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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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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.

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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

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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 (Fig. 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 1475 proteins with significant cis-associations in the ROSMAP dataset and 1139 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 ($P < 5 \times 10^{-5}$). 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 $P_{\mathrm{HEIDI}} > 0.01$ 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 1400 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).

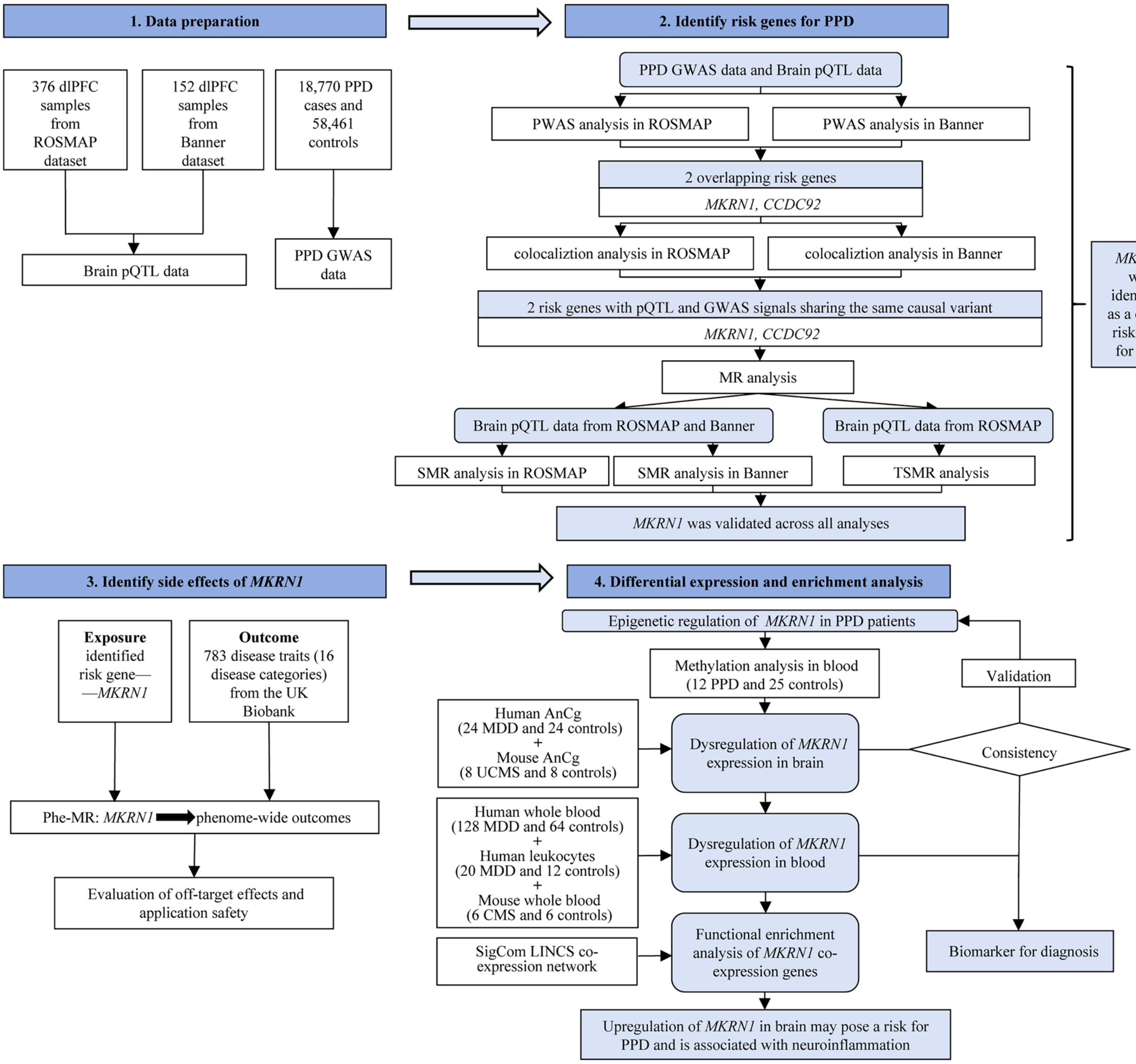

Fig. 1 Flowchart of the integrated analysis to identify risk genes and potential therapeutic targets for PPD. The study employed a three-step integrative approach to systematically identify risk genes associated with PPD and evaluate their potential as therapeutic targets. Risk Gene Identification: GWAS 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.

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].

