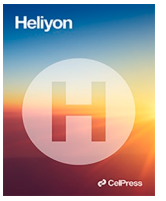
Heliyon 10 (2024) e37504

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Association of single nucleotide polymorphisms and gene-environment interactions with major depressive disorder in Chinese

Di Luan [a,b,c,*], Shi-zun Li [a,b,c], Can Zhang [a,b,c], Bin Ye [a,b,c,**]

[a] Department of Neurology, Bengbu Third People's Hospital, Bengbu, 233000, Anhui, China
[b] Department of Neurology, Bengbu Central Hospital, Bengbu, 233000, Anhui, China
[c] Department of Neurology, Bengbu Third People's Hospital Affiliated to Bengbu Medical University, Bengbu, 233000, Anhui, China

ARTICLE INFO

Keywords:
Major depressive disorder
Suicide ideation
Genetics
Gene-environment interaction

ABSTRACT

We conducted a case-control study to investigate the effects of genetics and gene-environment interactions on major depressive disorders (MDD) in the Chinese population. Using targeted-exome sequencing, we included 984 patients with MDD and 508 healthy controls in our study. A logistic regression model was employed to analyze the association between single nucleotide polymorphisms (SNPs) and MDD. Additionally, a linear regression model was utilized to examine the associations between (1) gene-environment interaction and the 17-item Hamilton Depression Rating Scale, (2) SNPs and the Beck Scale for Suicide Ideation-Chinese version, and gene-environment interaction and the Beck scale for suicide ideation-Chinese version. The association analysis between SNPs and MDD revealed that the following loci reached genome-wide significance: rs2305554 of the *cholinergic receptor nicotinic alpha 7 subunit*, rs9459173 of *synaptojanin 2*, rs372369000 of *beta-1,4-galactosyltransferase 6*, rs866666526 of *dopa decarboxylase*, rs1254882194 of *calcium/calmodulin dependent protein kinase ID*, rs199880487 of *reelin*, rs1167948188 of *reelin*, rs1390140186 of *QKI, KH domain containing RNA binding*, and rs1776342 of *period circadian regulator 3*. The association analysis between SNPs and the Beck Scale for Suicide Ideation-Chinese version indicated that rs264272 and rs1774784888 of *piezo type mechanosensitive ion channel component 2* reached genome-wide significance. These findings may enhance our understanding of MDD and contribute to the development of new potential targets for its diagnosis and treatment.

1. Introduction

Major depressive disorder (MDD) is a common mental illness [1]. In China, MDD is the second leading cause of disability adjusted life years [2]. Among individuals with MDD, 51.3 % have comorbidities with other mental disorders, including anxiety, substance use

* Corresponding author. Department of Neurology, Bengbu Third People's Hospital affiliated to Bengbu Medical University, 38 Shengli Road, Bengbu, 233000, Anhui Province, China.
** Corresponding author. Department of Neurology, Bengbu Third People's Hospital affiliated to Bengbu Medical University, 38 Shengli Road, Bengbu, 233000, Anhui Province, China.
E-mail addresses: mazuiluandi@163.com (D. Luan), ye7157@139.com (B. Ye).

https://doi.org/10.1016/j.heliyon.2024.e37504
Received 8 June 2024; Received in revised form 16 August 2024; Accepted 4 September 2024
Available online 5 September 2024

disorder, and impulse control disorder, and they experience significant social function impairments. The utilization rate of health services among MDD patients is 11.6 %, while the rate of adequate treatment is as low as 0.8 % [3]. Understanding the influence of genetic and psychosocial factors, as well as their interactions, on the incidence of MDD may help identify high-risk populations for early intervention, thereby reducing the incidence of MDD [4,5].

Due to differences in genetic backgrounds, the genetic basis and molecular mechanisms of most traits and disease phenotypes vary among populations [6]. The ChinaMAP project conducted deep whole-genome sequencing on over ten thousand Chinese individuals, identifying 136.7 million single nucleotide polymorphisms (SNPs) and 10.7 million indels, half of which were not included in common databases such as NCBI, 1000G, gnomAD, and TOPmed [7,8]. The CONVERGE Consortium conducted a whole-genome association analysis of recurrent MDD in Chinese women using sparse whole-genome sequencing technology, finding that rs12415800 of *sirtuin 1* (*SIRT1*) and rs35936514 of *phospholysine phosphohistidine inorganic pyrophosphate phosphatase* (*LHPP*) reached genome-wide significance [9]. Apart from CONVERGE, few other genome-wide or large-scale candidate gene association studies have been conducted on MDD in the Chinese population. The interaction between genes and the environment (G × E) is crucial to understanding the complexity of MDD. Genetic predispositions alone do not fully explain the onset and progression of MDD, as environmental factors play a significant role in modulating genetic susceptibility. Research has shown that various environmental stressors, such as childhood trauma, chronic stress, and social adversity, can interact with genetic variations to increase the risk of developing MDD [10,11]. Conducting G × E interaction analyses enables us to identify subgroups of individuals particularly vulnerable to MDD based on their unique combination of genetic and environmental exposures. This approach has the potential to lead to more personalized and targeted prevention and treatment strategies.

To identify novel genetic variations and gene-environment interactions associated with MDD inthe Chinese population, we conducted this case-control study based on targeted-exome sequencing. In addition to conventional genome-wide association analysis, the novelty of our study lies in the analysis of interactions between genetic and environmental factors. We collected psychosocial factors, including childhood trauma, family environment, and social support, from both healthy individuals and MDD patients. Through interaction analysis with genetic factors, we aim to discover the genetic variations and gene-environment interactions that influence the onset of MDD.

2. Materials and methods

2.1. Study design

This clinical study investigating the genetic factors and gene-environment interactions in MDD was conducted in a real-world clinical setting where patients received routine medical care without any artificial experimental manipulations. The study primarily enrolled adult inpatients with untreated MDD for several reasons: First, inpatients often exhibit more severe and complex symptoms, allowing for a more comprehensive assessment of the research variables. Second, the inpatient setting provides better control over data collection and follow-up, ensuring the accuracy and completeness of the data. Additionally, inpatients typically have a more stable medical condition and treatment plan, which reduces confounding factors and enhances the study's internal validity.

The research was conducted in the psycho-psychiatric department of a general hospital, which serves a diverse group of adult patients with various mental health disorders. This setting was chosen because it provides access to a sufficient number of inpatients within a controlled environment, facilitating the implementation and monitoring of the study protocol. The study also included healthy controls and targeted exome sequencing was performed to analyze the genetic factors and gene-environment interactions in MDD.

Sample size determination was based on a difference test to compare the rates of the two groups. Power analysis was conducted considering the type I error (α), power (1-β), group 1 proportion (*P1*), group 2 proportion (*P2*), and group allocation (κ) of the study. The significance level was set at 5×10^{-8} to minimize the risk of type I error. The desired power was set at 0.80 to ensure adequate sensitivity to detect a true effect. *P1* and *P2* were obtained from sequencing results. The group allocation $\kappa = 1.9$. In the case of rs2305554, $P1 = 0.1024$, $P2 = 0.2685$. Based on these parameters the power analysis indicated that a sample size of N1 = 351 and N2 = 668 would be sufficient to detect a meaningful difference in the desired level of statistical significance and power.

