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MKRN1 as a prioritized drug target for postpartum depression: evidence from druggable proteome profiling and multi-layer validation

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ABSTRACT

Postpartum depression (PPD) is a significant global health concern affecting women, yet effective and innovative therapeutic targets remain limited. Although genome-wide association studies (GWAS) have identified genetic risk loci, their underlying mechanisms and translational potential remain poorly understood. Therefore, we integrated PPD

GWAS data with protein quantitative trait loci from two independent datasets to identify risk genes through proteome-wide association studies (PWAS). Validation was performed using colocalization analysis and Mendelian randomization (MR). To assess the safety of genes as drug targets, phenome-wide MR (Phe-MR) was conducted using the UK Biobank disease data. Finally, we performed gene methylation analysis in PPD patients, alongside validation of expression in key brain regions including anterior cingulate gyrus (AnCg), dorsolateral prefrontal cortex, and nucleus accumbens, as well as in peripheral blood (whole blood and leukocytes), across depressive patients and chronic mild stress mice. Co-expression enrichment was used to identify biological pathways associated with risk genes. PWAS and colocalization analysis identified *MKRN1* and *CCDC92* as overlapping risk genes, with *MKRN1* validated in MR. Phe-MR showed non-significant association between *MKRN1* dysregulation and disease beyond depression and mood disorders, suggesting minimal off-target effects. Methylation analysis in PPD patients' blood revealed significant hypomethylation of *MKRN1*, consistent with expression analysis that confirmed its upregulation in AnCg and as a biomarker in blood. Enrichment analysis indicated *MKRN1* involvement in immune–inflammatory pathways. Our study identified *MKRN1* as a therapeutic target for PPD, integrating multi-omics evidence from genomics, proteomics, and druggable proteome profiling, and offering a promising path for targeted treatments.

INTRODUCTION

Postpartum depression (PPD) is a significant psychiatric disorder, defined by the onset of major depressive symptoms during pregnancy or within four weeks of delivery, as per the American Psychiatric Association[1]. The World Health Organization extended this timeframe to include the entire first postpartum year[2]. With an estimated prevalence of 13–19%[3], PPD presents with symptoms such as low mood, sleep disturbances, tearfulness, and confusion[4, 5]. Notably, compared to major depressive disorder (MDD), PPD is associated with a higher incidence of appetite

disturbance and fatigue[6], which can profoundly impair maternal caregiving ability[7]. This, in turn, adversely affects infant development across motor, cognitive, social, and emotional domains[8–10]. Early diagnosis and effective treatment are therefore essential[11].

Despite its prevalence and impact, therapeutic options for PPD remain limited. Only a few medications have been approved by the FDA specifically for PPD, targeting sites like the gamma-aminobutyric acid (GABA)-A receptor, but are associated with significant side effects[12, 13]. Traditional antidepressants are commonly used but carry risks for both maternal and neonatal health[14, 15]. Concerns about potential adverse effects, particularly on breastfeeding and infant development, often lead mothers to avoid pharmacological interventions[16, 17]. These challenges highlight the pressing need to develop novel and safe therapeutic strategies.

Genomic advances, particularly genome-wide association studies (GWAS), have identified risk loci associated with PPD[18, 19]. However, the ability of GWAS to provide biological insights is constrained, as these studies do not directly link genetic variants to functional pathways[20]. Proteome-wide association studies (PWAS), which integrate protein quantitative trait loci (pQTL) data with GWAS findings, offer a powerful complementary approach, enabling the identification of proteins associated with disease phenotypes[21]. Brain-derived pQTL data, in particular, has proven invaluable in identifying risk genes for neuropsychiatric conditions such as Alzheimer's disease and schizophrenia[22, 23]. Mendelian randomization (MR) further strengthens these findings by leveraging genetic variants as instrumental variables to infer causal relationships between protein expression and disease phenotypes[24]. While PWAS and MR have been extensively applied in psychiatric research[25–27], their use in PPD remains underexplored.

PPD shares several genetic[28] and symptomatic[4] features with MDD but is distinguished by unique risk factors

such as postpartum hormonal fluctuations[29–31] and caregiving stress[2, 32]. Both conditions are associated with dysregulation in brain regions critical for emotional and cognitive processing, including the anterior cingulate cortex (AnCg), dorsolateral prefrontal cortex (dlPFC), and nucleus accumbens (nAcc)[33, 34]. Peripheral factors, such as altered plasma levels of growth factors[35], immune markers[36], and transcriptional changes in leukocytes[37], further underscore the importance of integrating brain and peripheral data to identify clinically relevant biomarkers. Epigenetic mechanisms, particularly DNA methylation, also play a critical role in PPD by modulating gene expression in response to environmental and genetic factors[38]. Methylation changes in CpG islands, often leading to gene silencing[39], have been implicated in PPD, as exemplified by findings on *HP1BP3*[40, 41]. Additionally, animal models simulating PPD conditions, such as hormonal withdrawal and chronic stress, provide essential platforms for validating human findings[42–44].

In this study, we adopted an integrative multi-omics approach to identify and validate risk genes associated with PPD (Figure 1). Using PWAS, colocalization analysis, and MR, we identified candidate genes and evaluated their causal role in PPD. To assess the safety of these genes as potential therapeutic targets, phenome-wide MR (Phe-MR) was applied. Finally, we conducted differential expression analyses across tissues from depressive patients and mouse models to confirm the dysregulation of identified risk genes, along with functional enrichment to explore underlying mechanisms. This comprehensive approach aims to uncover novel molecular targets for PPD, offering potential pathways for therapeutic innovation.

MATERIALS AND METHODS

The overview of our study design was presented in Fig. 1.

PPD GWAS data

The GWAS data analyzed in this study were derived from a large-scale meta-analysis of PPD (Supplementary Table S1), encompassing 18,770 cases and 58,461 controls from 20 diverse cohorts[45]. These cohorts represented individuals of European, East Asian, and African ancestries. Genotyping data were processed uniformly across all ancestry groups, and potential issues of heterogeneity and population stratification were also addressed using genetic correlation analyses, leave-one-out sensitivity analyses, and ancestry-specific reference panel imputation. Full details on genotyping, quality control procedures, and statistical methods are available in the original study[45].

Human brain pQTL data

PWAS utilized human brain proteomic data from two large-scale datasets (Supplementary Table S1): the ROSMAP[46] and the Banner[47]. Both datasets included dlPFC tissue samples from individuals of European ancestry, comprising 376 participants in ROSMAP and 152 in Banner. Proteomic sequencing, conducted by Wingo et al.[48], identified cis-regulated proteins associated with genetic variants, integrating these data with significant single-nucleotide polymorphisms (SNPs) derived from GWAS. This approach yielded 1,475 proteins with significant cis-associations in the ROSMAP dataset and 1,139 in the Banner dataset[48], which were subsequently used as reference weights in the PWAS.