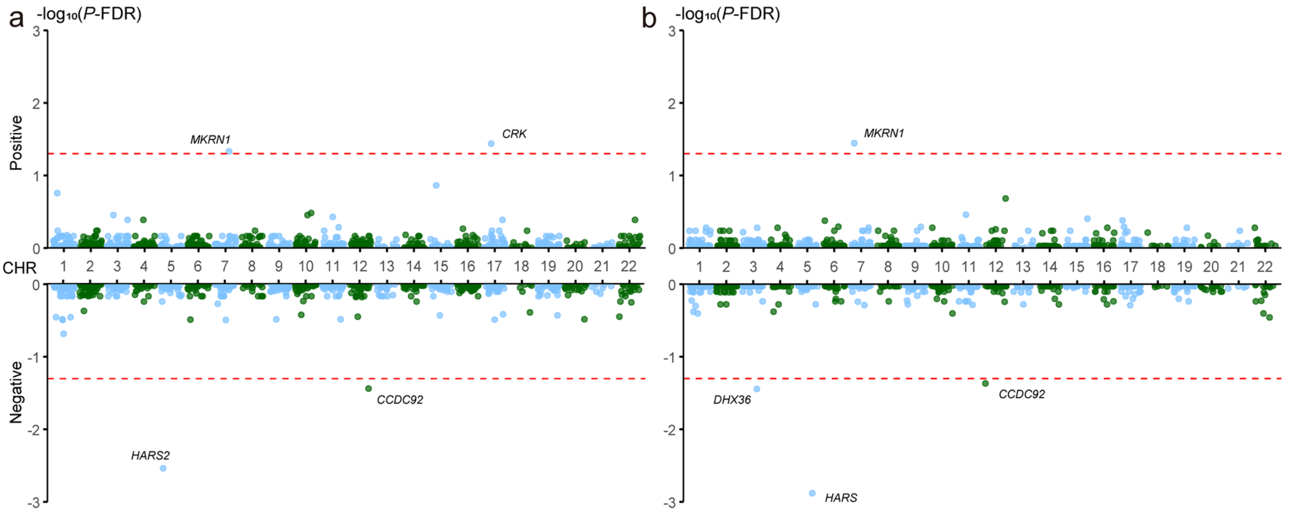

Fig. 2 Miami plot for the PWAS results. a Significant risk genes identified in ROSMAP. **b** Significant risk genes identified in Banner. Each point represents a single test of association between a gene and PPD ordered by genomic position on the *x* axis and the association strength on the *y* axis. "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.

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* ($P\text{-FDR}_{\text{ROSMAP}} = 4.66\text{E-02}$, $P\text{-FDR}_{\text{Banner}} = 3.59\text{E-02}$) and *CCDC92* ($P\text{-FDR}_{\text{ROSMAP}} = 3.65\text{E-02}$, $P\text{-FDR}_{\text{Banner}} = 4.28\text{E-02}$)—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 $P_{\text{SMR}} < 0.01$ (Supplementary Table S7, S8 and S9). Of these, *MKRN1* demonstrated consistent evidence across both databases ($P_{\text{SMR-ROSMAP}} = 8.59\text{E-04}$, $P_{\text{SMR-Banner}} = 2.62\text{E-03}$) with no significant horizontal pleiotropy observed ($P_{\text{HEIDI-ROSMAP}} = 3.64\text{E-01}$, $P_{\text{HEIDI-Banner}} = 2.75\text{E-01}$), 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

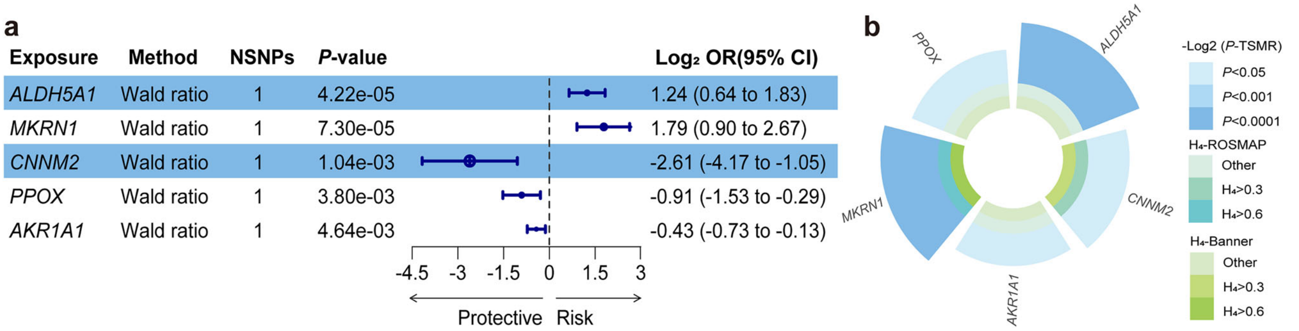

Fig. 3 TSMR results indicating causal effects between PPD and risk genes. a All the selected genes demonstrate consistent evidence across SMR and TSMR. Columns: Exposure, Method (causal effects estimating methods), NSNPs (number of SNPs included), Log$_2$OR(95% CI) (values >0 indicate increased PPD risk 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.