2.2. Procedures

The procedures were carried out in the following sequential steps:

Interviews: Trained interviewers conducted semi-structured interviews with potential participants to gather information on their medical history, symptoms, and current mental state. Administration of Scales: A series of validated scales—such as the Hamilton Depression Rating Scale (HAMD-17), Beck Scale for Suicide Ideation-Chinese Version (BSI-CV), 20-item Toronto Alexithymia Scale (TAS-20), Snaith-Hamilton Pleasure Scale (SHAPS), Childhood Trauma Questionnaire-Short Form (CTQ- SF), Social Support Rating Scale (SSRS), Family Environment Scale-Chinese Version (FES-CV), and Life Event Scale (LES)—were administered to objectively assess psychosocial factors and the severity and specific aspects of participants' psychiatric conditions. Gene sequencing: Genomic DNA was extracted from blood samples, and targeted sequencing was performed using the Illumina MiSeq high-throughput sequencing platform. The resulting data were analyzed using Plink 1.90.

2.3. Subjects

The study included both healthy controls (HC) and patients with MDD. The recruitment process was as follows: MDD Patients: Patients with MDD were enrolled in the Zhongda Hospital MDD inpatient database [12]. They were initially approached in-person communication during their hospital visits. Information about the study was provided, and their eligibility was screened based on predefined criteria. Those who met the eligibility criteria were invited to participate and provided with detailed informed consent. Inclusion Criteria for MDD Patients: The inclusion criteria for MDD patients were as follows: diagnosis according to the Diagnostic and Statistical Manual-IV (DSM-IV); a HAMD-17 score [13] greater than 17; depressive symptoms lasting for at least two weeks; and no medication or other treatment for at least two weeks prior to enrollment. The DSM-IV criteria were used because, at the time of the study's conception and design, it was the widely accepted diagnostic standard in the field. It provided a well-defined and validated framework for accurately diagnosing the conditions of interest in our study. Additionally, DSM-IV criteria have been extensively used in previous relevant research, ensuring for better comparability and consistency with existing literature. At the time of the study, DSM-V was not yet widely adopted in our country. Exclusion Criteria for MDD Patients: Exclusion criteria included a history of other DSM-IV Axis I diagnoses, personality disorders, mental retardation, pregnancy or breastfeeding, organic diseases or conditions affecting psychiatric evaluation, electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) within six months of enrollment, and manic episodes in the 12 months prior to enrollment. The absence of other psychiatric disorders and personality disorders was evaluated through a comprehensive assessment, which included a detailed review of participants' medical records, interviews with participants and their families or caregivers, and, if necessary, additional clinical evaluations by a multidisciplinary team. The basic information and scale evaluations for all enrolled subjects were completed and reviewed by an associate or chief psychiatrist with extensive clinical experience and rigorous training. For all evaluation items, the inter-rater reliability (Kappa value) was greater than 0.85. In cases where matters or terms could not be determined, the two chief psychiatrists conducted joint interviews and discussions to determine. HAMD-17, Beck scale for suicide ideation-Chinese version (BSI-CV) [14], 20-item Toronto alexithymia scale (TAS-20) [15], Snaith-Hamilton pleasure scale (SHAPS) [16] were administered after enrollment: HAMD-17 to assess depressive symptom, BSI-CV to assess suicidal ideation, TAS-20 to assess alexithymia, and SHAPS to assess anhedonia. Psychosocial factors were assessed using CTQ-SF [17], SSRS [18], FES-CV [19] and LES [20] after enrollment. Further details of the assessments and questionnaires used are provided in the supplementary materials. Healthy Controls: Healthy controls were selected based on the absence of any current or past history of mental disorders or major organic lesions, as determined through a detailed clinical interview and review of medical records. They were also screened to ensure the absence of any significant family history of mental illness. Recruitment methods for healthy controls included advertising the study in local communities and healthcare facilities. Potential participants were initially contacted via phone or WeChat and invited for an in-person screening session, during which, they underwent the aforementioned assessment to confirm their eligibility as healthy controls. The ratio of MDD patients to healthy controls was approximately 1.9. The data collection process began on April 11, 2017 and was completed by April 30, 2019. Each participant was followed for a period of 8 weeks. Psychosocial factors were assessed by CTQ-SF, SSRS, FES-CV, and LES after enrollment. Depressive-related symptoms were assessed by HAMD-17 at baseline and 2, 4, and 8 weeks after enrollment, and BSI-CV and TAS-20 at baseline, 2, and 8 weeks after enrollment. All patients and health controls provided written informed consents. The informed consent form clearly states that participation is voluntary and the information is confidential. Participants may refuse to participate or withdraw at any time without fear of discrimination or retaliation, and their medical treatment and rights will remain unaffected. Participants have the option to decline participation or withdraw from the study at any stage. Participants are not required to participate in this study for the purpose of treating the disease.

2.4. Targeted exome sequencing

Detailed information on gene selection and SNP genotyping has been described previously [12]. The gene selection process for targeted exome sequencing was based on a comprehensive literature review and an analysis of previously identified genes associated with MDD. We focused on genes known to play crucial roles in MDD-related biological pathways and those that have shown potential associations with MDD. Specifically, we selected a panel of genes that encompassed key regulators of the monoaminergic pathway, glutamatergic system, GABAenergic system, BDNF system, mTOR signaling pathway, neuroplasticity related genes, long-term potentiation, hypothalamic-pituitary-adrenal axis, immune system, G-protein linked signaling system, glycine pathway, cannabinoid system, purine system, estrogen system, folic acid system, renin-angiotensin system, melanocortin receptor, melatonin related genes, leptin system, circadian rhythm system, notch signaling pathway, cytochrome P450 genes, white matter lesion related genes, potassium channel genes, glutamate-NMDA-CaM signaling, PLC-DAG-PKC-CREB, other depression-related genes, as well as genes that have been implicated in MDD. The inclusion criteria for gene selection were based on their functional significance, prior evidence of association with MDD, and their potential to contribute to understanding the underlying mechanisms of the disorder. Ultimately, 1309 genes were subjected to targeted exome sequencing. For SNP genotyping, we employed the Illumina MiSeq high-throughput sequencing platform. Quality control (QC) measures included filtering out all variants with a minor allele frequency lower than 0.01, a missing call rate exceeding 0.05, and a Hardy-Weinberg equilibrium exact test P value below 1.0×10^{-6}.

