, we computed the LD scores for this cell type–specific annotation and added it to the baseline model of 53 functional annotations. We assessed the enrichment of tissue or cell types using the coefficient z scores and computed one-sided p values. We used the European samples in phase 3 of the 1000 Genomes Project as the reference panel. Results were corrected for multiple testing using false discovery rate within each data set.

RESULTS

Cohort Comparability

We identified 18 EUR cohorts that used a range of methods to ascertain cases with PPD (see Table S1 and the main supplement file in the online supplement). The methods used by these cohorts were thoroughly reviewed, and we assessed the comparability of the cohorts using summary-level data. We evaluated the comparability of these cohorts in two ways: 1) directly comparing our three largest cohorts (sample size >5,000) and 2) meta-analyzing cohorts with the same ascertainment methods. For each of these comparisons, we estimated the common variant genetic correlations (r_g) and performed targeted replication using a leave-one-out (LOO) approach (see the online supplement).

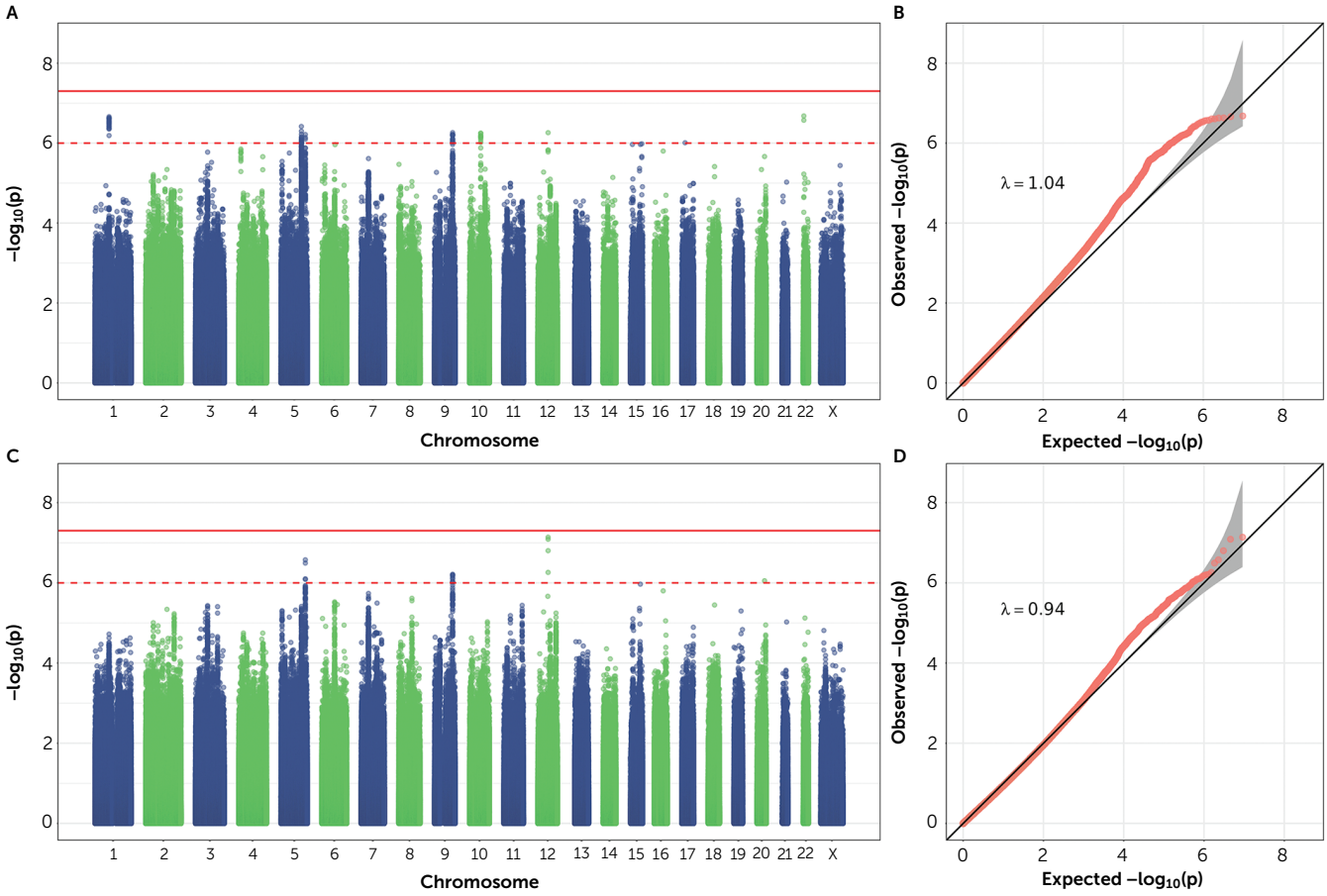
Among our three largest cohorts (from the Australian Genetics of Depression Study [AGDS], the Postpartum Depression: Action Towards Causes and Treatment Consortium [PACT], and UK Biobank), the weighted mean r_g was 0.73 (SE=0.14), supporting their comparability (see Table S2 in the online supplement). This estimate can be benchmarked against the weighted mean r_g of 0.76 (SE=0.03) between MDD GWAS cohorts (23). For LOO targeted replication, we meta-analyzed 17 EUR cohorts, leaving out one of the three cohorts listed above and using the left-out cohort as a replication sample. LD-independent SNPs from each meta-analysis were identified and used for replication. Sign tests were significant ($p<0.05$) for two of the three LOO analyses (LOO for AGDS: $p=2.93\times10^{-3}$; LOO for PACT: $p=5.45\times10^{-2}$; LOO for UK Biobank: $p=2.70\times10^{-2}$; see Table S2 in the online supplement), indicating consistent directions of effect across cohorts.

