The Genetic Structure of Pain in Depression Patients: A Genome-Wide Association Study and Proteome-Wide Association Study

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Abstract

Background

Pain symptoms are common in the patients with depression. Comparing with the general population, the pain in depression patients has more complex biological mechanism. We aim to explore the etiological mechanism of pain in depression patients from the perspective of genetics.

Methods

Utilizing the UK Biobank samples with self-reported depression status or PHQ score ≥ 10 , we conducted genome-wide association study (GWAS) of seven pain traits ($N=1,133-58,349$). The GWAS summary were then integrated with two different reference protein weights (ROS/MAP and Banner) for proteome-wide association study (PWAS) using the FUSION pipeline. Additionally, LDSC analysis was performed to explore the genetic correlation between pain traits in depression patients and common psychiatry disorders. And biological processes and functions that related to pain associated genes in depression patients were analyzed by gene set enrichment analysis.

Results

GWAS identified 3 significant genes associated with different pain traits in depression patients, including *TRIOBP* ($P_{\text{GWAS}} = 4.48 \times 10^{-8}$) for stomach or abdominal pain, *SLC9A9* ($P_{\text{GWAS}} = 2.77 \times 10^{-8}$) for multisite chronic pain (MCP) and *ADGRF1* ($P_{\text{GWAS}} = 1.51 \times 10^{-8}$) for neck or shoulder pain. PWAS also identified multiple candidate genes associated with different pain traits in depression patients, such as *TPRG1L* (permutation-based $P_{\text{PWAS-Banner}} = 3.38 \times 10^{-2}$) and *SIRPA* (permutation-based $P_{\text{PWAS-Banner}} = 3.65 \times 10^{-2}$) for MCP etc. LDSC analysis results showed that MCP was positively correlated with attention-deficit hyperactivity disorder (ADHD) (genetic correlation(rg) = 0.123, $P_{\text{LDSC}} = 0.039$) and post-traumatic stress disorder (PTSD) ($rg = 0.217$, $P_{\text{LDSC}} = 0.029$).

Conclusions

We reported multiple novel candidate genes and genetic correlations for pain traits in depression patients, providing novel clues for understanding the genetic mechanisms underlying the pain in depression patients.

Introduction

As one of the most common psychiatric disorders, depression not only causes changes in emotional state (affective disorder), but also usually causes major physical symptoms such as primarily fatigue, pain or sleep disturbances.¹ According to the World Health Organization's latest report, the prevalence of depression is steadily increasing worldwide, with an estimated 322 million people (4.4% of the world's population) living with depression.² Furthermore, depression is the single largest contributor to nonfatal health loss globally, accounting for 7.5% of all years of disability in 2015.² As a complex disease, depression not only reduces the health-related quality of life of patients, and increase the economic burden of individuals and social medical economic burden, which has become a public health problem of global concern.^{3,4}

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, and is an interaction of psychological, emotional, behavioral and social factors.⁵ Although pain is not a diagnostic symptom of depression, pain symptoms are common in people with depression and are closely related to depression. Previous studies have found that the prevalence of pain in depression patients was 59.1% (95% CI: 57.7%-60.7%)⁶, and pain occurred more frequently in patients with depression than in those without.⁷ A longitudinal study that excluded participants with a history of depression or anxiety showed that baseline pain symptoms were a major risk factor for depression.⁸ What's more, previous studies have shown that pain can adversely affect the prognosis and treatment of depression. For example, a systematic review indicates that patients with both pain and depression had reduced physical, mental and social functioning as opposed to those with depression or pain alone.⁹