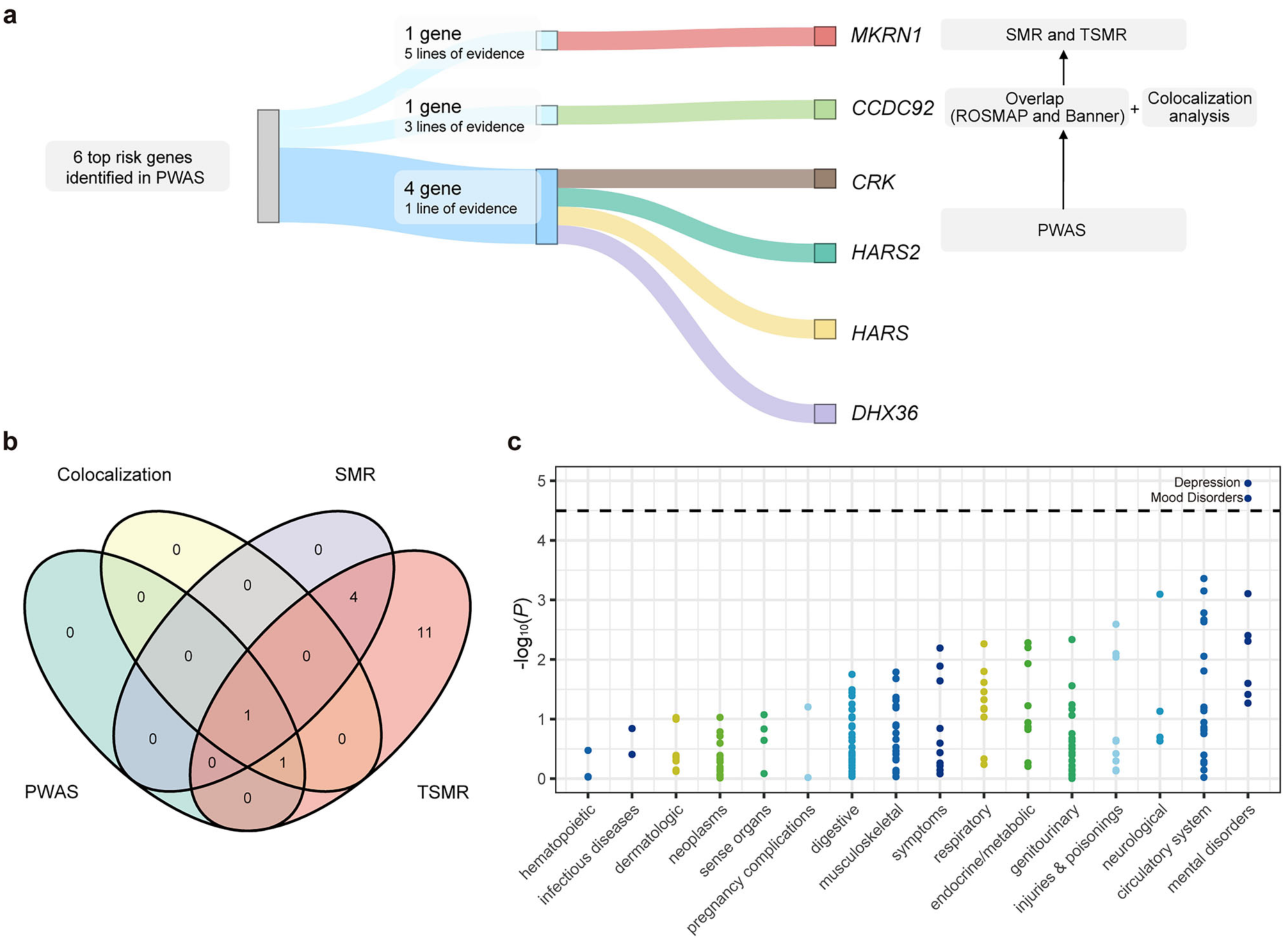

Fig. 4 Multi-stage identification of *MKRN1* as a risk gene for PPD and evaluation of its pleiotropic effects. a Sankey diagram illustrating the multi-stage analytical pipeline for prioritizing PPD risk genes. *MKRN1* was the only gene supported by all five lines of evidence. **b** Venn diagram showing 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 ($P = 0.05/783 = 6.39 \times 10^{-5}$).