Next, we compared meta-analyzed cohorts with similar ascertainment methods (clinical interview/ICD code, EPDS, minimal self-report). The weighted mean r_g was 0.56 (SE=0.10). For LOO target replication, sign tests were significant for two of the three LOO analyses (LOO for clinical interview/ICD code: $p=0.601$; LOO for EPDS: $p=1.97\times10^{-59}$; LOO for minimal self-report: $p=6.63\times10^{-61}$; see Table S2 in the online supplement), indicating consistent direction of effect across ascertainment methods.

European Ancestry Genome-Wide Association Study of PPD

Given the positive evidence for comparability of these cohorts, we performed a primary GWAS meta-analysis in

FIGURE 1. Results of genome-wide association meta-analyses for postpartum depression[a]



[a] Panel A is a Manhattan plot for association tests from fixed-effects meta-analysis of European ancestry (EUR) (17,339 postpartum depression [PPD] cases and 53,426 control participants). Genomic position (chromosomes 1–22 and X-chromosome) is shown on the x-axis, and statistical significance, as $-\log_{10}(p)$, is shown on the y-axis. The solid red horizontal line indicates the genome-wide significance threshold of 5×10^{-8}, and the dashed red horizontal line indicates the suggestive threshold of 1×10^{-6}. Panel B is an association test quantile-quantile plot of observed versus expected $-\log_{10}(p)$ values from the EUR meta-analysis. The 95% confidence interval of expected values is shown in gray. The test-statistic inflation value, λ, is 1.04. Panel C is a Manhattan plot for association tests from trans-ancestry random effects meta-analysis (18,770 PPD cases and 58,461 screened control participants). Panel D is an association test quantile-quantile plot of observed versus expected $-\log_{10}(p)$ values from the trans-ancestry meta-analysis. The test statistic inflation value, λ, is 0.94.

women of European ancestry, comprising of 9,750,447 SNPs in 17,339 women with a history of PPD and 53,426 control participants. No evidence of residual population stratification or systematic technical artifact was observed in the final meta-analysis ($\lambda=1.04$, $\lambda_{1000}=1.00$) (Figure 1B) or in any of the individual data sets (see Table S1 and Figures S1–S2 in the online supplement). LD score regression (35) indicated that 87% of the observed test-statistic inflation was attributable to an underlying genome-wide polygenic signal. We estimated the h^2_{SNP} to be 0.14 (SE=0.02; liability scale, assuming lifetime risk of 0.10; see Figure S3 in the online supplement).