Proteome-wide association studies

PWAS were performed using FUSION software, integrating precomputed reference weights from ROSMAP and Banner proteomes with GWAS summary statistics to estimate the relationship between protein abundance and PPD[49]. Weighted linear models were constructed by summing the products of *Z*-scores from GWAS data with

corresponding protein weights, thereby evaluating the impact of SNPs on protein expression. Default parameters in FUSION were applied for these calculations, and the 1000 Genomes Project European reference panel (phase 3) for linkage disequilibrium estimation was used to match the predominant European ancestry of the PPD GWAS and pQTL datasets. To control for false discoveries, the Benjamini-Hochberg (BH) procedure for false discovery rate (FDR) correction was employed, with significant associations identified at an FDR threshold of $P < 0.05$. This approach provided a robust framework for identifying proteins implicated in PPD pathogenesis.

Colocalization analysis

To determine whether the identified risk genes and PPD share common causal variants, Bayesian colocalization analysis was performed using pQTL data from the ROSMAP and Banner datasets. The analysis was conducted using the "coloc" R package[50], which calculated the posterior probability for hypothesis 4 (H_4), representing the likelihood that GWAS and pQTL associations shared a common causal variant. A threshold of $H_4 > 0.6$ was used to define colocalization[48], indicating supporting evidence for a shared genetic signal between PPD and protein expression traits.

Mendelian randomization

To validate the results from PWAS and colocalization analysis, MR was employed, including independent and robust SNPs ($R^2 < 0.1$) with genome-wide significance ($P < 5\times10^{-5}$). Initially, summary data-based Mendelian randomization (SMR) was conducted[51]. This method estimated the causal effect sizes of protein levels (proxied by cis-pQTLs) on PPD using pQTL data from both datasets. Additionally, two-sample Mendelian randomization (TSMR) was performed, using pQTL-associated SNPs from ROSMAP as instrumental variables (IVs), pQTL-related proteins as exposures, and PPD GWAS data as outcomes. For proteins associated with a single pQTL, the Wald ratio method was applied,

while the inverse variance-weighted method was used for proteins linked to multiple pQTLs. The threshold for statistical significance was set at $P < 0.01$ to capture robust associations[52, 53].

To detect potential pleiotropy, the heterogeneity in dependent instruments (HEIDI) test was applied during SMR. A $P_{HEIDI} > 0.01$ was considered indicative of no significant horizontal pleiotropy or linkage effects, thereby strengthening the validity of the causal inference[54].

Phenome-wide Mendelian randomization

To assess potential unintended off-target effects of the risk genes, Phe-MR was conducted on 783 clinical traits from the UK Biobank (UKB). GWAS summary statistics from the UKB cohort (408,961 White British European-ancestry participants comprising more than 1,400 binary disease phenotypes[55]) were accessed, and SNPs associated with protein abundance were used as IVs, with identified risk genes as exposures and clinical traits as outcomes. Traits were categorized using the "PheCodes" system with those retaining more than 500 cases included, and analyses were performed using the Scalable and Accurate Implementation of Generalized Mixed Model (SAIGE v0.29) to account for imbalanced case-control ratios[55]. Results were corrected for multiple testing using the Bonferroni method, ensuring robust statistical reliability. As a sensitivity analysis, association between case sample size and $-\log_{10}(P\text{-value})$ was evaluated using Spearman correlation across all phenotypes, assessing the influence of case number variation on association patterns. The threshold was set at $\rho < 0.2$ to define weak correlation[56–58].

Epigenetic methylation analysis of risk genes in PPD patients

To investigate the epigenetic influence of identified risk genes on the development of PPD, methylation data from a cohort of PPD patients were analyzed. These data were derived from a study by Guintivano et al.[40], involving 12

PPD patients (prepartum and postpartum) and 25 healthy controls assessed using the DSM-IV criteria for major depressive episodes. Blood samples were collected during this period to facilitate epigenetic profiling. For each CpG site, the β-value, representing the proportion of methylation, was calculated as:

β = (signal intensity of methylation-detecting probe) / (signal intensity of methylation-detecting probe + signal intensity of non-methylation-detecting probe+100).

This approach allowed for the systematic assessment of methylation levels at CpG sites of risk genes, providing insights into their potential regulatory roles in PPD pathophysiology. Detailed information on sample collection and data processing can be found in the original publication[40]. Considering the diverse effects of methylation, we performed differential analysis of methylation levels on both each individual probe targeting CpG sites and the average β-value of all probes.

Validation of risk gene expression in the AnCg, dlPFC, and nAcc

To further assess the transcriptional dysregulation of risk genes in PPD pathogenesis, we analyzed gene expression data from key brain regions (AnCg, dlPFC, and nAcc) implicated in depression. Data were drawn from two independent studies involving MDD patients and an unpredictable chronic mild stress (UCMS) mouse model, and may provide insights into the mechanisms underlying gene dysregulation in brain.

Human brain data were sourced from Ramaker et al., which collected postmortem brain tissues from 24 MDD patients and 24 controls[59]. Gene transcription level was analyzed in AnCg, dlPFC, and nAcc. For the mouse model, expression data for AnCg were provided by Hervé et al.[60], which included samples from eight mice subjected to an 8-week UCMS procedure, a model for depression, along with eight healthy mice raised under standard conditions.

Data were normalized in both studies to eliminate technical biases. Specific details regarding sample extraction, data processing, and normalization were elaborated in the original studies[59, 60].

Risk gene expression as a biomarker for depression

To broadly evaluate the reliability of risk genes as peripheral biomarkers for both PPD and MDD, we incorporated peripheral blood gene expression data from three additional studies, comprised samples from MDD patients along with ovariectomized (OVX) and chronic mild stress (CMS) mouse models, encompassing gene expression profiles from whole blood and leukocytes.

Human whole blood data were obtained from Leday et al.[61], containing expression data of 128 MDD patients and 64 controls from two independent case-control studies: the GlaxoSmithKline–High-Throughput Disease-specific Target Identification Program and the Janssen–Brain Resource Company study. Identical quality control, normalization, and annotation algorithms were applied to both studies. Human leukocyte data was sourced from Miyata et al.[62], which included 20 MDD patients and 12 age- and sex-matched controls from the Department of Psychiatry and Neuroscience at Gunma University Hospital. For the mouse model, data from whole blood was obtained from another study by Miyata et al.[63], where OVX and CMS was employed to establish a depression model. Gene expression profiling followed a similar protocol as described earlier for processing human samples. Detailed information on sample preparation and microarray analysis is available in the original studies[61–63].

For differential methylation and expression analysis, the Hommel method was applied for multiple testing correction across human and mouse tissues.

Functional enrichment of risk gene–associated co-expression network

To investigate the molecular mechanisms underlying the role of risk genes in PPD, we obtained co-expression gene networks consistent with the pathogenic direction of risk genes from the SigCom LINCS database[64, 65]. Gene Ontology (GO) functional enrichment analysis on these networks was performed using the "clusterProfiler" R package (v4.14.6)[66], with default parameters. Statistical significance was adjusted using the BH method, retaining terms with an adjusted *P*-value < 0.05.