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

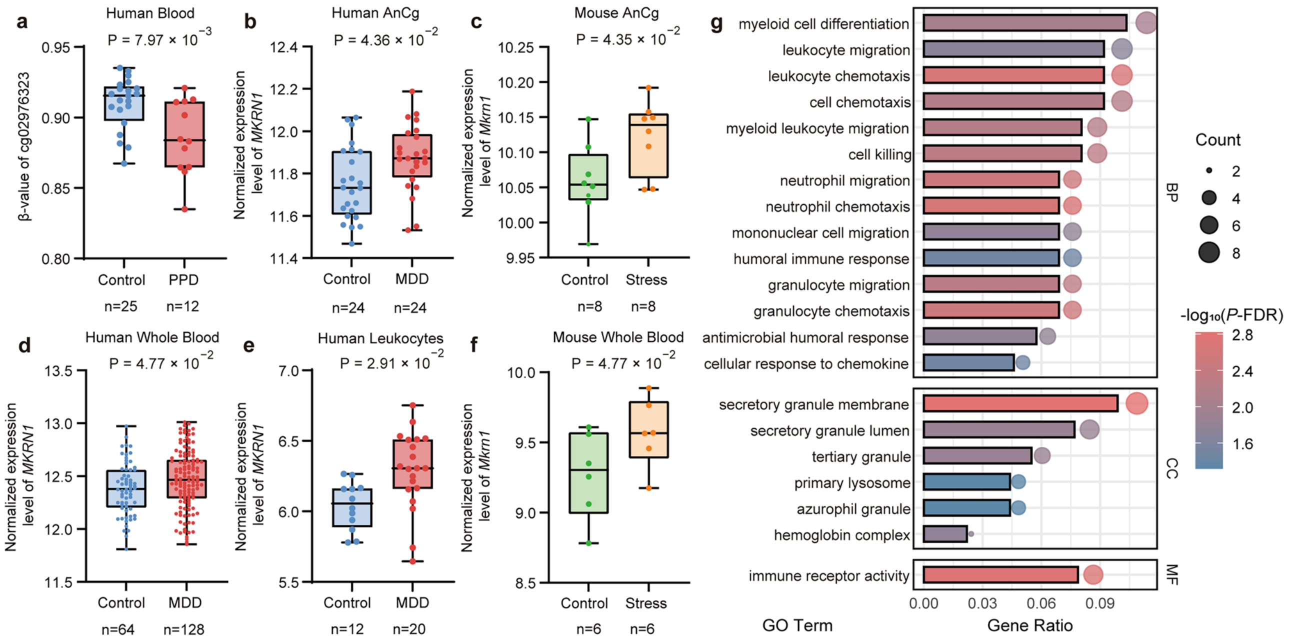

Fig. 5 Differential expression of *MKRN1* in various tissues of depressive patients and mice, and functional enrichment of its co-expression network. a The methylation degree of the CpG island of *MKRN1* is significantly decreased in blood samples of PPD patients. **b** *MKRN1* is significantly upregulated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

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].

REFERENCES

1. American Psychiatric Association, American Psychiatric Association (eds). *Diagnostic and statistical manual of mental disorders: DSM-5*. 5th ed. Washington, D.C: American Psychiatric Association, 2013.
2. Stewart DE, Robertson E, Dennis C-L, Grace SL, Wallington T Postpartum depression: Literature review of risk factors and interventions. *Tor Univ Health Netw Women's Health Program Tor Public Health* 2003; 1–289.
3. O'Hara MW, McCabe JE. Postpartum depression: current status and future directions. Annu Rev Clin Psychol. 2013;9:379–407.
4. Horáková A, Němcová H, Mohr P, Sebela A. Structural, functional, and metabolic signatures of postpartum depression: a systematic review. Front Psychiatry. 2022;13:1044995.
5. Pearlstein T, Howard M, Salisbury A, Zlotnick C. Postpartum depression. Am J Obstet Gynecol. 2009;200:357–64.
6. Tebeka S, Gauld C, Belzeaux R, Peyre H, Dubertret C. Major depressive episode and postpartum depression: A network analysis comparison on the IGEDEPP cohort. Eur Psychiatry J Assoc Eur Psychiatr. 2023;66:e51.
7. Saharoy R, Potdukhe A, Wanjari M, Taksande AB. Postpartum Depression and Maternal Care: Exploring the Complex Effects on Mothers and Infants. Cureus. 2023;15:e41381.
8. Nasreen H-E, Kabir ZN, Forsell Y, Edhborg M. Impact of maternal depressive symptoms and infant temperament on early infant growth and motor development: results from a population based study in Bangladesh. J Affect Disord. 2013;146:254–61.
9. Azak S. Maternal depression and sex differences shape the infants' trajectories of cognitive development. Infant Behav Dev. 2012;35:803–14.
10. Feldman R, Granat A, Pariente C, Kanety H, Kuint J, Gilboa-Schechtman E. Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. J Am Acad Child Adolesc Psychiatry. 2009;48:919–27.
11. Moore Simas TA, Whelan A, Byatt N. Postpartum depression-new screening recommendations and treatments. JAMA. 2023;330:2295–6.
12. Cardaci V, Carminati M, Tondello M, Pecorino B, Serretti A, Zanardi R. Understanding and treating postpartum depression: a narrative review. Int Clin Psychopharmacol. 2025;40:127–37. https://doi.org/10.1097/YIC.0000000000000560.
13. Dennis C-L, Singla DR, Brown HK, Savel K, Clark CT, Grigoriadis S, et al. Postpartum depression: a clinical review of impact and current treatment solutions. Drugs. 2024;84:645–59.
14. Weissman AM, Levy BT, Hartz AJ, Bentler S, Donohue M, Ellingrod VL, et al. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry. 2004;161:1066–78.
15. McDonald M, Alhusen J. A review of treatments and clinical guidelines for perinatal depression. J Perinat Neonatal Nurs. 2022;36:233.
16. O'Hara MW, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. Arch Gen Psychiatry. 2000;57:1039–45.
17. Pearlstein TB, Zlotnick C, Battle CL, Stuart S, O'Hara MW, Price AB, et al. Patient choice of treatment for postpartum depression: a pilot study. Arch Womens Ment Health. 2006;9:303–8.