2.5. Statistical analysis

For baseline data, given the substantial data volume and minimal missing values, we opted to eliminate any records with missing entries. The Kolmogorov-Smirnov and Levene tests were used to assess normality and homogeneity of variance, respectively. The

Mann-Whitney *U* test was applied for data with a skewed distribution, while an independent sample *t*-test was used for normally distributed data. Binary logistic regression was utilized for both univariate and multivariate analyses. In the multivariate analysis, covariates were selected based on their potential confounding effects on the relationship between independent and dependent variables. Covariates included in the model were either known to be associated with the outcome of interest based on prior literature or demonstrated a significant association ($P < 0.2$) in the univariate analysis. A *P*-value of 0.05 was considered statistically significant. "Enter" method in SPSS was used to include all selected covariates simultaneously in the model, allowing for a comprehensive assessment of their combined effects on the outcome variable.

The QC of sequencing data included both SNPs and sample QC. For SNPs, variants were filtered out if they had a minor allele frequency lower than 0.01, a missing call rate exceeding 0.05, or a Hardy-Weinberg equilibrium exact test *P* value below 1.0×10^{-6}. For samples, individuals with call rates below 0.95 or familial relationships exceeding 0.25 were excluded. Multidimensional scaling analysis (MDS) was employed for population stratification, and heterozygosity and allele frequency analysis were conducted for descriptive statistics of SNP data. Genotypic models, including additive, dominant, and recessive models, were used.

A logistic regression model was applied to analyze the association between SNPs and MDD. To reduce the influence of confounding factors on the analysis results, a sensitivity analysis was conducted using three models: Model 1: Unadjusted for any covariates. Model 2: Adjusted for MDS. Model 3: Additionally adjusted for age and gender. MDS, age, and gender were included as covariates in the logistic regression model for sensitivity analysis for the following reasons: MDS: Control for population stratification. Different populations may have distinct genetic backgrounds and characteristics, which MDS can help detect and quantify. Including MDS as a covariate corrects for spurious associations due to population stratification, improving the accuracy of association analysis and reducing the bias caused by population structure, thereby more accurately detecting genetic variants related to MDD. Age: The risk of MDD varies across different age groups, with higher prevalence observed in older age groups in China, potentially due to changes in gene expression and function. Age also reflects the cumulative effect of environmental factors individuals have been exposed to over time. Gender: In China, women are more susceptible to MDD, with a lifetime prevalence ratio of approximately 1.4 to men. Sensitivity analysis with MDS, age, and gender as covariates allows for more comprehensive and accurate assessment of the association between genetic variants and studied traits or diseases, reduces the influence of potential confounding factors, and improves the reliability and reproducibility of study results. The specific formulas for the three logistic regression models are as follows:

$$P_1(Y=1|X) = \frac{1}{1+e^{-(\beta_0+\beta_{SNP}\times X_{SNP})}}$$

$$P_2(Y=1|X) = \frac{1}{1+e^{-(\beta_0+\beta_{SNP}\times X_{SNP}+\beta_{MDS}\times X_{MDS})}}$$

$$P_3(Y=1|X) = \frac{1}{1+e^{-\left(\beta_0+\beta_{SNP}\times X_{SNP}+\beta_{MDS}\times X_{MDS}+\beta_{age}\times X_{age}+\beta_{gender}\times X_{gender}\right)}}$$

where β_{SNP}, β_{MDS}, β_{age}, and β_{gender} represent the impact of variants, MDS, age and gender term on the outcome, respectively.

A linear regression model was used to analyze the association between gene-environment interaction and HAMD-17, SNPs and BSI-CV, and gene-environment interaction and BSI-CV. The evaluation of the gene-environment interaction was carried out using a multifactorial approach. We collected detailed psychosocial factors including childhood trauma, family environment, and social support. These data were then combined with the genotyping results. Specifically, an association of SNP-by-psychosocial factors (PF) interactions with depressive symptom related scales was evaluated using the linear regression model. Finally, the genome-wide interaction model was as follows:

$$h(t) = \beta_{PF} \times PF + \beta_{SNP} \times SNP + \beta_{PF\times SNP} \times PF \times SNP + \sum \beta_C \times Cov$$

where β_{SNP} and $\beta_{PF\times SNP}$ represent the impact of variants and interaction terms on the outcome, respectively. $P < 5.0 \times 10^{-8}$ was considered genome-wide significant.

All statistical analysis was performed by IBM SPSS Statistics 22, R 4.1.1, RStudio April 1, 1717, and Plink 1.90 [21].

3. Results

As shown in Supplementary Table 1 and Supplementary Fig. 1, a total of 984 MDD patients and 508 HC were included in this study. Multivariate analysis revealed that emotional neglect in the CTQ-SF ($P = 0.006$), independence in the FES-CV ($P = 0.028$), and factor 1 in the TAS-20 ($P = 0.011$) were significantly associated with MDD (Supplementary Table 2).

The results of the SNP and MDD association analysis identified several SNPs reaching genome-wide significance, including rs2305554 in the *cholinergic receptor nicotinic alpha 7 subunit* (*CHRNA7*), rs9459173 in *synaptojanin 2* (*SYNJ2*), rs372369000 in *beta-1,4-galactosyltransferase 6* (*B4GALT6*), rs866666526 in *dopa decarboxylase* (*DDC*), rs1254882194 in *calcium/calmodulin dependent protein kinase ID* (*CAMK1D*), rs199880487 and rs1167948188 in *RELN*, rs1390140186 in *QKI, KH domain containing RNA binding* (*QKI*), and rs1776342 in *period circadian regulator 3* (*PER3*) (Table 1, Supplementary Figs. 2 and 3). We performed allele and genotypic tests on these nine SNPs identified in the association analysis, as shown in Supplementary Fig. 4.

The association analysis between gene-environment interaction and HAMD-17 did not reveal any SNPs with genome-wide significance (Supplementary Fig. 2). However, SNP rs2735611 in *period circadian regulator 1* (*PER1*) and *microRNA 6883* (*MIR6883*)

showed the lowest *P* value and interacted with the one year-social/other aspects of the LES, affecting the HAMD-17 score in MDD patients (Table 2, Supplementary Fig. 3). Additionally, we conducted a subgroup analysis for first-episode and recurrent MDD patients, as shown in Table 2.

A multivariate analysis involving 369 MDD patients without suicidal ideation and 462 MDD patients with suicidal ideation revealed that factors such as illness duration ($P = 0.015$), baseline SHAPS score ($P = 0.040$), baseline factor 2 in the TAS-20 ($P = 0.005$), and cohesion ($P = 0.007$), expressiveness ($P = 0.020$), intellectual cultural ($P = 0.030$) and Organization ($P = 0.007$) in the FES-CV were associated with suicidal ideation in MDD patients (Supplementary Tables 3 and 4).

The association analysis between SNPs and BSI-CV in 462 MDD patients with suicidal ideation identified rs264272 and rs1774784888 in *piezo type mechanosensitive ion channel component 2* (*PIEZO2*) as reaching genome-wide significance (Table 3, Supplementary Fig. 5). The linkage disequilibrium test between rs264272 and rs1774784888 showed that they were in strong linkage disequilibrium ($R^2 = 0.984$). MDD patients carrying the protective allele T of rs264272 and allele A of rs1774784888 had lower BSI-CV scores (Supplementary Fig. 5).