No SNP reached genome-wide significance ($p<5.0\times10^{-8}$) in the EUR GWAS meta-analysis. The most significant SNP, rs3788305, is located on chromosome 22q11.21 ($\beta=-0.09$, $p=2.09\times10^{-7}$) (Table 1; see also Figure S4 in the online supplement). rs3788305 lies within an intron of *TXNRD2* (thioredoxin reductase 2). Across the genome, we identified 62 SNPs with p values $<1\times10^{-6}$, which segregate into seven LD-independent loci. These loci were identified by LD pruning ($r^2<0.1$) followed by conditional association analyses controlling for the most significant SNP within each 2-Mb window and manual inspection of regional association plots to confirm the presence of supporting statistical evidence of association from nearby SNPs. These top seven LD-independent index SNPs are presented in Table 1 (see also Figures S4–S10 in the online supplement). (Full summary statistics are available at https://doi.org/10.6084/m9.figshare.24204843.)

Trans-Ancestry Genome-Wide Association Study of PPD

Next, we conducted a trans-ancestry random-effects meta-analysis comprising the 18 EUR cohorts, one EAS cohort (975 cases and 3,780 controls), and one AFR cohort (456 cases and 1,255 controls). No evidence of residual population stratification or systematic technical artifact was observed in any

TABLE 1. Top seven linkage disequilibrium–independent loci in the European ancestry postpartum depression GWAS meta-analysis[a]

SNP	CHR	BP	A1/A2	MAF	Odds Ratio	p	LD Block	Genes
rs3788305	22	19871778	G/A	0.464	1.09	2.09×10^{-7}	19867189–19872009	*TXNRD2*
rs6593605	1	96956775	G/A	0.313	1.07	2.18×10^{-7}	96909240–96972973	
rs13156549	5	139514964	C/T	0.209	0.922	3.83×10^{-7}	139514964–140219328	*ANKHD1, ANKHD1-EIF4EBP3, APBB3,CD14, CYSTM1, DND1, EIF4EBP3, HARS, HARS2, HBEGF, IK, NDUFA2, PCDHA1,PCDHA2, PCDHA3, PCDHA4, PCDHA5, PCDHA6, PCDHA7, PFDN1, SLC35A4, SLC4A9, SRA1, TMCO6, WDR55, ZMAT2*
rs7047038	9	123946947	T/G	0.297	0.931	5.46×10^{-7}	123640500–124127574	*C5, CNTRL, GSN, RAB14, STOM, TRAF1*
rs73140579	12	69904574	G/A	0.042	1.21	5.49×10^{-7}	69847907–70000236	*CCT2, FRS2*
rs61862567	10	76433367	A/G	0.495	0.937	5.64×10^{-7}	76060962–76525361	*ADK*
rs4869061	5	167030325	C/T	0.336	1.07	6.10×10^{-7}	166985224–167055936	*TENM2*

[a] A1/A2=allele 1/allele 2; BP=base pair position; CHR=chromosome; GWAS=genome-wide association study; LD=linkage disequilibrium; MAF=minor allele frequency; SNP=single-nucleotide polymorphism.

of these individual data sets (see Table S1 and Figures S11–S12 in the online supplement). The estimated h^2_{SNP} for the EAS ($h^2_{SNP}=0.17$, SE=0.15) and AFR ($h^2_{SNP}=0.36$, SE=0.19) cohorts (both on the liability scale, assuming lifetime risk of 0.10) were comparable to what was observed in our EUR meta-analysis. Among the seven LD-independent loci and SNPs in strong LD with each ($r^2>0.8$) from the EUR meta-analysis, 59% of SNPs (111 of 188 loci; binomial test $p<2.2\times10^{-16}$) showed consistent direction of effect in both the AFR and EAS cohorts (see Table S3 in the online supplement). This trans-ancestry GWAS consisted of 9,122,545 SNPs in 18,770 women with a history of PPD and 58,461 control participants. There was no evidence of residual population stratification ($\lambda=0.94$, $\lambda_{1000}=1.00$) (Figure 1D).