18. Li X, Takahashi N, Narita A, Nakamura Y, Sakurai-Yageta M, Murakami K, et al. Identification of risk loci for postpartum depression in a genome-wide association study. Psychiatry Clin Neurosci. 2024;78:712–20. https://doi.org/10.1111/pcn.13731.
19. Tebeka S, Gloaguen E, Mullaert J, He Q, Boland A, Deleuze J-F, et al. Genome-wide association study of early-onset and late-onset postpartum depression: the IGEDEPP prospective study. Eur Psychiatry J Assoc Eur Psychiatr. 2024;67:1–36.
20. Lewis CM, Knight J. Introduction to genetic association studies. Cold Spring Harb Protoc. 2012;2012:297–306.
21. Brandes N, Linial N, Linial M. PWAS: proteome-wide association study-linking genes and phenotypes by functional variation in proteins. Genome Biol. 2020;21:173.
22. Hu T, Parrish RL, Dai Q, Buchman AS, Tasaki S, Bennett DA, et al. Omnibus proteome-wide association study identifies 43 risk genes for alzheimer disease dementia. Am J Hum Genet. 2024;111:1848–63.
23. Wei W, Zhang H, Cheng B, Qin X, He D, Zhang N, et al. Identification of novel functional brain proteins for treatment-resistant schizophrenia: based on a proteome-wide association study. Eur Psychiatry J Assoc Eur Psychiatr. 2023;66:e33.
24. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. JAMA. 2017;318:1925–6.
25. Wingo TS, Gerasimov ES, Liu Y, Duong DM, Vattathil SM, Lori A, et al. Integrating human brain proteomes with genome-wide association data implicates novel proteins in post-traumatic stress disorder. Mol Psychiatry. 2022;27:3075–84.
26. Gu X, Dou M, Yuan M, Zhang W. Identifying novel proteins underlying loneliness by integrating GWAS summary data with human brain proteomes. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2023;48:1087–97.
27. Zhao H, Liu Y, Zhang X, Liao Y, Zhang H, Han X, et al. Identifying novel proteins for suicide attempt by integrating proteomes from brain and blood with genome-wide association data. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2024;49:1255–65.
28. Batt MM, Duffy KA, Novick AM, Metcalf CA, Epperson CN. Is postpartum depression different from depression occurring outside of the perinatal period? a review of the evidence. Focus Am Psychiatr Publ. 2020;18:106–19.
29. Bloch M, Daly RC, Rubinow DR. Endocrine factors in the etiology of postpartum depression. Compr Psychiatry. 2003;44:234–46.
30. Brummelte S, Galea LAM. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:766–76.
31. Brummelte S, Galea LAM. Postpartum depression: Etiology, treatment and consequences for maternal care. Horm Behav. 2016;77:153–66.
32. Agrawal I, Mehendale AM, Malhotra R. Risk factors of postpartum depression. Cureus. 2022;14:e30898.
33. Donofry SD, Roecklein KA, Wildes JE, Miller MA, Erickson KI. Alterations in emotion generation and regulation neurocircuitry in depression and eating disorders: a comparative review of structural and functional neuroimaging studies. Neurosci Biobehav Rev. 2016;68:911–27.
34. Tian H, Wang Z, Meng Y, Geng L, Lian H, Shi Z, et al. Neural mechanisms underlying cognitive impairment in depression and cognitive benefits of exercise intervention. Behav Brain Res. 2025;476:115218.
35. Bhandage AK, Cunningham JL, Jin Z, Shen Q, Bongiovanni S, Korol SV, et al. Depression, GABA, and age correlate with plasma levels of inflammatory markers. Int J Mol Sci. 2019;20:6172.