The association analysis between gene-environment interaction and BSI-CV did not identify any SNP with genome-wide significance (Supplementary Fig. 5). However, SNP rs2256111 in *interleukin 10 receptor subunit alpha* (*IL10*RA) showed the lowest *P* value and interacted with emotional abuse of the CTQ-SF, affecting BSI-CV scores in MDD patients (Table 4, Supplementary Fig. 5). Additionally, we performed a subgroup analysis for MDD patients with suicidal ideation, as shown in Table 4.

4. Discussion

Nine SNPs associated with MDD were identified in this study. The Bonferroni correction was performed to reduce false positives, and results showed that rs2305554 of *CHRNA7* (Bonferroni correction *P* value $= 4.35 \times 10^{-20}$), rs9459173 of *SYNJ2* (Bonferroni correction *P* value $= 3.18 \times 10^{-13}$), and rs372369000 of *B4GALT6* (Bonferroni correction *P* value $= 1.65 \times 10^{-12}$) still displayed

Table 1
Associations of SNPs with MDD.

SNPs	Genotypic model	Nearby gene	Model 1		Model 2		Model 3	
			OR (95 % CI)	*P* value	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
rs2305554	Additive model (TT = 0, TC = 1, CC = 2)	CHRNA7	3.448 (2.714, 4.379)	3.66E-24	3.450 (2.712, 4.388)	6.12E-24	3.628 (2.841, 4.635)	5.76E-25
	Dominant model (TT = 0, TC = 1, CC = 1)		4.587 (3.522, 5.973)	1.22E-29	4.596 (3.525, 5.994)	2.04E-29	4.894 (3.732, 6.416)	1.48E-30
rs9459173	Additive model (CC = 0, CT = 1, TT = 2)	SYNJ2	0.206 (0.143, 0.297)	2.67E-17	0.204 (0.141, 0.294)	1.90E-17	0.194 (0.134, 0.281)	5.13E-18
	Dominant model (CC = 0, CT = 1, TT = 1)		0.206 (0.143, 0.297)	2.67E-17	0.204 (0.141, 0.294)	1.90E-17	0.194 (0.134, 0.281)	5.13E-18
rs372369000	Additive model (CC = 0, C- = 1, – = 2)	B4GALT6	0.276 (0.203, 0.374)	1.39E-16	0.273 (0.201, 0.371)	1.14E-16	0.268 (0.197, 0.366)	9.43E-17
	Dominant model (CC = 0, C- = 1, – = 1)		0.276 (0.203, 0.374)	1.39E-16	0.273 (0.201, 0.371)	1.14E-16	0.268 (0.197, 0.366)	9.43E-17
rs866666526	Additive model (AA = 0, AT = 1, TT = 2)	DDC	2.050 (1.666, 2.522)	1.14E-11	2.034 (1.652, 2.504)	2.21E-11	2.021 (1.641, 2.491)	3.93E-11
	Dominant model (AA = 0, AT = 1, TT = 1)		2.686 (2.102, 3.432)	2.72E-15	2.662 (2.081, 3.405)	6.24E-15	2.640 (2.060, 3.383)	1.73E-14
rs1254882194	Additive model (CC = 0, CA = 1, AA = 2)	CAMK1D	5.132 (3.185, 8.270)	1.84E-11	5.112 (3.171, 8.242)	2.14E-11	5.143 (3.182, 8.313)	2.30E-11
	Dominant model (CC = 0, CA = 1, AA = 1)		5.132 (3.185, 8.270)	1.84E-11	5.112 (3.171, 8.242)	2.14E-11	5.143 (3.182, 8.313)	2.30E-11
rs199880487	Additive model (GG = 0, GA = 1, AA = 2)	RELN	4.074 (2.487, 6.675)	2.46E-08	4.081 (2.489, 6.692)	2.47E-08	4.149 (2.523, 6.821)	2.04E-08
	Dominant model (GG = 0, GA = 1, AA = 1)		4.074 (2.487, 6.675)	2.46E-08	4.081 (2.489, 6.692)	2.47E-08	4.149 (2.523, 6.821)	2.04E-08
rs1167948188	Additive model (GG = 0, GA = 1, AA = 2)	RELN	6.469 (3.354, 12.48)	2.55E-08	6.376 (3.303, 12.31)	3.35E-08	6.602 (3.409, 12.79)	2.18E-08
	Dominant model (GG = 0, GA = 1, AA = 1)		6.469 (3.354, 12.48)	2.55E-08	6.376 (3.303, 12.31)	3.35E-08	6.602 (3.409, 12.79)	2.18E-08
rs1390140186	Additive model (AA = 0, AC = 1, CC = 2)	QKI	3.497 (2.237, 5.468)	4.02E-08	3.498 (2.235, 5.475)	4.29E-08	3.646 (2.319, 5.731)	2.08E-08
	Dominant model (AA = 0, AC = 1, CC = 1)		3.497 (2.237, 5.468)	4.02E-08	3.498 (2.235, 5.475)	4.29E-08	3.646 (2.319, 5.731)	2.08E-08
rs1776342	Additive model (GG = 0, GA = 1, AA = 2)	PER3	0.340 (0.231, 0.501)	4.91E-08	0.334 (0.226, 0.493)	3.34E-08	0.317 (0.214, 0.470)	1.04E-08
	Dominant model (GG = 0, GA = 1, AA = 1)		0.340 (0.231, 0.501)	4.91E-08	0.334 (0.226, 0.493)	3.34E-08	0.317 (0.214, 0.470)	1.04E-08

Abbreviations: B4GALT6, beta-1,4-galactosyltransferase 6; CAMK1D, calcium/calmodulin dependent protein kinase ID; CHRNA7, cholinergic receptor nicotinic alpha 7 subunit; CI, confidence interval; DDC, dopa decarboxylase; MDD, major depressive disorder; OR, odds ratio; PER3, period circadian regulator 3; QKI, QKI, KH domain containing RNA binding; SNPs, single nucleotide polymorphisms; RELN, reelin; SYNJ2, synaptojanin 2.

Table 2
Association of gene-environment interaction with HAMD-17 in patients with MDD.