No SNP reached genome-wide significance ($p<5.0\times10^{-8}$) in the trans-ancestry analysis. The most significant SNP, rs10879002, is located on chromosome 12q15 ($\beta=0.15$, $p=7.26\times10^{-8}$) (see Figure S8 in the online supplement). This increases the significance of SNPs seen in the same region of the EUR-only meta-analysis (chr12: 69847907–70000236). rs10879002 is an intronic variant of *FRS2*, which encodes fibroblast growth factor receptor substrate 2. In total, the trans-ancestry analysis increased the number of significant SNPs ($p<1\times10^{-6}$) in three of the seven loci identified in the EUR ancestry analysis (see Figures S7, S8, and S10 in the online supplement). (Full summary statistics are available at https://doi.org/10.6084/m9.figshare.24204843.)

Genetic Correlations With Postpartum Depression

Clinical studies have shown that PPD is associated with a wide range of other disorders and traits. To assess the shared genetic architecture between PPD and psychiatric disorders, medical diseases, and biomedical traits, r_g values were calculated with our meta-analyzed summary statistics of EUR ancestry using LD score regression. Figure 2 shows the significant r_g values with false discovery rate <0.05, and Table S4 in the online supplement contains the full results. First, the genetic correlation between PPD and the most recent MDD GWAS was indistinguishable from 1 ($r_g=0.95$, SE=0.05; H_0: $r_g=0$, $p=1.34\times10^{-80}$; H_0: $r_g=1$, $p=0.30$). Additionally, the genetic correlation of PPD with bipolar II disorder ($r_g=0.51$, SE=0.09, $p=3.38\times10^{-9}$) was statistically greater ($p=1.24\times10^{-142}$) than the correlation of PPD with bipolar I disorder ($r_g=0.25$, SE=0.05, $p=1.89\times10^{-6}$).