Results

PWAS identified *MKRN1* and *CCDC92* as key overlapping risk genes for PPD

In the two-stage PWAS, we integrated proteome reference weights from both the ROSMAP and Banner datasets. In ROSMAP, we identified four candidate genes: *MKRN1*, *CCDC92*, *CRK*, *HARS2*, that were significantly associated with PPD, using a threshold of *P*-FDR < 0.05 (Fig. 2 and Supplementary Table S2). Likewise, there were four candidate genes identified in Banner: *MKRN1*, *CCDC92*, *HARS*, *DHX36*. Notably, two risk genes—*MKRN1* (*P*-FDR_{ROSMAP} = 4.66E-02, *P*-FDR_{Banner} = 3.59E-02) and *CCDC92* (*P*-FDR_{ROSMAP} = 3.65E-02, *P*-FDR_{Banner} = 4.28E-02)—were found to overlap between both datasets (Supplementary Table S3 and S4), suggesting their crucial role in the pathogenesis of PPD. The positive *Z*-scores for *MKRN1* in both datasets indicated a strong association between its upregulation and PPD, while negative *Z*-scores for *CCDC92* suggested its downregulation was significantly linked to the disease.

Colocalization analysis confirmed shared causal variants for PPD risk genes

To estimate the probability that shared causal variants drive both GWAS and pQTL signals in PPD, we conducted the

Bayesian colocalization analysis in ROSMAP and Banner datasets. Using a threshold of $H_4 > 0.6$, we identified two overlapping genes across both datasets (Supplementary Table S5 and S6), including *MKRN1* (H_4-ROSMAP = 8.45E-01, H_4-Banner = 6.46E-01) and *CCDC92* (H_4-ROSMAP = 8.38E-01, H_4-Banner = 7.57E-01). Their evidence observed in both PWAS and colocalization analysis underscored their pivotal roles in PPD pathogenesis.

MR highlighted *MKRN1* as a high-confidence risk gene for PPD

We performed SMR, selecting the top significant genes from both the ROSMAP and Banner datasets based on a threshold of $P_{SMR} < 0.01$ (Supplementary Table S7, S8 and S9). Of these, *MKRN1* demonstrated consistent evidence across both databases ($P_{SMR\text{-}ROSMAP}$ = 8.59E-04, $P_{SMR\text{-}Banner}$ = 2.62E-03) with no significant horizontal pleiotropy observed ($P_{HEIDI\text{-}ROSMAP}$ = 3.64E-01, $P_{HEIDI\text{-}Banner}$ = 2.75E-01), while *CCDC92* was excluded for failing to meet the threshold. In subsequent TSMR, causal relationships between the protein levels of genes and PPD were calculated using the Wald ratio or inverse variance-weighted method. Among the significant genes ($P < 0.01$) (Supplementary Table S10), verification was achieved for *MKRN1* (*P*-TSMR = 7.30E - 05, OR: 3.45, 95% CI: 1.87 – 6.36) (Fig. 3), underscoring its essential contributions to the development of PPD.

Phe-MR of *MKRN1* on 783 disease traits

We integrated the results from PWAS, colocalization analysis, and MR and observed consistent evidence for *MKRN1* across all analyses, further supporting its role as a risk gene for PPD (Fig. 4a).

To characterize the potential off-target effects of *MKRN1*, we conducted Phe-MR on 783 disease traits (categorized into 16 categories) from the UK Biobank. Based on Bonferroni-corrected *P*-values ($P = 0.05/783 = 6.39 \times 10^{-5}$), we detected that *MKRN1* upregulation was a significant risk factor for depression ($P = 1.10 \times 10^{-5}$; OR: 3.98, 95% CI:

2.15–7.37) and mood disorders ($P = 1.98 \times 10^{-5}$; OR: 3.72, 95% CI: 2.03–6.80) but not significantly associated with other diseases (Fig. 4b and Supplementary Table S11). Spearman correlation showed a weak association ($\rho = 0.18$), suggesting a minor influence of case number variation on test results and supporting the reliability of the observed association signals. These findings aligned with results from other analyses in our study, further confirming *MKRN1* as a promising candidate therapeutic target for PPD and offers a foundational clue for future drug development efforts.

Differential expression analysis validated the upregulation of *MKRN1*

To further investigate the role of *MKRN1* in PPD, we conducted an integrative analysis combining gene methylation and expression data across specific tissue types, including key brain regions and peripheral blood samples (Supplementary Table S12 and S13). Statistical significance was determined using a two-sample *t*-test (adjusted $P < 0.05$), with a focus on cross-dataset consistency in the direction of effects.

In PPD patient samples, the CpG island of *MKRN1* revealed significantly reduced comprehensive methylation levels compared to healthy controls (mean β-value reduction: $P = 7.97 \times 10^{-3}$, $t = -3.71$) (Fig. 5a). Among all probes, 5 of 16 CpG sites showed significant methylation loss, collectively indicating a pattern of predominant hypomethylation likely contributing to regulated *MKRN1* transcriptional activity. Expanding on this, we interrogated expression datasets from key brain regions to ascertain our finding. Notably, in the AnCg—a region intricately linked to mood regulation—*MKRN1* was significantly overexpressed in MDD patients ($P = 4.36 \times 10^{-2}$, $t = 2.54$) (Fig. 5b) and UCMS mouse model ($P = 4.35 \times 10^{-2}$, $t = 2.43$) (Fig. 5c), implicating its involvement in depressive pathophysiology. Peripheral validation mirrored these observations: *MKRN1* expression was elevated in whole blood ($P = 4.77 \times 10^{-2}$, $t = 2.17$) (Fig. 5d) and leukocytes ($P = 2.91 \times 10^{-2}$, $t = 2.82$) (Fig. 5e) of MDD patients, as well as in whole blood of OVX and CMS mouse model ($P = 4.77 \times 10^{-2}$, $t = 1.84$) (Fig. 5f), which provided further validation of *MKRN1* as a

reliable risk gene and adds weight to its candidacy as a biomarker.

These findings across tissues and species highlight the *MKRN1*'s potential as both a diagnostic marker and therapeutic target in PPD pathogenesis, where epigenetic changes drove its transcriptional upregulation and subsequent protein abundance.

***MKRN1* was implicated in immune-inflammatory processes**

GO enrichment analysis of the *MKRN1*-co-upregulated gene network revealed significant involvement in immune-related biological pathways, including leukocyte and neutrophil migration and chemotaxis, immune granule and secretory vesicle components, and immune receptor activity (Fig. 5g) (Supplementary Table S15), suggesting a potential role of *MKRN1* and its interacting pathways in mediating immune–inflammatory responses.

Discussion

In our study, we began by integrating findings from PWAS and colocalization analysis, identifying two PPD risk genes, *MKRN1* and *CCDC92*. Notably, *MKRN1* was further corroborated through MR, pointing to the significant involvement of its upregulation in PPD pathology. To evaluate the feasibility of *MKRN1* as a druggable protein, we conducted Phe-MR to investigate potential safety concerns. Recognizing the intricate etiology of PPD and its epigenetic underpinnings, we performed methylation analysis on blood samples from PPD patients. To substantiate this, validation was expanded to differential expression analysis in key brain regions to investigate the etiology of depression, and in peripheral blood samples to evaluate the potential of risk genes as biomarkers. These analyses were conducted in MDD patients and depressive mouse models, aiming to validate *MKRN1* dysregulation at the expression

level and support its application as a therapeutic target. Epigenetic analysis unveiled hypomethylation of *MKRN1* CpG islands, a modification that may drive transcriptional activation. Subsequent differential expression analysis revealed significant *MKRN1* upregulation in the AnCg, whole blood, and leukocytes, which converged with methylation results and provided compelling evidence for its involvement in the pathogenesis of PPD. Briefly, these findings established *MKRN1* as a pivotal gene in PPD, underscoring its promise as a biomarker and a therapeutic target.