SNPs	Nearby gene	Variables	Additive model		Dominant model	
			Effect size (95 % CI)	*P* value	Effect size (95 % CI)	*P* value
Association of gene-environment interaction with HAMD-17 in MDD patients (first-episode and recurrence)						
rs2735611	PER1 and MIR6883	rs2735611	0.232 (−0.198, 0.663)	0.2902	0.399 (−0.185, 0.983)	0.1806
		LES: One year-Social/other aspects	0.226 (0.132, 0.319)	2.54E-06	0.268 (0.165, 0.372)	4.66E-07
		interaction	−0.129 (−0.181, −0.078)	9.34E-07	−0.292 (−0.401, −0.183)	1.97E-07
Association of gene-environment interaction with HAMD-17 in the first-episode MDD patients						
rs1791921	P2RY2	rs1791921	−4.659 (−6.797, −2.522)	2.29E-05	−5.939 (−8.553, −3.325)	1.03E-05
		CTQ-SF: Emotional neglect	−0.050 (−0.153, 0.054)	0.3477	−0.063 (−0.169, 0.042)	0.2407
		interaction	0.365 (0.211, 0.519)	4.45E-06	0.460 (0.272, 0.647)	2.05E-06
rs211014	GABRG2	rs211014	−5.635 (−7.934, −3.336)	2.01E-06	−8.673 (−11.98, −5.369)	3.72E-07
		FES-CV: Independence	−0.882 (−1.289, −0.475)	2.50E-05	−1.048 (0.227, −1.492)	4.72E-06
		interaction	0.876 (0.498, 1.254)	6.83E-06	1.349 (0.799, 1.900)	2.04E-06
Association of gene-environment interaction with HAMD-17 in the recurrence MDD patients						
rs2273686	SLC1A2	rs2273686	1.534 (0.639, 2.430)	8.59E-04	1.482 (0.450, 2.514)	0.00511
		LES: Family life events	0.047 (0.026, 0.068)	1.93E-05	0.046 (0.025, 0.068)	3.33E-05
		interaction	−0.072 (−0.100, −0.043)	1.59E-06	−0.073 (−0.105, −0.042)	5.28E-06

Abbreviations: CI, confidence interval; CTQ-SF, childhood trauma questionnaire-short form; FES-CV, family environment scale-Chinese version; GABRG2, gamma-aminobutyric acid type A receptor subunit gamma2; HAMD-17, 17-item Hamilton depression rating scale; LES, life event scale; MDD, major depressive disorder; MIR6883, microRNA 6883; P2RY2, purinergic receptor P2Y2; PER1, period circadian regulator 1; SLC1A2, solute carrier family 1 member 2; SNP, single nucleotide polymorphisms.

Table 3
Association of SNPs with BSI-CV in MDD patients with suicidal ideation.

Model	SNPs	Nearby gene	Additive model		Recessive model	
			Effect size (95 % CI)	*P* value	Effect size (95 % CI)	*P* value
Model 1	rs264272	PIEZO2	−2.660 (−1.644, −3.677)	4.31E-07	−5.581 (−3.695, −7.468)	1.25E-08
	rs1774784888	PIEZO2	−2.651 (−1.630, −3.673)	5.34E-07	−5.581 (−3.695, −7.468)	1.25E-08
Model 2	rs264272	PIEZO2	−2.648 (−1.621, −3.675)	6.30E-07	−5.589 (−3.689, −7.488)	1.49E-08
	rs1774784888	PIEZO2	−2.640 (−1.608, −3.672)	7.68E-07	−5.589 (−3.689, −7.488)	1.49E-08
Model 3	rs264272	PIEZO2	−2.636 (−1.606, −3.666)	7.58E-07	−5.584 (−3.680, −7.487)	1.66E-08
	rs1774784888	PIEZO2	−2.628 (−1.593, −3.663)	9.26E-07	−5.584 (−3.680, −7.487)	1.66E-08

Abbreviations: BSI-CV, Beck scale for suicide ideation-Chinese version; CI, confidence interval; MDD, major depressive disorder; PIEZO2, piezo type mechanosensitive ion channel component 2; SNPs, single nucleotide polymorphisms.

Table 4
Association of gene-environment interaction with BSI-CV in MDD patients.

SNP	Nearby gene	Variables	Additive model		Dominant model	
			Effect size (95 % CI)	*P* value	Effect size (95 % CI)	*P* value
Association of gene-environment interaction with BSI-CV in MDD patients (with and without suicidal ideation)						
rs2256111	IL10RA	rs2256111	−5.648 (−7.868, −3.412)	8.15E-07	−7.366 (−10.27, −4.458)	8.36E-07
		CTQ-SF: Emotional abuse	−0.008 (−0.325, 0.310)	0.9624	−0.076 (−0.413, 0.260)	0.6572
		interaction	0.966 (0.620, 1.313)	5.96E-08	1.222 (0.783, 1.660)	6.39E-08
Association of gene-environment interaction with BSI-CV in MDD patients with suicidal ideation						
rs70937086	PDK1	rs70937086	−8.112 (−12.23, −3.995)	0.00013	−7.991 (−12.21, −3.777)	0.000229
		FES-CV: Intellectual cultural	−0.523 (−0.955, −0.091)	0.01804	−0.520 (−0.953, −0.088)	0.01876
		interaction	2.952 (1.653, 4.251)	1.07E-05	2.933 (1.626, 4.240)	1.38E-05

Abbreviations: BSI-CV, Beck scale for suicide ideation-Chinese version; CI, confidence interval; CTQ-SF, childhood trauma questionnaire-short form; FES-CV, family environment scale-Chinese version; IL10RA, interleukin 10 receptor subunit alpha; MDD, major depressive disorder; PDK1, pyruvate dehydrogenase kinase 1; SNP, single nucleotide polymorphism.

genome-wide significant differences.

CHRNA7 encodes the neuronal acetylcholine receptor subunit alpha-7 (alpha-7 nAchR), which has Ca^{2+} permeability and mediates rapid signal transduction at synapses. CHRNA7 knockout mice exhibit a depressive-like phenotype [22,23]. The expression of *CHRNA7* in the prefrontal cortex of MDD patients' autopsy brain tissue was higher than that of healthy controls [24]. CHRNA7 exerts an antidepressant effect by regulating intestinal flora to ameliorate systemic inflammation [25,26]. *SYNJ2*, highly expressed in the brain, is a member of the inositol-polyphosphate 5-phosphatase family and interacts with ras-related C3 botulinum toxin substrate 1, resulting in its translocation to the plasma membrane and inhibition of clathrin-mediated endocytosis [27]. *B4GALT6* is essential for myelination in mice [28] and regulates microglia activation, playing a role in central nervous system inflammation by enhancing astrocyte

synthesis of GM-CSF [29]. Proteins encoded by *DDC* are key enzymes in dopamine and serotonin pathways and are involved in the pathophysiological process of MDD [30,31]. The protein encoded by *CAMK1D* activates CREB-dependent gene transcription and promotes the growth of basal dendrites in hippocampal neurons [32,33]. Reelin, encoded by *RELN*, is involved in neurodevelopmental disorders and the antidepressant effect of ketamine [34,35]. QKI is an RNA-binding protein crucial for myelination [36]. *QKI* expression was reduced in the autopsy brain tissues of MDD suicidal patients compared with healthy controls [37]. Notably, rs1776342 is a missense variation located in the herpes virus major outer envelope glycoprotein (BLLF1) region of *period circadian regulator 3* (*PER3*). *PER3* polymorphic variants are associated with depressive symptoms in the elderly and can predict adverse effects of selective serotonin reuptake inhibitors [38,39]. Whether these variations are functional and the pathophysiological mechanisms involved in MDD require further exploration.