36. Costi S, Morris LS, Collins A, Fernandez NF, Patel M, Xie H, et al. Peripheral immune cell reactivity and neural response to reward in patients with depression and anhedonia. Transl Psychiatry. 2021;11:565.
37. Iga J, Ueno S, Ohmori T. Molecular assessment of depression from mRNAs in the peripheral leukocytes. Ann Med. 2008;40:336–42. https://doi.org/10.1080/07853890802082088.
38. Rupanagunta GP, Nandave M, Rawat D, Upadhyay J, Rashid S, Ansari MN. Postpartum depression: aetiology, pathogenesis and the role of nutrients and dietary supplements in prevention and management. Saudi Pharm J SPJ. 2023;31:1274–93.
39. Hattori N, Liu Y-Y, Ushijima T. DNA Methylation Analysis. Methods Mol Biol Clifton NJ. 2023;2691:165–83.
40. Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. Mol Psychiatry. 2013;19:560.
41. Osborne L, Clive M, Kimmel M, Gispen F, Guintivano J, Brown T, et al. Replication of epigenetic postpartum depression biomarkers and variation with hormone levels. Neuropsychopharmacology. 2015;41:1648.
42. Stoffel EC, Craft RM. Ovarian hormone withdrawal-induced “depression” in female rats. Physiol Behav. 2004;83:505–13.
43. Suda S, Segi-Nishida E, Newton SS, Duman RS. A postpartum model in rat: behavioral and gene expression changes induced by ovarian steroid deprivation. Biol Psychiatry. 2008;64:311.
44. Fei F, Chen Z, Tao Y, Jiang X, Xu X, Ma Y, et al. Comparison of CUMS at different pregnancy stages, maternal separation, and their effects on offspring in postpartum depression mouse models. Heliyon. 2024;10:e35363.
45. Guintivano J, Byrne EM, Kiewa J, Yao S, Bauer AE, Aberg KA, et al. Meta-Analyses of genome-wide association studies for postpartum depression. Am J Psychiatry. 2023;180:884–95.
46. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious orders study and rush memory and aging project. J Alzheimers Dis JAD. 2018;64:S161–S189.
47. Beach TG, Adler CH, Sue LI, Serrano G, Shill HA, Walker DG, et al. Arizona study of aging and neurodegenerative disorders and brain and body donation program. Neuropathol Off J Jpn Soc Neuropathol. 2015;35:354–89.
48. Wingo AP, Liu Y, Gerasimov ES, Gockley J, Logsdon BA, Duong DM, et al. Integrating human brain proteomes with genome-wide association data implicates new proteins in Alzheimer’s disease pathogenesis. Nat Genet. 2021;53:143–6.
49. Gusev A, Ko A, Shi H, Bhatia G, Chung W, Penninx BWJH, et al. Integrative approaches for large-scale transcriptome-wide association studies. Nat Genet. 2016;48:245–52.
50. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet. 2014;10:e1004383.
51. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet. 2016;48:481–7.
52. Liu J, Xu Y, Liu Y, Zhu Y, Li X. Associations between type 1 diabetes and autoimmune skin diseases: Mendelian randomization analysis. Heliyon. 2024;10:e32781.
53. Guo Y, Yan J. Association between tobacco smoke exposure and depression: the NHANES 2005-2018 and Mendelian randomization study. Arch Public Health. 2024;82:100.
54. Chauquet S, Zhu Z, O’Donovan MC, Walters JTR, Wray NR, Shah S. Association of antihypertensive drug target genes with psychiatric disorders: a mendelian randomization study. JAMA Psychiatry. 2021;78:623–31.
55. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet. 2018;50:1335–41.
56. Akoglu H. User’s guide to correlation coefficients. Turk J Emerg Med. 2018;18:91–93.
57. Kovács K, Farkas Z, Bajić D, Kalapis D, Daraba A, Almási K, et al. Suboptimal global transcriptional response increases the harmful effects of loss-of-function mutations. Mol Biol Evol. 2021;38:1137–50.
58. Fernandez-Fernandez J, Jiménez-Treviño L, Andreo-Jover J, Ayad-Ahmed W, Bascarán TB, Canal-Rivero M, et al. Network analysis of influential risk factors in adolescent suicide attempters. Child Adolesc Psychiatry Ment Health. 2024;18:152.
59. Ramaker RC, Bowling KM, Lasseigne BN, Hagenauer MH, Hardigan AA, Davis NS, et al. Post-mortem molecular profiling of three psychiatric disorders. Genome Med. 2017;9:72.
60. Hervé M, Bergon A, Le Guisquet A-M, Leman S, Consoloni J-L, Fernandez-Nunez N, et al. Translational identification of transcriptional signatures of major depression and antidepressant response. Front Mol Neurosci. 2017;10:248.
61. Leday GGR, Vértes PE, Richardson S, Greene JR, Regan T, Khan S, et al. Replicable and coupled changes in innate and adaptive immune gene expression in two case-control studies of blood microarrays in major depressive disorder. Biol Psychiatry. 2018;83:70–80.
62. Miyata S, Kurachi M, Okano Y, Sakurai N, Kobayashi A, Harada K, et al. Blood transcriptomic markers in patients with late-onset major depressive disorder. PLoS One. 2016;11:e0150262.
63. Miyata S, Kurachi M, Sakurai N, Yanagawa Y, Ishizaki Y, Mikuni M, et al. Gene expression alterations in the medial prefrontal cortex and blood cells in a mouse model of depression during menopause. Heliyon. 2016;2:e00222.