MKRN1, or Makorin Ring Finger Protein 1, is a highly transcribed, intron-containing gene that forms the evolutionary basis of a mammalian gene family encoding unique zinc finger proteins[67]. It has been found to be highly expressed across various tissues, including different regions of the brain[67], suggesting its essential role in neural development. To date, copy number variations of *MKRN1* have been found to be significantly associated with neurodevelopmental disorders such as autism spectrum disorder and schizophrenia[68]. Additionally, *MKRN1* has also been implicated in other structural neurological abnormalities[69, 70], further underscoring its potential importance in neurological diseases. However, few studies have reported the connection between *MKRN1* and PPD.

Kim et al. demonstrated that *MKRN1* acts as an E3 ubiquitin ligase, promoting TERT degradation and telomere shortening in human cells[71], a process linked to cellular senescence[72] and diseases such as schizophrenia[73], cognitive impairment[74], diabetes[75], and cirrhosis[76]. Notably, telomere shortening has been observed in blood samples from Latina women with PPD[77]. Many studies have also shown the association between telomere shortening in leukocytes and depressive symptoms[78, 79]. These findings support our hypothesis, based on differential expression analysis (Fig. 5a, d, e, f), that *MKRN1* is significantly upregulated in depressed patients and might induce telomere shortening.

Similarly, *MKRN1* mediates the ubiquitination and degradation of proteins such as p53, AMPK[80]. The close

connection between p53, AMPK and MDD has been confirmed in previous studies[81–83]. Interestingly, we found that the inhibitory effects of *MKRN1* on p53, AMPK, and TERT, as well as the consequences such as cellular senescence caused thereby, can all lead to an increase in oxidative stress[84–87]. Meanwhile, this degradation inhibits p53's activation of AMPK and its protective effect on telomeres, further amplifying oxidative stress[82, 88]. These findings collectively suggest that the upregulation of *MKRN1* may be pivotal in oxidative stress at the cellular level. Oxidative stress is a key mechanism in neurodegenerative[89] and psychiatric diseases (especially depression[90–94]). Notably, increased oxidative stress in the AnCg has been strongly associated with depressive symptoms[95, 96], suggesting that *MKRN1* may contribute to the onset of depressive symptoms by mediating oxidative stress in the AnCg, aligning with the upregulation of *MKRN1* observed in our differential expression analysis (Fig. 5b, c). Interestingly, we found the GABA level in the AnCg of depressed patients was significantly decreased[97, 98]. When oxidative stress level increases, the GABA level also tends to decline[99]. This indicates that *MKRN1*-mediated oxidative stress may contribute to depression by disrupting the GABA system, consistent with the mechanisms of the two existing FDA-approved anti-PPD drugs, as they both act as positive allosteric modulators of the GABA-A receptor[12].

Oxidative stress in depression frequently coexists with neuroinflammation, and the two processes can mutually reinforce each other[100, 101]. Likewise, AMPK has been shown to alleviate depressive-like behaviors through anti-inflammatory mechanisms[102], telomere length in depressed patients is negatively correlated with inflammatory burden[103], and p53 can attenuates inflammation by suppressing NF-κB, whose activation promotes inflammatory cascades that may drive depressive pathogenesis[104]. These lines of evidence are consistent with our enrichment results, where genes co-upregulated with *MKRN1* are significantly enriched for immune- and inflammation-related pathways (Fig. 5g).

Collectively, AnCg was identified as a key pathogenic region in PPD where *MKRN1* may induce depression by regulating oxidative stress and neuroinflammation via the p53/AMPK/TERT pathway, suggesting *MKRN1* as a promising biomarker for PPD identification, consistent with previous research linking telomere length, oxidative stress, neuroinflammation, and depression[105–107]. This provides new insights into the underlying mechanisms and potential therapeutic targets.

DNA methylation constitutes a key layer of epigenetic regulation and has been extensively studied in neurodegenerative and psychiatric disorders[108, 109]. As one of the most critical regulating areas, promoter CpG methylation is often, but not invariably, associated with transcriptional repression[110, 111]. In peripheral blood samples from PPD patients, we observed significant average hypomethylation across the *MKRN1* promoter CpG island, with 5 out of 16 probes showing significantly reduced methylation. This finding suggests a potential epigenetic mechanism underlying *MKRN1*'s dysregulation, consistent with the elevated protein and mRNA levels observed in our PWAS and differential expression analyses. Nevertheless, the complex relationship between methylation and gene expression, along with limitations arising from inconsistencies between epigenetic and transcriptomic cohorts, necessitates caution in interpretation, which emphasizes the need for large-scale, multi-layered profiling in future studies. Given the advantage of QTL data in directly testing genetic associations, we also propose that well-powered methylation quantitative trait locus (meQTL) analyses in PPD cohorts would facilitate the validation and elaboration of the findings presented in future study.

In the drug development process, serious adverse reactions during treatment often lead to project failures[112]. The current medications targeting potential causal proteins identified in the present study were summarized in Supplementary Table S14. As an extension of MR, Phe-MR assesses the associations between genetic variations and

a range of disease phenotypes. This approach allows for an effective evaluation of the potential side effects of drug targets, thereby providing a preliminary prediction of side effects in clinical targeted therapy. Our Phe-MR revealed that *MKRN1* exhibited significant associations with depression and mood disorders, without notable effects on other diseases, reducing the likelihood of severe off-target effects and laying the groundwork for translational drug research. However, despite the weak correlation between variations in case numbers and the association results, the potential impact of sample imbalance on statistical power remains hard to be excluded, and further rigorous evaluation is required to confirm the associations with other diseases and the safety of *MKRN1* as a drug target.

Beyond *MKRN1*, our multi-omics framework highlighted other genes warranting investigation. *CCDC92*, an interferon-stimulated protein involved in innate immunity[113], has been previously linked to depression and schizophrenia[114, 115]. *HARS* and *HARS2* belong to the family of histidyl-tRNA synthetases, which are responsible for synthesizing histidyl-tRNA, a process crucial for the synthesis of proteins containing histidine[116]. *HARS* has been implicated in peripheral neuropathy and cognitive impairment[117, 118], while *HARS2* primarily exerts its function within mitochondria[119] and is associated with bipolar disorder and schizophrenia[120].

Our study has several strengths. First, we combined PWAS, MR, and colocalization analysis, incorporating pQTL data from multiple sources to identify high-confidence results and effectively control for potential biases. Second, the Phe-MR results ruled out adverse effects of *MKRN1* on other critical systems or organs, enhancing its value as a drug target. Finally, differential expression analysis using external datasets confirmed the directionality and significance of *MKRN1*'s effects, increasing the reliability of our conclusions.