Previous research on between depression and pain symptoms has shown that because of the complex interaction between depression and pain symptoms, multiple common neurobiological mechanisms, genetics, environmental and cognitive factors must be considered when trying to unravel their association.¹⁰ One widely accepted theory holds that depression and painful symptoms follow the same descending pathways of the central nervous system. That is, in the nerves of the downward pain regulation system, key structures of the brainstem pain regulation circuit (periaqueductal gray(PAG) and rostral-ventromedial medulla(RVM)) receives many projections from the brain regions involved in the production of emotions (medial prefrontal cortex, insular cortex(IC), prefrontal cortex(PFC), hypothalamus and amygdala), and jointly constructs the pathway of pain regulation.¹¹ In addition, previous studies have found that depression and pain, specifically chronic pain, share common pathophysiological pathways that contribute to the long-term existence of depression, such as inflammatory processes, hypothalamic–pituitary–adrenocortical axis abnormalities and altered neurotransmitter receptivity in descending pathways of the central nervous system.^{10,12} These common neural circuits and neurochemicals enable depression and pain symptoms to interact at multiple levels within and between brain regions, between cells, and through neurochemical signals, where changes in circuit activity and neurochemical levels caused by either side can affect the other. Due to the complex interaction of these two diseases, compared with the general population's pain symptoms, the pain in depression patients has more complex biological mechanism, and depression itself is more serious, longer course of disease, and worse prognosis. Thus, it is necessary to pay attention to the pain in patients with depression and propose more effective strategies for the treatment and prognosis of depression.

It is worth noting that several previous studies have emphasized individual differences in susceptibility to depression and pain responses, indicating that genetic factors may have some common roles in the pathogenesis of depression and pain.^{12,13} Multivariate models of a twin study estimated 39% (95% CI: 22%-53%) heritability for depression and 25% (95% CI: 9%-41%) heritability for pain.¹⁴ Meng et al. conducted the cross-trait linkage disequilibrium score regression (LD) analysis for different pain phenotypes, and identified significant and positive genetic associations of multiple pain phenotypes with depression and neuroticism, revealing that pain and depression have partially overlapping genetic risk factors.¹⁵ Moreover, a genome-wide association study (GWAS) of multisite chronic pain based on data from the UK Biobank (UKB) cohort identified 39 susceptibility genes significantly associated with chronic pain, including *DCC*, *MAML3* and *FOXP2*, with functions implicated neuronal development, neurogenesis and neural connectivity.¹⁶ Summary of previous studies on depression and pain symptoms have found that due to the complex interactions and common genetic risk factors between them, there may be differences in the biological mechanism of pain symptoms between depression patients and the general population. However, few studies have conducted GWAS of pain in depression patients, and the corresponding susceptibility genes are unknown.

Utilizing the UK Biobank cohort, we conducted GWAS of different pain traits in depression patients. Then, the GWAS summary data were further subjected to PWAS and LDSC analysis in order to explore the potential biological mechanism related to pain in depression patients from the perspective of genetics. Finally, gene enrichment analysis was conducted to further reveal the possible biological pathway of genes related to pain phenotype in patients with depression. It is hoped to provide a new direction for the etiological mechanism study of depression and pain symptoms.

Materials And Methods

UK Biobank Cohort

The UK Biobank is a large prospective cohort study that collected health-related information, including phenotypes and genotypes, from approximately 500,000 participants aged between 40 and 69 years from around the United Kingdom in 2006 and 2010.¹⁷ All participants were asked to report a range of demographic information and health status through questionnaires and interviews, and approved to use their anonymous data for any health-related research. The UK Biobank provides informed consent to all participants. Our study was approved by the UK Biobank (Application 46478) and health-related records of participants were obtained.¹⁷

Depression Patients from UK Biobank

According to the definition of depression phenotype in the previous study,¹⁸ we selected the depression patients from the participants of UK Biobank cohort. Briefly, the depression patients were determined based on self-report depression status (UK Biobank data fields: 20002, 20126, and 20544) or Patient Health Question-9 (PHQ) score ≥ 10 . For self-reported depression, depression patients were selected based on the code 1286 from ID 20002, code 3,4 or 5 from ID 20126 and code 11 from ID 20544. In order to classify depression patients as closely as possible, we used the Patient Health Question-9 (PHQ)¹⁹ as strict inclusion and exclusion criteria. PHQ is a classification scale with an overall score (0-27) that focuses on nine symptoms and signs of depression and is used to screen and measure the severity of depression. Detailed classification of depression is presented in the Supplementary Information. Our analysis was limited to white British individuals (UK biobank data domain :21000).