The rs2735611 interacts with the one-year social/other aspects of LES to influence the HAMD-17 score. For patients carrying the rs2735611-G allele, more severe one-year social/other aspects of LES are associated with more severe depressive symptoms in MDD patients. Multi-tissue expression Quantitative Trait Loci (eQTL) comparisons in the GTEx database showed that rs2735611 reduced the expression of *CST telomere replication complex component 1* (*CTC1*) ($P = 9.30 \times 10^{-91}$) (Supplementary Fig. 6). Specifically, the rs2735611: (1) reduced the expression of *CTC1* in pituitary ($P = 2.02 \times 10^{-5}$), gastroesophageal junction ($P = 2.24 \times 10^{-6}$), tibial nerve ($P = 6.75 \times 10^{-11}$), thyroid ($P = 1.10 \times 10^{-11}$), esophageal muscularis ($P = 2.40 \times 10^{-8}$), and tibial artery ($P = 9.05 \times 10^{-7}$); (2) increased the expression of *ArfGAP with coiled-coil, ankyrin repeat and PH domains 1* (*ACAP1*) in subcutaneous adipose ($P = 4.45 \times 10^{-5}$); and (3) increased *solute carrier family 25 member 35* (*SLC25A35*) expression in the pancreas ($P = 1.41 \times 10^{-6}$) (Supplementary Fig. 7). The splicing Quantitative Trait Loci (sQTLs) analysis showed that the rs2735611 reduced the intron-expression ratio of *period circadian regulator 1* (*PER1*) in skeletal muscle ($P = 4.10 \times 10^{-38}$), esophageal muscularis ($P = 4.60 \times 10^{-26}$), gastroesophageal junction ($P = 8.80 \times 10^{-14}$), and fibroblasts ($P = 4.30 \times 10^{-8}$). In view of this, rs2735611 may be a functional variant.

To comprehensively explore genetic and gene-environment interaction factors associated with MDD, we conducted additional analyses but did not identify any SNPs with genome-wide significance. Specifically, we performed association analyses: (1) to explore SNPs associated with recurrence in MDD patients (Supplementary Tables 5 and 6), the SNP with the lowest *P* value was rs1021117118 (OR, 0.408; 95 % CI, 0.264–0.631; $P = 5.48 \times 10^{-5}$) of the *contactin associated protein 2* (*CNTNAP2*). The rs1021117118-C allele serves as a risk allele for relapse among patients with MDD. (2) To explore the SNPs associated with severity of the depressive symptoms HAMD-17 in patients with MDD, the top SNP was rs34466559 (Effect size, 2.014; 95 % CI, 1.131–2.898; $P = 8.76 \times 10^{-6}$) of the *N-acylsphingosine amidohydrolase 1* (*ASAH1*) and the *ASAH1 antisense RNA 1* (*LOC101929066*); Patients with MDD who have the rs34466559-C allele exhibit more severe depressive symptoms compared to those with the rs34466559-A allele. (3) To explore the SNPs associated with severity of the depressive symptoms HAMD-17 in first-episode and recurrence patients with MDD, respectively, for the first-episode patients, the SNP with the lowest *P* value was rs1049874 (Effect size, 1.727; 95 % CI, 0.935–2.519; $P = 2.25 \times 10^{-5}$), a missense variant of the *ASAH1*; For first-episode MDD patients, those with the rs1049874-C allele presented more severe depressive symptoms compared to those with the rs1049874-T allele. For recurrent MDD patients, the top SNP was rs1486148120 (Effect size, −3.04; low 95 % CI, −4.474; up 95 % CI, −1.606; $P = 3.96 \times 10^{-5}$) of the *basic helix-loop-helix family member e40* (*BHLHE40*) and the *BHLHE40 antisense RNA 1* (*BHLHE40-AS1*); This implies that patients with the rs1486148120-T allele have fewer symptoms than those with the rs1486148120-C allele. (4) To explore the gene-environment interaction associated with recurrence in MDD patients, the SNP rs865832 of the *sphingosine-1-phosphate lyase 1* (*SGPL1*) presenting the lowest *P* value, interaction with negative events of the LES, affecting the recurrence in patients with MDD (Supplementary Table 7). MDD patients possessing the rs865832-C allele had a higher propensity to relapse when they encountered a greater number of negative life events.

Our study found that rs70937086 interacted with intellectual cultural factors in FES-CV to influence BSI-CV scores in MDD patients. One of the risk loci for MDD identified by Als et al. [40], namely chr2:172472180-172980181, includes rs70937086. This finding supports the emerging consensus on the role of rs70937086 in the etiology of MDD. However, other SNPs identified in our study have not been confirmed by other studies. We also attempted to validate genes confirmed by previous genetic, genome-wide association, and meta-analysis studies related to MDD diagnosis. Eight genes showed significant differences ($P < 0.05$), as shown in Supplementary Table 8. The poor reproducibility of some studies may be attributed to disparities in study populations. Our subjects were from the Chinese Han population, whereas most genome-wide association studies of MDD were conducted in Europe or North America. Variations in genetic testing and analysis approach, including distinct technical means, detection platforms, or data analysis algorithms, might cause differences in identifying and interpreting genetic variants. The relatively small sample size in our study might have limited the detection of some genuine associations due to inadequate statistical power. Larger sample sizes in other studies may yield more reliable findings. Discrepancies in study design, such as gene screening scope, covariate control, and follow-up time, could also result in inconsistent outcomes.

Recent studies have made significant advancements in understanding gene-environment interactions in MDD. Research increasingly focuses on identifying specific environmental triggers and their interactions with genetic variations to better predict disease susceptibility and prognosis [41–43]. Similar efforts are underway in other psychiatric disorders [44]. However, challenges remain, including the need for larger sample sizes and more precise measurements of environmental factors to further validate and expand these findings.

The control group in this study comprised about half the number of cases. To reduce bias, we included confounding factors such as age, gender, and population stratification as covariables in the model. Candidate gene targeted-exome sequencing may miss potential loci and genes compared to whole-genome or whole-exome sequencing. We did not perform functional verification of the loci identified in the association analysis to determine if these loci are functional variants and if they are involved in the pathophysiological process of MDD. The relatively small sample size may have hindered the precise detection of some genuine associations due to inadequate statistical power. Larger samples would provide greater statistical power and allow for more refined subgroup analyses,

potentially uncovering subtler associations and reducing the risk of type II errors. We also did not comprehensively consider various environmental and lifestyle factors such as diet, physical activity, and socioeconomic status. These factors could potentially confound or modify the observed relationships between genetic variations and MDD, and their omission may have limited our understanding of the complex etiology of MDD. The cross-sectional design of our study provides only a snapshot of associations at a single point in time and does not allow for causal inferences or the assessment of temporal relationships between genetic factors and the development or progression of MDD over time. Additionally, we did not address the phenotypic heterogeneity within the MDD population. MDD is a heterogeneous disorder, and different subtypes or symptom profiles may have distinct underlying genetic and environmental contributions. Failing to account for this heterogeneity might have obscured specific associations and reduced the clinical applicability of our findings. Future studies with larger sample sizes, longitudinal designs, and comprehensive assessments of environmental and lifestyle factors, as well as accounting for phenotypic heterogeneity, are warranted to further validate and expand upon our current findings.