Our study has limitations. First, while the included GWAS data cover populations from Europe, East Asia, and Africa, biases may arise due to incomplete representation across age groups and ethnic backgrounds, requiring larger studies.

Second, brain pQTL resources from ROSMAP and Banner remain modest in scale, constraining statistical power for protein discovery. Third, the extrapolation of pQTL effects from mixed-sex, aging cohorts to postpartum women assumes shared genetic regulation across biological states, an assumption that requires validation in pregnancy-specific molecular datasets.

Methodologically, PWAS, SMR, and TWAS analyses leverage mathematically related frameworks using overlapping genomic resources, which may partially explain their convergent findings. Meanwhile, each method has distinct features and provides complementary perspectives in terms of interpretation and hypothesis testing, thus we believe these approaches together offer different layers of evidence that strengthen the validation of the observed gene–phenotype relationships and provide indirect sensitivity support for single-variant associations tested in SMR. For HEIDI tests, some proteins had fewer than 10 available SNPs after LD-based clumping, reflecting inherent constraints in current pQTL datasets that may reduce statistical power. Additionally, while blood-based methylation data provide accessible systemic profiling, tissue-specific regulatory differences between blood and brain limit direct pathological interpretations. Future work will be needed to validate these findings and to further explore the relationship of shared biomarkers between blood and brain. Finally, our validation using MDD samples and chronic stress models, while reasonable approximations given PPD-specific data scarcity, cannot fully capture the unique neurobiology of the peripartum period.

In summary, we have identified *MKRN1* as a risk gene for PPD, supported by comprehensive multi-omics evidence spanning genomics, proteomics, and druggable proteome profiling. The strong correlation between *MKRN1* and depression underscores its viability as a novel peripheral biomarker and therapeutic target with preliminary support for lowering unintended effect risks in clinical use, highlighting *MKRN1*'s role in shaping both the molecular

understanding and clinical management of the disorder.

DATA AVAILABILITY

The data used in the study can be accessed and downloaded from original studies[40, 45–48, 59–63].

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AUTHOR CONTRIBUTIONS

All authors are grateful for participation in our research. CZ contributed to the conception and design of the work; CZ, CY, TJ managed the literature searches and analyses. CY, SH, LX and AL contributed to visualization; TJ and CY contributed to the drafting; FQ and YH accessed and verified the data. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no competing interests and financial relationships with commercial interests.

ETHICS

This study exclusively used de-identified, publicly available human and animal datasets from previously published studies. All original studies were approved by their respective named institutional review boards or ethics committees, including the Institutional Review Board of Rush University Medical Center[46], Banner Sun Health Research Institute[47], University of California, Irvine[59], Gunma University Hospital[62, 63], and CPP Sud Méditerranée II (Marseille, France)[60]. All procedures were conducted in accordance with the Declaration of Helsinki and relevant institutional and national guidelines.

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FIGURE LEGENDS

Fig. 1 Flowchart of the integrated analysis to identify risk genes and potential therapeutic targets for PPD. The study employed a three-step integrative approach to systematically identify risk genes associated with PPD and evaluate their potential as therapeutic targets. Risk Gene Identification: GWAS data for PPD were integrated with two independent human brain pQTL datasets, including the Religious Orders Study and Rush Memory and Aging Project (ROSMAP) and the Banner Sun Health Research Institute (Banner) datasets, to perform a two-stage PWAS. Significant genes were further validated using colocalization analysis and MR, ensuring convergent evidence for their association with PPD. Safety Evaluation: Phenome-wide association studies using Phe-MR were conducted to assess the safety of identified genes as drug targets by excluding associations with potential adverse phenotypic outcomes. Validation and Characterization of Gene Dysregulation: Differential methylation analysis was conducted on blood samples from PPD patients to investigate the epigenetic effects of risk genes. RNA expression analysis was performed on key brain regions (AnCg, dlPFC, and nAcc) and blood samples (whole blood and leukocytes) from MDD patients and mouse models, confirming the abnormal expression of risk genes in brain and their potential as peripheral biomarkers. This step validated the dysregulation of the identified genes in the context of depression. Functional enrichment of co-expression network further highlighted underlying biological effects of risk genes.

Fig. 2 Miami plot for the PWAS results. (a) Significant risk genes identified in ROSMAP. (b) Significant risk genes identified in Banner. Each point represents a single test of association between a gene and PPD ordered by genomic position on the *x* axis and the association strength on the *y* axis. “Positive” and “negative” displayed above and below the central axis indicate the direction of association. The red horizontal line reflects the significant threshold of the *P*-

FDR < 0.05.

Fig. 3 TSMR results indicating causal effects between PPD and risk genes. (a) All the selected genes demonstrate consistent evidence across SMR and TSMR. Columns: Exposure, Method (causal effects estimating methods), NSNPs (number of SNPs included), Log_2OR(95% CI) (values > 0 indicate increased PPD risk and < 0 indicate decreased risk). (b) Integrated summary of evidence for each gene. The concentric rings, from outermost to innermost, display: the significance of the TSMR analysis (*P*-value), the posterior probability of colocalization (H_4) in the ROSMAP dataset, and the H_4 in the Banner dataset. Among these genes, only *MKRN1* pass the colocalization analysis in both the ROSMAP and Banner datasets.