Pain Phenotypes of UK Biobank

According to the specific pain related questionnaire adapted by the UK Biobank, the pain phenotype was measured by a question: "whether the participant reported having suffered from various types of body pain in the previous 3 months? The options were: 1. headache, 2. facial pain, 3. neck or shoulder pain, 4. back pain, 5. stomach or abdominal pain, 6. hip pain, 7. knee pain, 8. pain all over the body, 9. none of the above. More than one option could be selected (UK Biobank Category ID 100048)." Eight different pain phenotypes were defined based on pain at different sites reported by participants for the past 3 months or more, and complete definitions of the eight pain phenotypes can be found in the supplementary information. For each pain phenotype, cases were defined as people who chose the option of having pain at a specific site for 3 months or more in response to the above question. The controls were those who chose "none of the above" or "pain in a specific site did not last 3 months." Due to the small sample size for general pain for 3+ months (Field ID:2956) and facial pains for 3+ months (Field ID:4067), our study excluded these two pain phenotypes. In addition, we defined multisite chronic pain (MCP) based on the UK Biobank pain phenotype of seven different body sites with a pain score questionnaire (score 0-7). Once participants chose the most recent pain in one or more body sites or all over the body, they were also asked if the pain had been ongoing for three months or more (defined as chronic pain). Thus, MCP is defined as the total number of body sites that record chronic pain (lasting at least 3 months) :0 to 7. Those who chose "pain over the body" were excluded from our study because of the difference between widespread pain and localized chronic pain.¹⁶

Genotyping, Imputation and Quality Control of UK Biobank

In UK Biobank cohort, a total of 488,377 participants were genotyped by either the Affymetrix UK BiLEVE Axiom array or the UK Biobank Axiom array.²⁰ Subsequently, these genotypes results were imputed and quality controlled based on the Haplotype Reference Consortium (HRC) reference panel and UK10K project Reference panels.²¹ The details of array design, genotyping and quality control procedures are described elsewhere.²² Then, we deleted those participants who reported discrepancies between genetic gender and self-reported gender, as well as without ethical consent and interpolation data. Additionally, we excluded variants with the Hardy–Weinberg equilibrium (HWE) test P -values $> 1.0 \times 10^{-5}$, a genotype missing rate of > 0.05 and a minor allele frequency (MAF) of < 0.01 . Ultimately, we used KING software (<http://people.virginia.edu/~wc9c/KING/index.html>) to exclude the genetically related individuals.

Genome-Wide Association Study (GWAS)

We performed GWAS studies of seven different pain phenotypes in depression patients from the UK Biobank cohort. That is, the additive genetic effect logistic regression model of PLINK2.0 was used to conduct association analysis with adjusted sex, age, smoke consumption, alcohol consumption, body mass index(BMI), PC1, PC2 and PC3 as covariables.²³For quality control, we select high quality SNPs through a quality control filters: SNPs with low call rates (<0.90), high SNP-level missingness (> 0.1), high individual-level missingness (> 0.1), low MAF (<0.01) and low HWE exact test *P*-values (<0.001) were excluded. $P_{\text{GWAS}} < 5.0 \times 10^{-8}$ and $P_{\text{GWAS}} < 1.0 \times 10^{-5}$ were defined as significant and suggestive associations, respectively. GWAS results were visualized with the Manhattan plots generated by the "CMplot" R script. (<https://github.com/YinLiLin/R-CMplot>)

Linkage Disequilibrium Score Regression (LDSC) Analysis

According to the LDSC software(v1.0.0,<https://github.com/bulik/ldsc>), we used the cross-trait LDSC method to calculate the genetic correlation between different pain phenotypes and seven mental disorders²⁴, including Alzheimer’s disease(AD)²⁵, anxiety²⁶, attention-deficit hyperactivity disorder(ADHD)²⁷, autism spectrum disorder(ASD)²⁸, bipolar disorder(BD)²⁹, major depressive disorder(MDD)³⁰ and post-traumatic stress disorder(PTSD)³¹. The GWAS data of these seven psychiatric disorders were obtained from the published articles by the Psychiatric Genomics Consortium (PGC) (<https://www.med.unc.edu/pgc/download-results/>). The LDSC analysis is not affected by sample overlap and is fast, making it a reliable and powerful method to calculate genetic correlations between different phenotypes using GWAS summary-level results data.^{24,32}

Proteome-Wide Association Study (PWAS)

We separately integrated two different reference human brain proteomes(the ROS/MAP brain proteome reference weights³³ and Banner brain proteome reference weights³⁴) with our GWAS summary of pain in depression patients for PWAS using FUSION pipeline, respectively. Specifically, FUSION pipeline was used to calculate PWAS association statistics (PWAS Z-score), and then combined with the pre-calculated brain proteome reference weight (Z-score × proteome weight) to evaluate the effects of significant SNP in the pain GWAS of depression patients on the protein abundance. Finally, FUSION identifies the candidate genes associated with pain in patients with depression that act by regulating the abundance of proteins in the brain. To control the potential effect of multiple testing on study results, the permutation-based *P*-value (named PERM.PV) was calculated for each gene by FUSION. The permutation-based *P*-value (P_{PWAS}) <0.05 was used as significance threshold in our PWAS analysis.