In conclusion, eight genes with nine single nucleotide variation loci were identified as potentially associated with MDD. The SNPs rs264272 and rs1774784888 in *PIEZO2* may be associated with suicidal ideation in MDD patients. These findings could broaden our understanding and help develop new potential targets for the diagnosis and treatment of MDD.

Ethics approval

This study was approved by the ethics committees of Zhongda Hospital, Southeast University (2016ZDSYLL100-P01)

Data availability statement

The authors do not have permission to share data.

CRediT authorship contribution statement

Di Luan: Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Shi-zun Li:** Software, Methodology. **Can Zhang:** Methodology, Formal analysis. **Bin Ye:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank the subjects who participated in this study for their kind cooperation and willingness. The authors thank the Anhui Provincial Key clinical Specialty Construction Project for their support. This work was partly supported by the China Stroke Association Whole Course Management of Cerebrovascular Disease-Sailing Fund (202001), the Anhui Provincial University Scientific Research Project (2023AH051924), and the Postgraduate Research Innovation Program of Bengbu Medical University (Byycx22117).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37504.

References

[1] Y. Huang, Y. Wang, H. Wang, Z. Liu, X. Yu, J. Yan, Y. Yu, C. Kou, X. Xu, J. Lu, et al., Prevalence of mental disorders in China: a cross-sectional epidemiological study, Lancet Psychiatr. 6 (3) (2019) 211–224.
[2] G. Yang, Y. Wang, Y. Zeng, G.F. Gao, X. Liang, M. Zhou, X. Wan, S. Yu, Y. Jiang, M. Naghavi, et al., Rapid health transition in China, 1990-2010: findings from the global burden of disease study 2010, Lancet 381 (9882) (2013) 1987–2015.
[3] J. Lu, X. Xu, Y. Huang, T. Li, C. Ma, G. Xu, H. Yin, X. Xu, Y. Ma, L. Wang, et al., Prevalence of depressive disorders and treatment in China: a cross-sectional epidemiological study, Lancet Psychiatr. 8 (11) (2021) 981–990.
[4] S.H. Leu, J.Y. Chou, P.C. Lee, H.C. Cheng, W.C. Shao, W.L. Hsien, C.L. Huang, V.C. Chen, Validity and reliability of the Chinese version of the sheehan disability scale (SDS-C), Asia Pac. Psychiatr. 7 (2) (2015) 215–222.
[5] R.C. Kessler, P. Berglund, O. Demler, R. Jin, D. Koretz, K.R. Merikangas, A.J. Rush, E.E. Walters, P.S. Wang, R. National Comorbidity Survey, The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R), JAMA 289 (23) (2003) 3095–3105.
[6] L.H. Goetz, L. Uribe-Bruce, D. Quarless, O. Libiger, N.J. Schork, Admixture and clinical phenotypic variation, Hum. Hered. 77 (1–4) (2014) 73–86.
[7] Y. Cao, L. Li, M. Xu, Z. Feng, X. Sun, J. Lu, Y. Xu, P. Du, T. Wang, R. Hu, et al., The ChinaMAP analytics of deep whole genome sequences in 10,588 individuals, Cell Res. 30 (9) (2020) 717–731.
[8] L. Li, P. Huang, X. Sun, S. Wang, M. Xu, S. Liu, Z. Feng, Q. Zhang, X. Wang, X. Zheng, et al., The ChinaMAP reference panel for the accurate genotype imputation in Chinese populations, Cell Res. 31 (12) (2021) 1308–1310.
[9] C. consortium, Sparse whole-genome sequencing identifies two loci for major depressive disorder, Nature 523 (7562) (2015) 588–591.