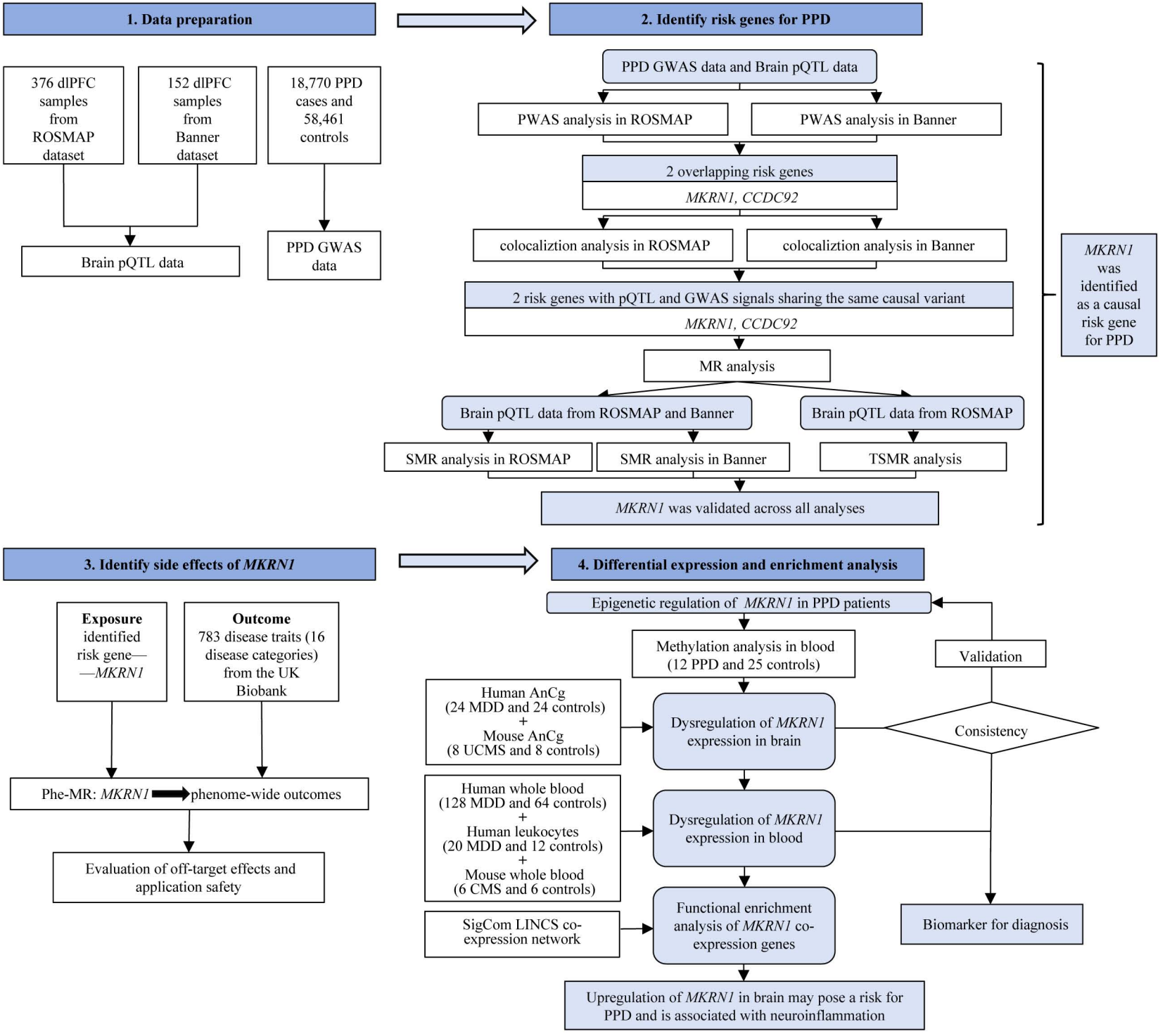
OR, Odds Ratio; CI, Confidence Interval.

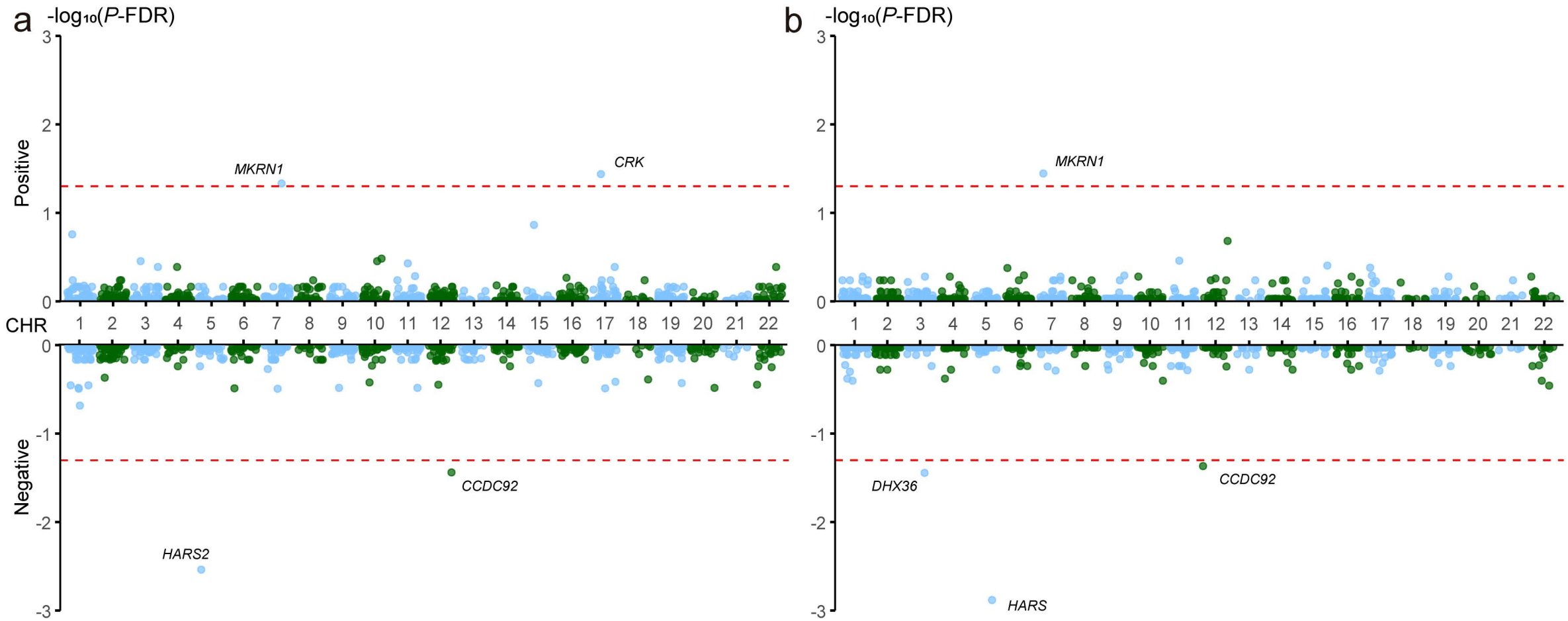
Fig. 4 Multi-stage identification of *MKRN1* as a risk gene for PPD and evaluation of its pleiotropic effects.

(a) Sankey diagram illustrating the multi-stage analytical pipeline for prioritizing PPD risk genes. *MKRN1* was the only gene supported by all five lines of evidence. (b) Venn diagram showing common targets across PWAS, colocalization analysis, SMR, and TSMR, with *MKRN1* identified as the only gene supported by all methods. (c) Manhattan plot for Phe-MR of *MKRN1* across 783 disease traits. Horizontal coordinates represent different disease categories, with each dot representing a disease trait. The dashed line corresponds to *P*-value adjusted by the Bonferroni method ($P = 0.05/783 = 6.39 \times 10^{-5}$).

Fig. 5 Differential expression of *MKRN1* in various tissues of depressive patients and mice, and functional enrichment of its co-expression network. (a) The methylation degree of the CpG island of *MKRN1* is significantly decreased in blood samples of PPD patients. (b) *MKRN1* is significantly upregulated in the AnCg of MDD patients.

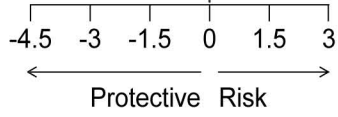
(c) *MKRN1* is significantly upregulated in the AnCg of UCMS mouse model. (d) *MKRN1* is significantly upregulated in whole blood of MDD patients. (e) *MKRN1* is significantly upregulated in leukocytes of MDD patients. (f) *MKRN1* is significantly upregulated in the whole blood of OVX and CMS mouse model. In panel a, the β-value shows the average methylation level across all probes that correspond to a CpG island in the *MKRN1*. In panels b–f, *MKRN1* expression levels were normalized. (g) Gene Ontology (GO) terms enriched for *MKRN1* co-expression network. BP: Biological Processes; CC: Cellular Components; MF: Molecular Functions.