Two different reference human brain proteomics used in our study were from Religious Orders Study and Rush Memory³³ and Aging Project (ROS/MAP) and the Banner Sun Health Research Institute (Banner)³⁴. According to previous study of human brain proteome³⁵, proteome was sequenced and combined with significant SNPs in GWAS database to identify cis-regulated proteins that were significantly related to genetic variation. Detailed information on proteome sequencing, quality control, and standardization can be obtained in the study by Wingo et al.³⁵ After analysis and quality control, the ROS/MAP proteome (N=376) identified a total of 1,475 proteins that showed a significant cis-association with genetic variation. The Banner proteome (N=152) identified 1,139 proteins that showed a significant cis-association with genetic variation.

Functional exploration of identified candidate genes

We used Metascape's online analytical tool (<http://metascape.org>) to explore the functions of genes identified by our GWAS and PWAS, including Gene Ontology (GO), pathway analysis. GO was used for gene function classification and annotation, Pathway Analysis was used to analyze a specific classical metabolic or regulatory network of genes, proteins or molecules. All genes in the genome are used as the enrichment background. The terms with *P*-value<0.05, minimum count of 3, and enrichment factor>1.5 were collected, then group them into clusters based on the similarity of their members.

Results

General population characteristics

In our study, we analyzed seven different pain phenotypes in two depression samples, defined by self-reported depression status and PHQ score ≥ 10. Table 1 details the general characteristics of study samples.

Table 1. General population characteristics of depression patients

Study samples	Pain phenotypes	Number/ (Case/Control)	Sex (Male)	Age ± SD
Self-reported depression	Headache	8310/7742	4765(29.68%)	53.84 ± 7.59
	Neck or shoulder pain	12062/4432	5524(33.49%)	55.56 ± 7.64
	Stomach or abdominal pain	4287/2828	2318(32.58%)	53.94 ± 7.97
	Back pain	13248/4636	6418(35.89%)	55.63 ± 7.80
	Hip pain	6713/1622	2378(28.53%)	56.95 ± 7.50
	Knee pain	11514/2669	5091(35.90%)	56.51 ± 7.50
	Multisite chronic pain	58349	20345(34.87%)	55.72 ± 7.74
PHQ score ≥ 10	Headache	1296/1066	762(32.26%)	51.90 ± 7.31
	Neck or shoulder pain	1724/537	839(37.11%)	53.32 ± 7.55
	Stomach or abdominal pain	744/390	379(33.42%)	51.90 ± 7.64
	Back pain	1848/579	951(39.18%)	53.09 ± 7.83
	Hip pain	944/189	359(31.69%)	54.65 ± 7.62
	Knee pain	1556/301	742(39.96%)	53.98 ± 7.54
	Multisite chronic pain	6593	2460(37.31%)	53.13 ± 7.67

Abbreviations: SD, age was described as mean ± standard deviation (SD), PHQ score, patient health questionnaire (PHQ) is used to describe the depression.

GWAS analysis results

For self-reported depression samples, significant associations ($P_{\text{GWAS}} < 5.0 \times 10^{-8}$) were found at the rs12627973 ($P_{\text{GWAS}} = 4.48 \times 10^{-8}$), rs2627943 ($P_{\text{GWAS}} = 4.73 \times 10^{-8}$) and rs62236743 ($P_{\text{GWAS}} = 4.76 \times 10^{-8}$) of *TRIOBP* gene for the stomach or abdominal pain, as well as rs56154708 ($P_{\text{GWAS}} = 2.77 \times 10^{-8}$) of *SLC9A9* gene for MCP. Additionally, four SNPs of *SLC9A9* gene showed suggestive association signals for MCP, including rs10513209 ($P_{\text{GWAS}} = 9.19 \times 10^{-8}$), rs765265245 ($P_{\text{GWAS}} = 9.16 \times 10^{-8}$), rs62269778 ($P_{\text{GWAS}} = 9.07 \times 10^{-8}$), and rs62269777 ($P_{\text{GWAS}} = 9.06 \times 10^{-8}$).