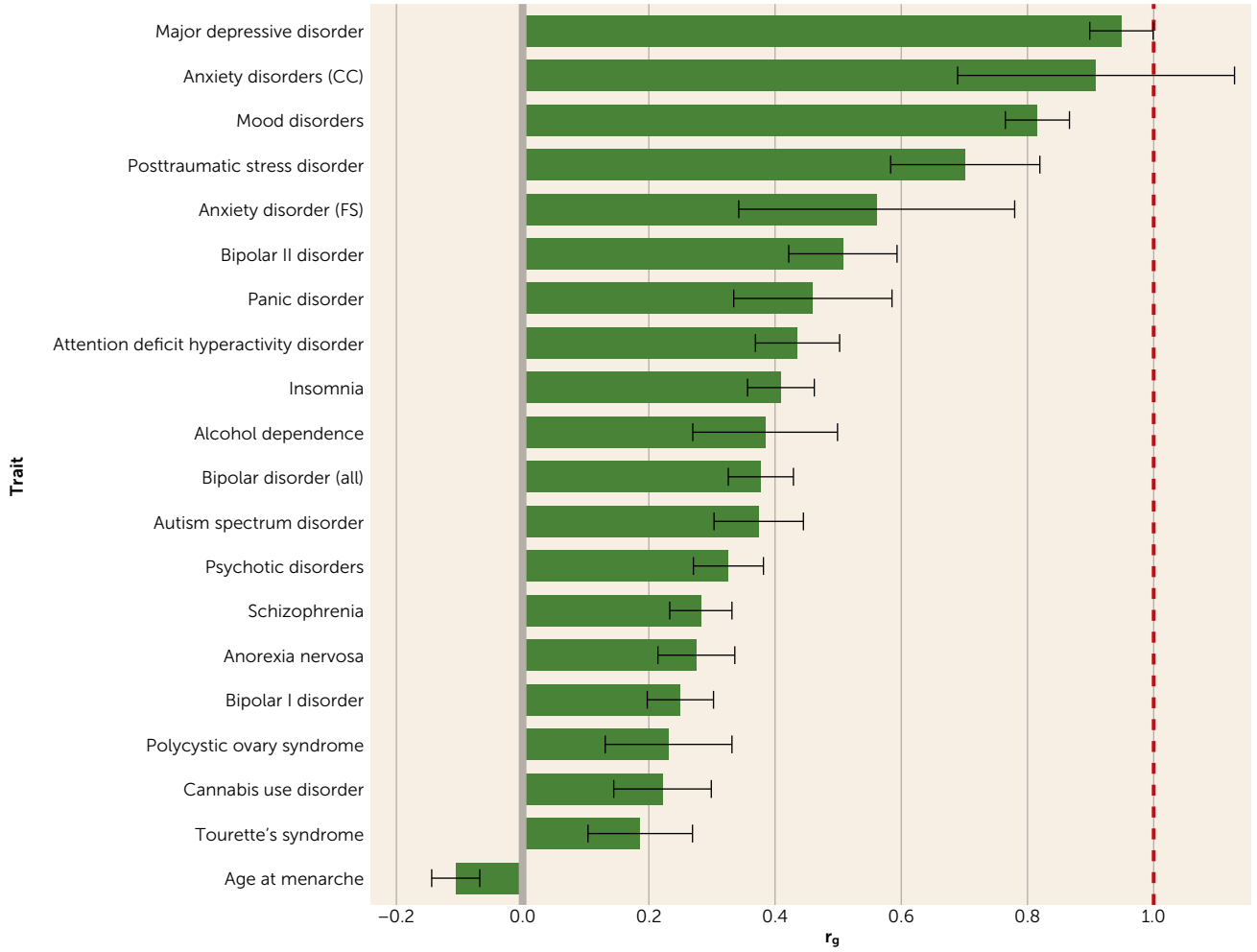
Second, we observed significant positive genetic correlations between PPD and anxiety disorders ($r_g=0.91$, SE=0.22, $p=3.43\times10^{-5}$), specifically posttraumatic stress disorder ($r_g=0.70$, SE=0.12, $p=2.98\times10^{-9}$) and panic disorder ($r_g=0.46$, SE=0.13, $p=2.00\times10^{-4}$). Furthermore, there were significant genetic correlations across many psychiatric disorders, including attention deficit hyperactivity disorder ($r_g=0.44$, SE=0.07, $p=6.70\times10^{-11}$) and schizophrenia ($r_g=0.28$, SE=0.05, $p=9.87\times10^{-9}$).

Lastly, the common variant genetic architecture of PPD was correlated with insomnia ($r_g=0.41$, SE=0.05, $p=9.83\times10^{-15}$). In addition, we also saw significant correlations with the reproductive hormone–related traits age at menarche ($r_g=-0.11$, SE=0.04, $p=5.40\times10^{-3}$) and polycystic ovary syndrome (PCOS) ($r_g=0.23$, SE=0.10, $p=2.12\times10^{-2}$).

Tissue and Cell-Type Enrichment Analyses

Integrating GWAS results with data from RNA sequencing studies characterizing specific tissues and cell types aids in understanding the biological implications of PPD-associated loci. We used partitioned LD score regression to evaluate the enrichment of the PPD GWAS findings in 27 human tissues (GTEx; see Table S5 in the online supplement) (39) and 39 cell types (see Table S6 in the online supplement) that consist

FIGURE 2. Genetic correlations (r_g) between postpartum depression and psychiatric disorders, medical diseases, and biomedical traits[a]



[a] Significant r_g values with false discovery rate <0.05 are shown. Error bars indicate standard error. The dashed vertical line indicates r_g=1. CC=case-control status; FS=factor score.