1. Data preparation
376 dlPFC samples from ROSMAP dataset
152 dlPFC samples from Banner dataset
18,770 PPD cases and 58,461 controls
Brain pQTL data
PPD GWAS data
2. Identify risk genes for PPD
PPD GWAS data and Brain pQTL data
PWAS analysis in ROSMAP
PWAS analysis in Banner
2 overlapping risk genes
MKRN1, CCDC92
colocaliztion analysis in ROSMAP
colocaliztion analysis in Banner
2 risk genes with pQTL and GWAS signals sharing the same causal variant
MKRN1, CCDC92
MR analysis
Brain pQTL data from ROSMAP and Banner
Brain pQTL data from ROSMAP
SMR analysis in ROSMAP
SMR analysis in Banner
TSMR analysis
MKRN1 was validated across all analyses
MKRN1 was identified as a causal risk gene for PPD
3. Identify side effects of MKRN1
Exposure identified risk gene——MKRN1
Outcome 783 disease traits (16 disease categories) from the UK Biobank
Phe-MR: MKRN1 phenome-wide outcomes
Evaluation of off-target effects and application safety
4. Differential expression and enrichment analysis
Epigenetic regulation of MKRN1 in PPD patients
Methylation analysis in blood (12 PPD and 25 controls)
Validation
Human AnCg (24 MDD and 24 controls) + Mouse AnCg (8 UCMS and 8 controls)
Dysregulation of MKRN1 expression in brain
Consistency
Human whole blood (128 MDD and 64 controls) + Human leukocytes (20 MDD and 12 controls) + Mouse whole blood (6 CMS and 6 controls)
Dysregulation of MKRN1 expression in blood
SigCom LINCS co-expression network
Functional enrichment analysis of MKRN1 co-expression genes
Biomarker for diagnosis
Upregulation of MKRN1 in brain may pose a risk for PPD and is associated with neuroinflammation

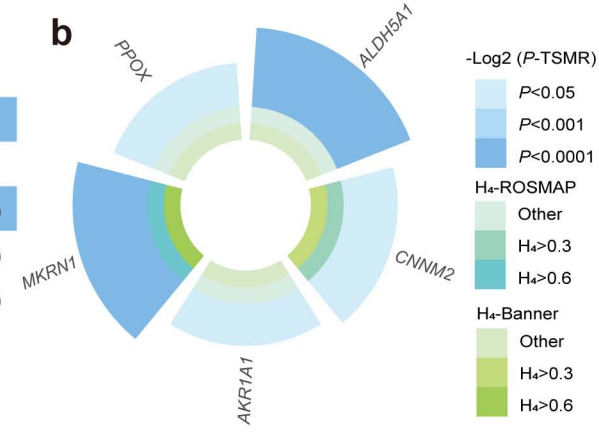

a
-log10(P-FDR)
Positive
Negative
CHR
MKRN1
CRK
CCDC92
HARS2
b
-log10(P-FDR)
MKRN1
DHX36
CCDC92
HARS

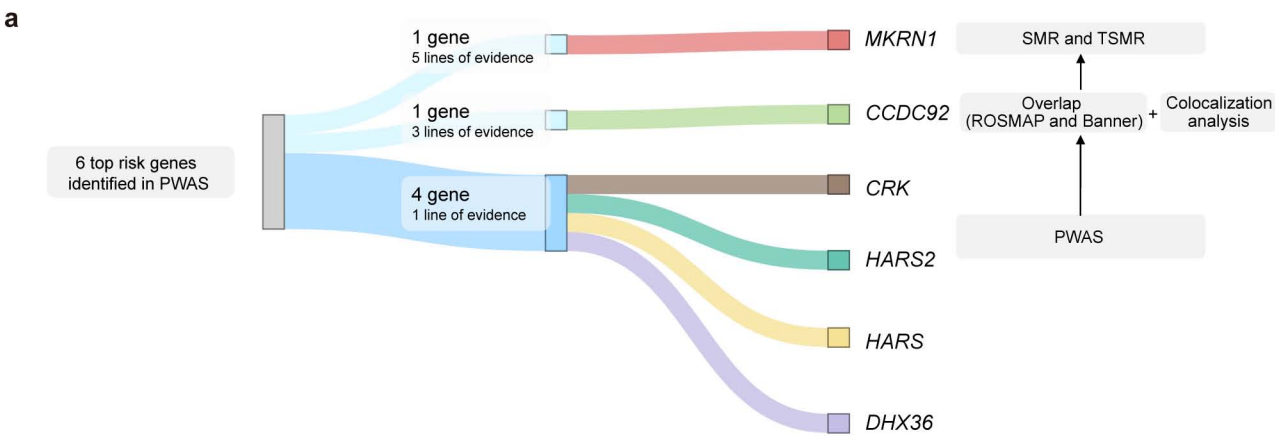
a

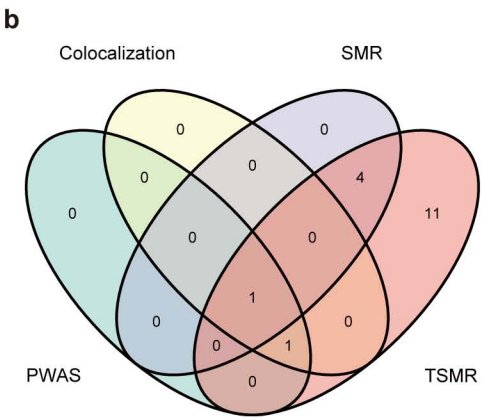
Exposure	Method	NSNPs	*P*-value	Log_2 OR(95% CI)
ALDH5A1	Wald ratio	1	4.22e-05	1.24 (0.64 to 1.83)
MKRN1	Wald ratio	1	7.30e-05	1.79 (0.90 to 2.67)
CNNM2	Wald ratio	1	1.04e-03	-2.61 (-4.17 to -1.05)
PPOX	Wald ratio	1	3.80e-03	-0.91 (-1.53 to -0.29)
AKR1A1	Wald ratio	1	4.64e-03	-0.43 (-0.73 to -0.13)