64. Evangelista JE, Clarke DJB, Xie Z, Lachmann A, Jeon M, Chen K, et al. SigCom LINCS: data and metadata search engine for a million gene expression signatures. Nucleic Acids Res. 2022;50:W697–W709.
65. Lachmann A, Torre D, Keenan AB, Jagodnik KM, Lee HJ, Wang L, et al. Massive mining of publicly available RNA-seq data from human and mouse. Nat Commun. 2018;9:1366.
66. Wu T, Hu E, Xu S, Chen M, Guo P, Dai Z, et al. clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. Innov. 2021;2:100141.
67. Gray TA, Hernandez L, Carey AH, Schaldach MA, Smithwick MJ, Rus K, et al. The ancient source of a distinct gene family encoding proteins featuring RING and C(3)H zinc-finger motifs with abundant expression in developing brain and nervous system. Genomics. 2000;66:76–86.
68. Zarrei M, Burton CL, Engchuan W, Young EJ, Higginbotham EJ, MacDonald JR, et al. A large data resource of genomic copy number variation across neurodevelopmental disorders. NPJ Genomic Med. 2019;4:26.
69. Dyke J, Calapre L, Beasley A, Gray E, Allcock R, Bentel J. Application of multiplex ligation-dependent probe amplification (MLPA) and low pass whole genome sequencing (LP-WGS) to the classification / characterisation of low grade glioneuronal tumours. Pathol Res Pract. 2022;229:153724.
70. AlShail E, Alahmari AN, Dababo AAM, Alsagob M, Al-Hindi H, Khalil H, et al. A molecular study of pediatric pilomyxoid and pilocytic astrocytomas: genome-wide copy number screening, retrospective analysis of clinicopathological features and long-term clinical outcome. Front Oncol. 2023;13:1034292.
71. Kim JH, Park S-M, Kang MR, Oh S-Y, Lee TH, Muller MT, et al. Ubiquitin ligase MKRN1 modulates telomere length homeostasis through a proteolysis of hTERT. Genes Dev. 2005;19:776–81.
72. Jones-Weinert C, Mainz L, Karlseder J. Telomere function and regulation from mouse models to human ageing and disease. Nat Rev Mol Cell Biol. 2024;26:297–313.
73. Ayora M, Fraguas D, Abregú-Crespo R, Recio S, Blasco MA, Moises A, et al. Leukocyte telomere length in patients with schizophrenia and related disorders: a meta-analysis of case-control studies. Mol Psychiatry. 2022;27:2968–75.
74. Gurvich C, Thomas N, Hudaib A-R, Van Rheenen TE, Thomas EHX, Tan EJ, et al. The relationship between cognitive clusters and telomere length in bipolar-schizophrenia spectrum disorders. Psychol Med. 2023;53:5119–26.
75. Salpea KD, Talmud PJ, Cooper JA, Maubaret CG, Stephens JW, Abelak K, et al. Association of telomere length with type 2 diabetes, oxidative stress and UCP2 gene variation. Atherosclerosis. 2010;209:42–50.
76. Nault J-C, Ningarhari M, Rebouissou S, Zucman-Rossi J. The role of telomeres and telomerase in cirrhosis and liver cancer. Nat Rev Gastroenterol Hepatol. 2019;16:544–58.
77. Incollingo Rodriguez AC, Polcari JJ, Nephew BC, Harris R, Zhang C, Murgatroyd C, et al. Acculturative stress, telomere length, and postpartum depression in latinx mothers. J Psychiatr Res. 2022;147:301–6.
78. Hartmann N, Boehner M, Groenen F, Kalb R. Telomere length of patients with major depression is shortened but independent from therapy and severity of the disease. Depress Anxiety. 2010;27:1111–6.
79. Pisanu C, Tsermpini EE, Skokou M, Kordou Z, Gourzis P, Assimakopoulos K, et al. Leukocyte telomere length is reduced in patients with major depressive disorder. Drug Dev Res. 2020;81:268–73.
80. Wang T, Liu W, Wang C, Ma X, Akhtar MF, Li Y, et al. MRKNs: gene, functions, and role in disease and infection. Front Oncol. 2022;12:862206.
81. Mahmood S, Evinová A, Škereňová M, Ondrejka I, Lehotský J. Association of EGF, IGFBP-3 and TP53 gene polymorphisms with major depressive disorder in slovak population. Cent Eur J Public Health. 2016;24:223–30.
82. Zhang H, Liu S, Qin Q, Xu Z, Qu Y, Wang Y, et al. Genetic and pharmacological inhibition of astrocytic Mysm1 Alleviates depressive-like disorders by promoting ATP production. Adv Sci Weinh Baden-Wurtt Ger. 2022;10:e2204463.
83. Aldossary KM, Saad Ali L, Abdallah MS, Bahaa MM, Elmasry TA, Elberri EI, et al. Corrigendum: Effect of a high dose atorvastatin as added-on therapy on symptoms and serum AMPK/NLRP3 inflammasome and IL-6/STAT3 axes in patients with major depressive disorder: randomized controlled clinical study. Front Pharmacol. 2024;15:1464358.
84. Bullone M, Lavoie J-P. The contribution of oxidative stress and inflamm-aging in human and equine asthma. Int J Mol Sci. 2017;18:2612.
85. Liu X, Fan L, Lu C, Yin S, Hu H. Functional Role of p53 in the regulation of chemical-induced oxidative stress. Oxid Med Cell Longev. 2020;2020:6039769.
86. Jeon S-M, Chandel NS, Hay N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. Nature. 2012;485:661–5.