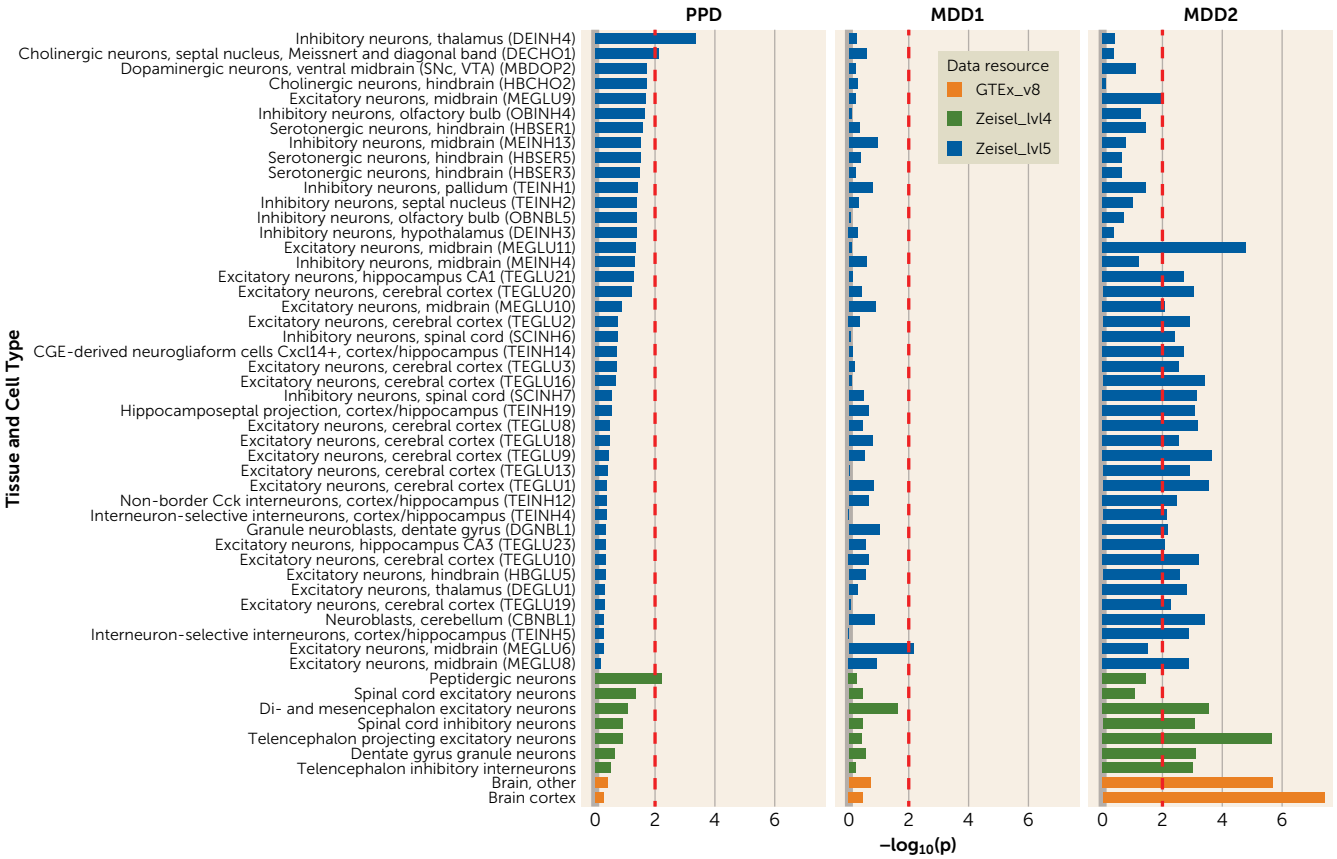
of 265 more refined cell types (see Table S7 in the online supplement) in the mouse central and peripheral nervous system (41). We did not find clear enrichment for any bulk tissue RNA-seq GTEx tissues. For cell types, the strongest signals identified were for inhibitory neurons in the thalamus (DEINH4; $p=4.50\times10^{-4}$; $q=5.64\times10^{-2}$) and cholinergic neurons within septal nuclei of the hypothalamus (DECHO1; $p=7.64\times10^{-3}$; q=0.205, indicating that we should expect 20.5% of all the results with q value less than this [N=35] to be false positives). Analyses of single-cell data more broadly implicate peptidergic neurons ($p=5.84\times10^{-3}$; q=0.114). Together these cell types can be characterized by their shared role as GABAergic neurons (41). These patterns differ from those seen in either the first MDD GWAS (MDD1) (20), whose sample size is similar to that in our PPD analysis, or the most recent MDD GWAS (MDD2) (23) (Figure 3). Comparing the enrichment ratios for these cell types (DEINH4 and DECHO1) between PPD and MDD2, we observe significant differences (DEINH4: PPD enrichment=2.19, MDD2 enrichment=1.03, $p=3.50\times10^{-3}$; DECHO1: PPD enrichment=1.79, MDD2 enrichment=1.02, p=0.02). The nominally significant cell-type enrichments for PPD were more modest in both prior MDD analyses, suggesting unique targets for PPD.