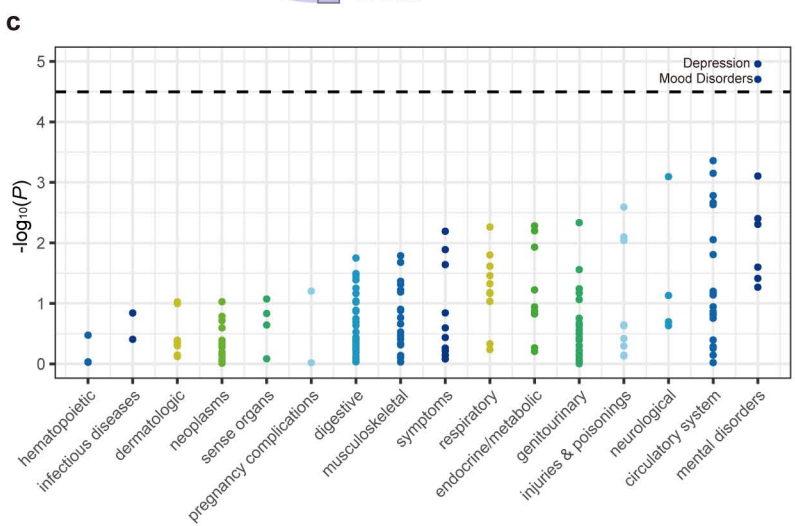


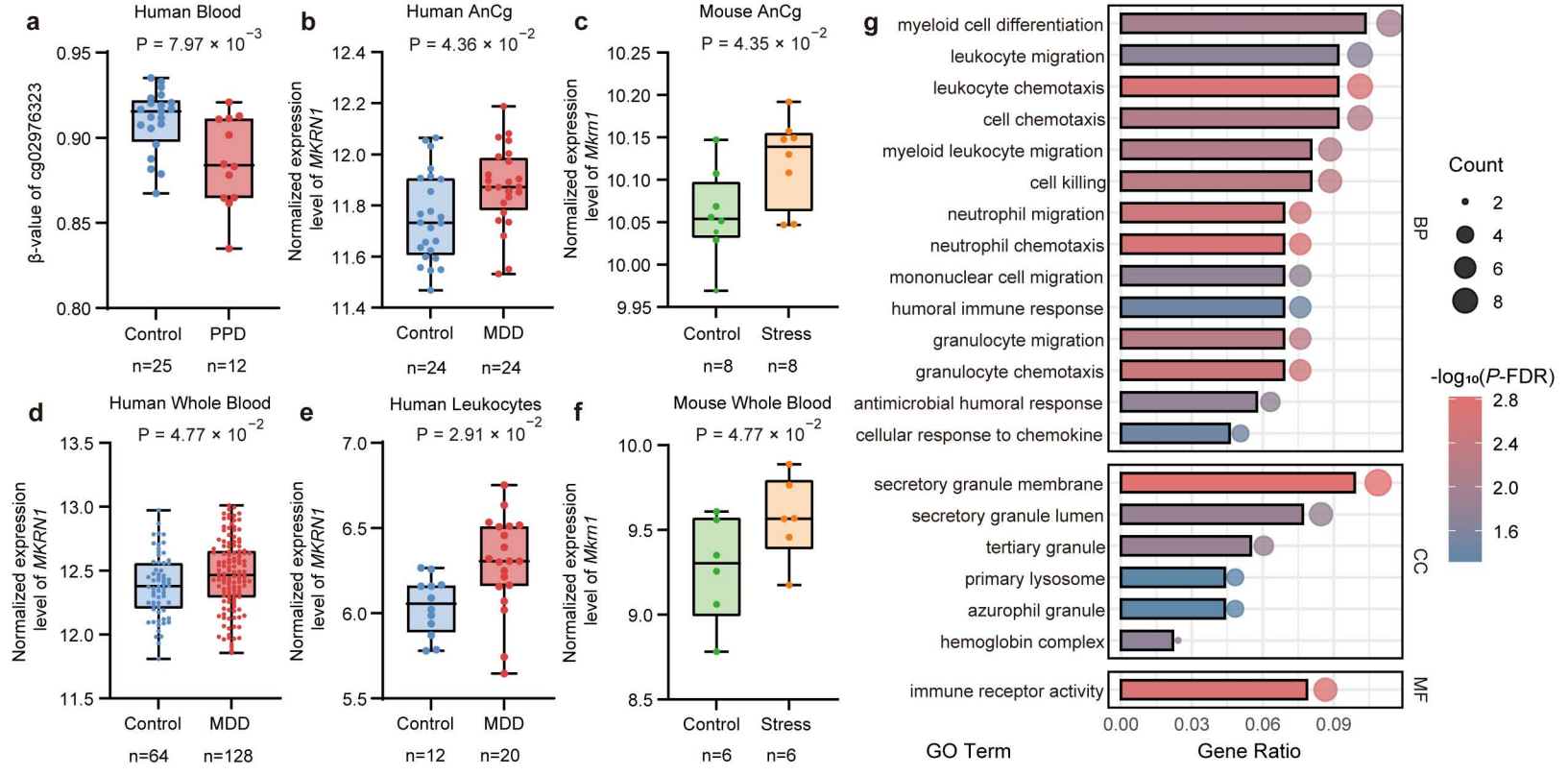
b




a
6 top risk genes identified in PWAS
1 gene
5 lines of evidence
1 gene
3 lines of evidence
4 gene
1 line of evidence
MKRN1
CCDC92
CRK
HARS2
HARS
DHX36
SMR and TSMR
Overlap (ROSMAP and Banner)
+
Colocalization analysis
PWAS


b
Colocalization
SMR
PWAS
TSMR
0
0
0
0
4
11
0
0
0
1
0
0
1
0
0


c
Depression
Mood Disorders
-log10(P)
0
1
2
3
4
5
hematopoietic
infectious diseases
dermatologic
neoplasms
sense organs
pregnancy complications
digestive
musculoskeletal
symptoms
respiratory
endocrine/metabolic
genitourinary
injuries & poisonings
neurological
circulatory system
mental disorders


a
Human Blood
P = 7.97 × 10−3
β-value of cg02976323
0.95
0.90
0.85
0.80
Control
PPD
n=25
n=12
b
Human AnCg
P = 4.36 × 10−2
Normalized expression level of MKRN1
12.4
12.2
12.0
11.8
11.6
11.4
Control
MDD
n=24
n=24
c
Mouse AnCg
P = 4.35 × 10−2
Normalized expression level of Mkrn1
10.25
10.20
10.15
10.10
10.05
10.00
9.95
Control
Stress
n=8
n=8
d
Human Whole Blood
P = 4.77 × 10−2
Normalized expression level of MKRN1
13.5
13.0
12.5
12.0
11.5
Control
MDD
n=64
n=128
e
Human Leukocytes
P = 2.91 × 10−2
Normalized expression level of MKRN1
7.0
6.5
6.0
5.5
Control
MDD
n=12
n=20
f
Mouse Whole Blood
P = 4.77 × 10−2
Normalized expression level of Mkrn1
10.0
9.5
9.0
8.5
Control
Stress
n=6
n=6
g
myeloid cell differentiation
leukocyte migration
leukocyte chemotaxis
cell chemotaxis
myeloid leukocyte migration
cell killing
neutrophil migration
neutrophil chemotaxis
mononuclear cell migration
humoral immune response
granulocyte migration
granulocyte chemotaxis
antimicrobial humoral response
cellular response to chemokine
secretory granule membrane
secretory granule lumen
tertiary granule
primary lysosome
azurophil granule
hemoglobin complex
immune receptor activity
BP
CC
MF
0.00
0.03
0.06
0.09
GO Term
Gene Ratio
Count
2
4
6
8
-log10(P-FDR)
2.8
2.4
2.0
1.6