For the depression patients with PHQ score ≥ 10, significant associations were detected at rs201595898 ($P_{\text{GWAS}} = 1.51 \times 10^{-8}$), rs45511696 ($P_{\text{GWAS}} = 1.63 \times 10^{-8}$) and rs45598235 ($P_{\text{GWAS}} = 1.64 \times 10^{-8}$) of *ADGRF1* gene for the neck or shoulder pain. The visualization of the results is shown in Figure 1. Other detailed results are shown in Table 2.

Table 2. GWAS results of different pain phenotypes in depression patients.

Objects	Pain phenotypes	SNP	CHR	Gene	OR	SE	P-Value
Self-reported depression	Multisite chronic pain	rs56154708	3	SLC9A9	0.932	0.013	2.77×10^{-8}
		rs10513209	3	SLC9A9	0.935	0.013	9.19×10^{-8}
		rs765265245	3	SLC9A9	0.933	0.013	9.16×10^{-8}
		rs62269778	3	SLC9A9	0.935	0.013	9.07×10^{-8}
		rs62269777	3	SLC9A9	0.935	0.013	9.06×10^{-8}
	Stomach or abdominal pain	rs12627973	22	TRIOBP	0.745	0.054	4.48×10^{-8}
		rs1004890	22	–	0.745	0.054	4.57×10^{-8}
		rs12627943	22	TRIOBP	0.746	0.054	4.73×10^{-8}
		rs62236743	22	TRIOBP	0.746	0.054	4.76×10^{-8}
PHQ score ≥ 10	Neck or shoulder pain	rs201595898	6	ADGRF1	0.305	0.209	1.51×10^{-8}
		rs45511696	6	ADGRF1	0.318	0.203	1.63×10^{-8}
		rs45598235	6	ADGRF1	0.318	0.203	1.64×10^{-8}

Abbreviations: SNP, single nucleotide polymorphism, CHR, chromosome, OR, odds ratios, SE, standard error, PHQ score, patient health questionnaire (PHQ) is used to describe the depression. $P_{\text{GWAS}} < 5.0 \times 10^{-8}$ and $P_{\text{GWAS}} < 1.0 \times 10^{-5}$ were defined as significant and suggestive associations, respectively.

LDSC analysis results

LDSC analysis identified multiple genetic correlations between pain traits and mental disorders, such as MCP and ADHD ($\text{genetic correlation}(\text{rg}) = 0.123$, $P_{\text{LDSC}} = 0.039$), MCP and PTSD ($\text{rg} = 0.217$, $P_{\text{LDSC}} = 0.029$) in self-reported depression patients. In addition, neck or shoulder pain ($\text{rg} = 0.222$, $P_{\text{LDSC}} = 0.001$) and MCP ($\text{rg} = 0.223$, $P_{\text{LDSC}} = 0.012$) were correlated with ADHD in depression patients with PHQ score ≥ 10 . Table 3 showed the genetic associations between different pain phenotypes and seven psychiatric disorders in depression populations.

Table 3. The genetic correlation between different pain phenotypes and seven psychiatric disorders in depression patients.

Objects	Pain phenotypes	AD		Anxiety		ADHD		ASD		BD		MDD		PTSD	
		rg	P	rg	P	rg	P	rg	P	rg	P	rg	P	rg	P
Self-reported depression	Knee pain	0.309	0.256	0.388	0.375	0.109	0.572	0.475	0.302	0.029	0.821	0.039	0.685	0.0061	0.978
	Multisite chronic pain	0.111	0.222	0.191	0.201	0.123	0.039	0.053	0.361	0.019	0.683	0.083	0.050	0.217	0.029
PHQ score ≥ 10	Neck or shoulder pain	0.135	0.243	0.263	0.221	0.222	0.001	0.100	0.124	0.069	0.204	0.026	0.564	0.002	0.987
	Stomach or abdominal pain	-0.083	0.597	-0.244	0.651	0.035	0.842	-0.067	0.790	-0.111	0.488	0.059	0.433	-0.093	0.649
	Multisite chronic pain	0.661	0.048	0.120	0.285	0.223	0.012	0.077	0.367	0.027	0.676	0.105	0.056	-0.078	0.508

Abbreviations: AD, alzheimer's disease, ADHD, attention-deficit hyperactivity disorder, ASD, autism spectrum disorder, BD, bipolar disorder, MDD, major depressive disorder, PTSD, post-traumatic stress disorder, SCZ, schizophrenia. PHQ score, patient health questionnaire (PHQ) is used to describe the depression. rg, genetic correlation. P values < 0.005 were considered as significant for genetic correlations. Those significant P values were in bold.