DISCUSSION

We report on the first GWAS meta-analyses for PPD (EUR ancestry and trans-ancestry). This represents the largest and most comprehensive genetic study of PPD to date. While no loci reached genome-wide significance, our analyses provide valuable insights into the genetic basis of PPD. First, we found many significant genetic correlations between PPD and other psychiatric disorders, medical diseases, and biomedical traits. In addition, cell-type enrichment analyses implicate GABAergic neurons in the pathogenesis of PPD.

Of particular note, the results for PPD implicate inhibitory neurons in the thalamus and cholinergic neurons of the septal nucleus in the hypothalamus. This pattern of results may be unique to PPD, as it was not observed in large GWASs

FIGURE 3. Cell-type enrichment analyses performed using partitioned LD score regression[a]



[a] Nominally significant values with p<0.05 are shown. Labels indicate the enriched tissue or cell type. Solid red line indicates findings with p<0.01. PPD=postpartum depression; MDD1=first major depressive disorder GWAS, conducted in 2013 (20); MDD2=major depressive disorder GWAS, conducted in 2018 (23); GTEx_v8=Genotype-Tissue Expression (GTEx) Project, version 8 data set (39); Zeisel_lvl4=cell types defined as level 4 within the Zeisel et al. data set (41); Zeisel_lvl5=cell types defined as level 5 within the Zeisel et al. data set (41).

of MDD (Figure 3) (23). These findings are salient because the two neuronal populations can be characterized by the neurotransmitter GABA (41), the primary inhibitory neurotransmitter in the CNS. These findings converge with evidence from transgenic rodent models (44) and human imaging studies (45) that suggest alterations in hypothalamic/thalamic regions to be associated with PPD. This is particularly intriguing in light of our results implicating GABAergic neurons, which is the target system of brexanolone, the only FDA-approved medication with a specific indication for PPD (14, 15). Brexanolone is a synthetic formulation of allopregnanolone and is a positive allosteric modulator of $GABA_A$ receptors (46). Given the broad distribution of $GABA_A$ receptors throughout the CNS, our results may help clarify the mechanism of action of this PPD therapeutic.

In order to achieve genome-wide-significant results for PPD, larger sample sizes are needed. Locus discovery for PPD can be expected to follow a trajectory similar to that seen for MDD, where robust SNP discovery required samples in excess of 100,000 cases (23). Equally important, however, will be ensuring that increases in sample size are accompanied by diversity of ancestry representation. As of 2019, a disproportionate majority (>78%) of participants in published GWASs were of European ancestry (47). Increasing representation of more diverse populations not only results in enhanced power of genomic studies and experimental methods (e.g., locus discovery, fine-mapping, genetic scores), but more importantly, it addresses the widespread health disparities that exist across research and medicine (48, 49). We estimated the h^2_{SNP} to be 0.14, which supports PPD as a complex disorder with genetic and environmental risk factors. As future studies work to increase participants of non-European ancestry, they should also take the opportunity to collect data on environmental contributors that have been shown to increase PPD risk and disproportionately affect women of color, such as adverse life events and discrimination (50–53).

With this work, we take some of the first steps toward increasing diversity in psychiatric genomics. PPD indiscriminately affects women in every part of the world. Therefore, we made every effort to include genetic data from all women who chose to participate in research. These early efforts to diversify our analyses already show promise. Our trans-ancestry analysis increased statistical associations of two loci compared with the EUR-ancestry analysis alone,

with one falling just below genome-wide levels of significance (rs10879002, $p=7.26\times10^{-8}$).