87. Wang S, Zhang M, Liang B, Xu J, Xie Z, Liu C, et al. AMPKalpha2 deletion causes aberrant expression and activation of NAD(P)H oxidase and consequent endothelial dysfunction in vivo: role of 26S proteasomes. Circ Res. 2010;106:1117–28.
88. Tutton S, Azzam GA, Stong N, Vladimirova O, Wiedmer A, Monteith JA, et al. Subtelomeric p53 binding prevents accumulation of DNA damage at human telomeres. EMBO J. 2016;35:193–207.
89. Feitosa CM, da Silva Oliveira GL, do Nascimento Cavalcante A, Morais Chaves SK, Rai M. Determination of parameters of oxidative stress in vitro models of neurodegenerative diseases-a review. Curr Clin Pharmacol. 2018;13:100–9.
90. Ji N, Lei M, Chen Y, Tian S, Li C, Zhang B. How oxidative stress induces depression?. ASN Neuro. 2023;15:17590914231181037.
91. Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BWJH. Is depression associated with increased oxidative stress? a systematic review and meta-analysis. Psychoneuroendocrinology. 2015;51:164–75.
92. Bhatt S, Nagappa AN, Patil CR. Role of oxidative stress in depression. Drug Discov Today. 2020;25:1270–6.
93. Palta P, Samuel LJ, Miller ER, Szanton SL. Depression and oxidative stress: results from a meta-analysis of observational studies. Psychosom Med. 2014;76:12–19.
94. Lindqvist D, Dhabhar FS, James SJ, Hough CM, Jain FA, Bersani FS, et al. Oxidative stress, inflammation and treatment response in major depression. Psychoneuroendocrinology. 2017;76:197–205.
95. Poletti S, Paolini M, Mazza MG, Palladini M, Furlan R, Querini PR, et al. Lower levels of glutathione in the anterior cingulate cortex associate with depressive symptoms and white matter hyperintensities in COVID-19 survivors. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2022;61:71–77.
96. Tian S, Liu M, Yang C, Du W, Gao B, Li M, et al. The impact of ACTH levels on neurotransmitters and antioxidants in patients with major depressive disorder: a novel investigation. J Affect Disord. 2024;365:587–96.
97. Gabbay V, Mao X, Klein RG, Ely BA, Babb JS, Panzer AM, et al. Anterior cingulate cortex γ-aminobutyric acid in depressed adolescents: relationship to anhedonia. Arch Gen Psychiatry. 2012;69:139–49.
98. Gabbay V, Bradley KA, Mao X, Ostrover R, Kang G, Shungu DC. Anterior cingulate cortex γ-aminobutyric acid deficits in youth with depression. Transl Psychiatry. 2017;7:e1216.
99. Tsai GE, Ragan P, Chang R, Chen S, Linnoila VM, Coyle JT. Increased glutamatergic neurotransmission and oxidative stress after alcohol withdrawal. Am J Psychiatry. 1998;155:726–32.
100. Bakunina N, Pariante CM, Zunszain PA. Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology. 2015;144:365–73.
101. Correia AS, Cardoso A, Vale N. Oxidative stress in depression: the link with the stress response, neuroinflammation, serotonin, neurogenesis and synaptic plasticity. Antioxidants. 2023;12:470.
102. Odaira-Satoh T, Nakagawasai O, Takahashi K, Shimada M, Nemoto W, Tan-No K. AMPK activation improves depression-like symptoms in olfactory bulbectomized mice by regulating microglia M1/M2 polarization in the hippocampus. Brain Behav Immun - Health. 2025;46:101008.
103. Wolkowitz OM, Mellon SH, Epel ES, Lin J, Dhabhar FS, Su Y, et al. Leukocyte telomere length in major depression: correlations with chronicity, inflammation and oxidative stress-preliminary findings. PLoS One. 2011;6:e17837.
104. Jiang Y, Cheng X, Zhao M, Zhao T, Zhang M, Shi Z, et al. Gypenoside-14 Reduces Depression via Downregulation of the Nuclear Factor Kappa B (NF-kB) Signaling Pathway on the Lipopolysaccharide (LPS)-Induced Depression Model. Pharmaceuticals. 2023;16:1152.
105. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR. Depression and telomere length: a meta-analysis. J Affect Disord. 2016;191:237–47.
106. Jiménez-Fernández S, Gurpegui M, Díaz-Atienza F, Pérez-Costillas L, Gerstenberg M, Correll CU. Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta-analysis. J Clin Psychiatry. 2015;76:1658–67.
107. Liu T, Zhong S, Liao X, Chen J, He T, Lai S, et al. A meta-analysis of oxidative stress markers in depression. PLoS One. 2015;10:e0138904.
108. Rasmi Y, Shokati A, Hassan A, Aziz SG-G, Bastani S, Jalali L, et al. The role of DNA methylation in progression of neurological disorders and neurodegenerative diseases as well as the prospect of using DNA methylation inhibitors as therapeutic agents for such disorders. IBRO Neurosci Rep. 2023;14:28–37.
109. Grayson DR, Guidotti A. The dynamics of DNA methylation in schizophrenia and related psychiatric disorders. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2013;38:138–66.
110. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013;38:23–38.
111. Dhar GA, Saha S, Mitra P, Nag Chaudhuri R. DNA methylation and regulation of gene expression: guardian of our health. Nucl. 2021;64:259–70.
112. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov. 2015;14:475–86.
113. Kuroda M, Halfmann PJ, Hill-Batorski L, Ozawa M, Lopes TJS, Neumann G, et al. Identification of interferon-stimulated genes that attenuate Ebola virus infection. Nat Commun. 2020;11:2953.
114. Baranova A, Liu D, Chandhoke V, Cao H, Zhang F. Unraveling the genetic links between depression and type 2 diabetes. Prog Neuropsychopharmacol Biol Psychiatry. 2025;137:111258.
115. Jia N, Yin X, Zhu Z, Hou W, Yang Q, Zhu H, et al. Comprehensive transcriptome analysis and lncRNA-miRNA-mRNA establishment of schizophrenia based on induced pluripotent stem cells. Schizophr Res. 2025;281:22–29.
116. Freist W, Verhey JF, Rühlmann A, Gauss DH, Arnez JG. Histidyl-tRNA synthetase. Biol Chem. 1999;380:623–46.
117. Royer-Bertrand B, Tsouni P, Mullen P, Campos Xavier B, Mittaz Crettol L, Lobrinus AJ, et al. Peripheral neuropathy and cognitive impairment associated with a novel monoallelic HARS variant. Ann Clin Transl Neurol. 2019;6:1072–80.
118. Safka Brozkova D, Deconinck T, Griffin LB, Ferbert A, Haberlova J, Mazanec R, et al. Loss of function mutations in HARS cause a spectrum of inherited peripheral neuropathies. Brain J Neurol. 2015;138:2161–72.
119. Pierce SB, Chisholm KM, Lynch ED, Lee MK, Walsh T, Opitz JM, et al. Mutations in mitochondrial histidyl tRNA synthetase HARS2 cause ovarian dysgenesis and sensorineural hearing loss of perrault syndrome. Proc Natl Acad Sci USA. 2011;108:6543–8.
120. Zhang C, Yang Z, Li X, Zhao L, Guo W, Deng W, et al. Unraveling NEK4 as a potential drug target in schizophrenia and bipolar i disorder: a proteomic and genomic approach. Schizophr Bull. 2024;50:1185–96.

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COMPETING INTERESTS

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.

ADDITIONAL INFORMATION

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