[10] X. Gonda, P. Petschner, N. Eszlari, D. Baksa, A. Edes, P. Antal, G. Juhasz, G. Bagdy, Genetic variants in major depressive disorder: from pathophysiology to therapy, Pharmacol. Ther. 194 (2019) 22–43.
[11] R.J. Musci, J.L. Augustinavicius, H. Volk, Gene-environment interactions in psychiatry: recent evidence and clinical implications, Curr. Psychiatr. Rep. 21 (9) (2019) 81.
[12] D. Luan, D. You, Y. Wu, F. Wu, Z. Xu, L. Li, J. Jiao, A. Zhang, H. Feng, Y. Kong, et al., Effects of interaction between single nucleotide polymorphisms and psychosocial factors on the response to antidepressant treatment in patients with major depressive disorder, J Genet Genomics 49 (6) (2022) 587–589.
[13] G. Grunder, H. Wetzel, E. Hammes, O. Benkert, Roxindole, a dopamine autoreceptor agonist, in the treatment of major depression, Psychopharmacology (Berl) 111 (1) (1993) 123–126.
[14] T.I. Oei, W.M. Verhoeven, H.G. Westenberg, F.M. Zwart, J.M. van Ree, Anhedonia, suicide ideation and dexamethasone nonsuppression in depressed patients, J. Psychiatr. Res. 24 (1) (1990) 25–35.
[15] R.M. Bagby, J.D. Parker, G.J. Taylor, The twenty-item Toronto Alexithymia Scale–I. Item selection and cross-validation of the factor structure, J. Psychosom. Res. 38 (1) (1994) 23–32.
[16] R.P. Snaith, M. Hamilton, S. Morley, A. Humayan, D. Hargreaves, P. Trigwell, A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale, Br. J. Psychiatry 167 (1) (1995) 99–103.
[17] D.P. Bernstein, J.A. Stein, M.D. Newcomb, E. Walker, D. Pogge, T. Ahluvalia, J. Stokes, L. Handelsman, M. Medrano, D. Desmond, et al., Development and validation of a brief screening version of the Childhood Trauma Questionnaire, Child Abuse Negl. 27 (2) (2003) 169–190.
[18] K.J. Nan, Y.C. Wei, F.L. Zhou, C.L. Li, C.G. Sui, L.Y. Hui, C.G. Gao, Effects of depression on parameters of cell-mediated immunity in patients with digestive tract cancers, World J. Gastroenterol. 10 (2) (2004) 268–272.
[19] M.R. Phillips, C.L. West, Q. Shen, Y. Zheng, Comparison of schizophrenic patients' families and normal families in China, using Chinese versions of FACES-II and the Family Environment Scales, Fam. Process 37 (1) (1998) 95–106.
[20] I.N. Sandler, Social support resources, stress, and maladjustment of poor children, Am. J. Community Psychol. 8 (1) (1980) 41–52.
[21] C.C. Chang, C.C. Chow, L.C. Tellier, S. Vattikuti, S.M. Purcell, J.J. Lee, Second-generation PLINK: rising to the challenge of larger and richer datasets, GigaScience 4 (2015) 7.
[22] Y. Pu, Y. Tan, Y. Qu, L. Chang, S. Wang, Y. Wei, X. Wang, K. Hashimoto, A role of the subdiaphragmatic vagus nerve in depression-like phenotypes in mice after fecal microbiota transplantation from Chrna7 knock-out mice with depression-like phenotypes, Brain Behav. Immun. 94 (2021) 318–326.
[23] J.C. Zhang, W. Yao, Q. Ren, C. Yang, C. Dong, M. Ma, J. Wu, K. Hashimoto, Depression-like phenotype by deletion of alpha7 nicotinic acetylcholine receptor: role of BDNF-TrkB in nucleus accumbens, Sci. Rep. 6 (2016) 36705.
[24] Y. Kunii, W. Zhang, Q. Xu, T.M. Hyde, W. McFadden, J.H. Shin, A. Deep-Soboslay, T. Ye, C. Li, J.E. Kleinman, et al., CHRNA7 and CHRFAM7A mRNAs: co-localized and their expression levels altered in the postmortem dorsolateral prefrontal cortex in major psychiatric disorders, Am. J. Psychiatr. 172 (11) (2015) 1122–1130.
[25] Y. Yang, A. Eguchi, C. Mori, K. Hashimoto, Splenic nerve denervation attenuates depression-like behaviors in Chrna7 knock-out mice via the spleen-gut-brain axis, J. Affect. Disord. 362 (2024) 114–125.
[26] Y. Yang, A. Eguchi, X. Wan, L. Chang, X. Wang, Y. Qu, C. Mori, K. Hashimoto, A role of gut-microbiota-brain axis via subdiaphragmatic vagus nerve in depression-like phenotypes in Chrna7 knock-out mice, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 120 (2023) 110652.
[27] Y. Chuang, X. Xu, A. Kwiatkowska, G. Tsapraillis, H. Hwang, K. Petritis, D. Flynn, M. Symons, Regulation of synaptojanin 2 5'-phosphatase activity by Src, Cell Adhes. Migrat. 6 (6) (2012) 518–525.
[28] T. Yoshihara, H. Satake, T. Nishie, N. Okino, T. Hatta, H. Otani, C. Naruse, H. Suzuki, K. Sugihara, E. Kamimura, et al., Lactosylceramide synthases encoded by B4galt5 and 6 genes are pivotal for neuronal generation and myelin formation in mice, PLoS Genet. 14 (8) (2018) e1007545.
[29] L. Mayo, S.A. Trauger, M. Blain, M. Nadeau, B. Patel, J.I. Alvarez, I.D. Mascanfroni, A. Yeste, P. Kivisakk, K. Kallas, et al., Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation, Nat Med 20 (10) (2014) 1147–1156.
[30] M. Gupta, D. Neavin, D. Liu, J. Biernacka, D. Hall-Flavin, W.V. Bobo, M.A. Frye, M. Skime, G.D. Jenkins, A. Batzler, et al., TSPAN5, ERICH3 and selective serotonin reuptake inhibitors in major depressive disorder: pharmacometabolomics-informed pharmacogenomics, Mol. Psychiatr. 21 (12) (2016) 1717–1725.
[31] H.M. Jia, Y.F. Feng, Y.T. Liu, X. Chang, L. Chen, H.W. Zhang, G. Ding, Z.M. Zou, Integration of (1)H NMR and UPLC-Q-TOF/MS for a comprehensive urinary metabonomics study on a rat model of depression induced by chronic unpredictable mild stress, PLoS One 8 (5) (2013) e63624.
[32] A. Kamata, H. Sakagami, H. Tokumitsu, Y. Owada, K. Fukunaga, H. Kondo, Spatiotemporal expression of four isoforms of Ca2+/calmodulin-dependent protein kinase I in brain and its possible roles in hippocampal dendritic growth, Neurosci. Res. 57 (1) (2007) 86–97.
[33] H. Sakagami, A. Kamata, H. Nishimura, J. Kasahara, Y. Owada, Y. Takeuchi, M. Watanabe, K. Fukunaga, H. Kondo, Prominent expression and activity-dependent nuclear translocation of Ca2+/calmodulin-dependent protein kinase Idelta in hippocampal neurons, Eur. J. Neurosci. 22 (11) (2005) 2697–2707.
[34] T.D. Folsom, S.H. Fatemi, The involvement of Reelin in neurodevelopmental disorders, Neuropharmacology 68 (2013) 122–135.
[35] J.W. Kim, J. Herz, E.T. Kavalali, L.M. Monteggia, A key requirement for synaptic Reelin signaling in ketamine-mediated behavioral and synaptic action, Proc Natl Acad Sci U S A 118 (20) (2021).
[36] K. Aberg, P. Saetre, N. Jareborg, E. Jazin, Q.K.I. Human, A potential regulator of mRNA expression of human oligodendrocyte-related genes involved in schizophrenia, Proc Natl Acad Sci U S A 103 (19) (2006) 7482–7487.
[37] T.A. Klempan, C. Ernst, V. Deleva, B. Labonte, G. Turecki, Characterization of QKI gene expression, genetics, and epigenetics in suicide victims with major depressive disorder, Biol Psychiatry 66 (9) (2009) 824–831.
[38] J.E. Maglione, C.M. Nievergelt, N. Parimi, D.S. Evans, S. Ancoli-Israel, K.L. Stone, K. Yaffe, S. Redline, G.J. Tranah, et al., Study of Osteoporotic Fractures in W, Associations of PER3 and RORA circadian gene polymorphisms and depressive symptoms in older adults, Am. J. Geriatr. Psychiatr. 23 (10) (2015) 1075–1087.
[39] Y. Xu, H. Ma, T. Zhao, D. Wen, Y. Wen, D. Qiao, Z. Liu, Association between period 3 gene polymorphisms and adverse effects of antidepressants for major depressive disorder, Genet. Test. Mol. Biomarkers 23 (12) (2019) 843–849.
[40] T.D. Als, M.I. Kurki, J. Grove, G. Voloudakis, K. Therrien, E. Tasanko, T.T. Nielsen, J. Naamanka, K. Veerapen, D.F. Levey, et al., Depression pathophysiology, risk prediction of recurrence and comorbid psychiatric disorders using genome-wide analyses, Nat Med 29 (7) (2023) 1832–1844.
[41] S. Bonk, N. Eszlari, K. Kirchner, A. Gezsi, L. Garvert, M. Kuokkanen, I. Cano, H.J. Grabe, P. Antal, G. Juhasz, et al., Impact of gene-by-trauma interaction in MDD-related multimorbidity clusters, J. Affect. Disord. 359 (2024) 382–391.
[42] M. Turner, Neurobiological and psychological factors to depression, Int. J. Psychiatr. Clin. Pract. (2024) 1–14.
[43] R. Wang, Y. Su, K. O'Donnell, J. Caron, M. Meaney, X. Meng, Y. Li, Differential interactions between gene expressions and stressors across the lifespan in major depressive disorder, J. Affect. Disord. 362 (2024) 688–697.
[44] J. Meijsen, K. Hu, M.D. Krebs, G. Athanasiadis, S. Washbrook, R. Zetterberg, E.S.R.N. Avelar, J.R. Shorter, J.R. Gadin, J. Bergstedt, et al., Quantifying the relative importance of genetics and environment on the comorbidity between mental and cardiometabolic disorders using 17 million Scandinavians, Nat. Commun. 15 (1) (2024) 5064.