In analyses of the genetic relationships of PPD with other psychiatric disorders, diseases, and biomedical traits, we found the largest and most significant genetic correlation with MDD. However, this could be due in part to selection bias of our cases. Many of our PPD cases were identified as part of larger MDD collections, most notably UK Biobank (where PPD was identified using MDD algorithms) and AGDS, which combined make up 45% of all our PPD cases. Furthermore, the genetic correlations reflect the diverse clinical presentations of PPD despite its diagnostic categorization as a subtype of MDD (54–56). A previous history of MDD or anxiety disorders is a known risk factor for PPD, which is consistent with the high genetic correlations we observed. Additionally, the significant genetic correlation with insomnia suggests a potential role for this phenotype in PPD pathology, given that the postpartum period is often associated with disrupted sleep (57–62). Finally, genetic correlations with traits such as age at menarche and PCOS support a model for PPD pathology related to fluctuations in reproductive hormones (63, 64). These associations are supported by previous work identifying enrichment of ovarian tissue genes among PPD-associated variants (10). Notably, the r_g with PCOS has not been reported with MDD, supporting potentially distinct biological underpinnings between PPD and MDD.

This study also has limitations that should be kept in mind when interpreting the results. First, our study follows the conventional GWASs examining PPD control status. All cases reported depression in the postpartum period, and a majority of control participants screened had no reported depression and a pregnancy. This approach, however, does not account for the heterogeneity in PPD risk factors (e.g., previous psychiatric diagnoses) or presentation (e.g., symptom combinations, onset, duration, severity). These features are critical in defining PPD, but are not always collected. Within the cohorts used here, there was a range of psychiatric histories (e.g., MDD, bipolar disorder, unknown), a broadly defined postpartum period (up to 12 months in some cases), and multiple ascertainment methods. Increased phenotyping should take place alongside efforts to increase sample sizes, which would also power appropriate conditional analyses. Furthermore, it should be noted that sex is a confounder in our r_g and cell-type enrichment analyses. The summary statistics used in these analyses, specifically MDD, all include males. This leads to the possibility that the observed patterns of correlation and enrichment reflect etiological differences in depression between men and women generally, rather than something specific to PPD. However, in GWASs that have stratified by sex, there is high r_g between the sexes (65, 66). Further, secondary analyses were limited to European-ancestry summary statistics. This highlights the lack of trans-ancestry analyses available. As more diverse GWASs are performed, post-GWAS analyses need to be developed that utilize trans-ancestry results to identify causes and inform therapeutics development for PPD and other complex disorders.

PPD has a more homogeneous presentation compared with MDD, although there is still substantial phenotypic heterogeneity in the presentation of PPD. Symptom onset, duration, and severity are all important aspects of the disorder to consider when examining etiological factors. However, PPD is not an often collected phenotype, making it difficult to include specific symptom dimensions in work like GWASs. We recommend that future data collection efforts utilize screening tools, such as the lifetime version of the EPDS (28), to ascertain a more complete symptom profile in addition to case status. Biological sample collection and maternal psychiatric screening, including psychiatric history, can be incorporated as a part of perinatal or early pediatric clinic visits. These visits present the opportunity to collect a large amount of data as part of routine care for new mothers, which can increase sample sizes for future GWASs and address PPD heterogeneity.

In summary, we report the first genome-wide association meta-analyses for PPD. While no genome-wide significant loci were identified, this report contributes valuable new data about the genetic contributions to PPD. A direct comparison between PPD and MDD suggests a common genetic contribution between the two disorders. However, heritability estimates, cell-type enrichments, and other genetic correlations suggest genetic components that may distinguish PPD from MDD. Notably, top GWAS loci implicate GABAergic neurons, which converges with imaging studies and the only current medication specifically indicated for PPD. Studies incorporating larger and more diverse samples are needed to further clarify the genetic architecture of PPD.

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