PWAS analysis results

Figure 2 and 3 summarizes the results of PWAS of different pain traits in depression patients. For PWAS with Banner reference weights, a total of 15 genes related to cis-regulated brain protein abundance were identified for the stomach or abdominal pain, such as *MLC1* ($P_{\text{PWAS-Banner}} = 4.80 \times 10^{-3}$) and *GSTM3* ($P_{\text{PWAS-Banner}} = 3.38 \times 10^{-2}$), etc. And 17 significant related genes were identified for MCP, such as *SIRPA* ($P_{\text{PWAS-Banner}} = 3.65 \times 10^{-2}$) and *TPRG1L* ($P_{\text{PWAS-Banner}} = 3.38 \times 10^{-2}$). 8 genes were identified for the neck or shoulder pain, such as *MCEE* ($P_{\text{PWAS-Banner}} = 6.00 \times 10^{-4}$) and *P2RX7* ($P_{\text{PWAS-Banner}} = 3.54 \times 10^{-2}$). Comparing the significant genes, there were 2 overlapping genes (*GSTM3* and *MLC1*) identified for both the stomach or abdominal pain phenotype and MCP, while 1 overlapping gene (*MCEE*) for stomach or abdominal pain and neck or shoulder pain, as well as 1 overlapped gene (*NAV1*) for MCP and neck or shoulder pain.

For PWAS using Rosmap reference weights, multiple genes were also identified, such as *MICAL1* ($P_{\text{PWAS-Rosmap}} = 3.43 \times 10^{-3}$) and *STAM2* ($P_{\text{PWAS-Rosmap}} = 1.19 \times 10^{-2}$) for stomach or abdominal pain phenotype, *SIRPA* ($P_{\text{PWAS-Rosmap}} = 2.24 \times 10^{-2}$) and *TPRG1L* ($P_{\text{PWAS-Rosmap}} = 3.29 \times 10^{-2}$) for MCP, *SLC30A9* ($P_{\text{PWAS-Rosmap}} = 2.78 \times 10^{-3}$) and *MRPL10* ($P_{\text{PWAS-Rosmap}} = 4.30 \times 10^{-2}$) for neck or shoulder pain phenotype. Comparing the significant genes found 1 overlapping gene (*ARHGEF10*) identified for both stomach or abdominal pain and MCP.

We also compared above PWAS results using respectively the Banner and Rosmap reference weights. We found two overlapping genes, *SIRPA* ($P_{\text{PWAS-Banner}} = 3.65 \times 10^{-2}$, $P_{\text{PWAS-Rosmap}} = 2.24 \times 10^{-2}$) and *TPRG1L* ($P_{\text{PWAS-Banner}} = 3.38 \times 10^{-2}$, $P_{\text{PWAS-Rosmap}} = 3.29 \times 10^{-2}$) for MCP. Detailed PWAS analysis results can be found in Supplementary Information Table 3.

Functional exploration results

After pathways and processes enrichment analysis of the significant genes identified by GWAS and PWAS, a total of 56 GO terms were obtained. These GO terms are mainly involved in sulfur compound metabolic process, regulation of actin filament organization, tRNA metabolic process, signal release, chemical synaptic transmission et al. The biological processes or functional pathways of the 16 clusters detected in the enrichment analysis were summarized by the Bubble plot, and the detailed results were shown in Figure 4.

Discussions

Previous studies on pain symptoms have suggested that pain mainly involves peripheral, spinal and central effects, including various factors that affect nociceptive perception, inflammatory response, and the neural pathways of pain centers and pain signals in the brain.^{36,37} In addition, a large number of studies have found that there are complex interactions and common genetic risk factors between depression and pain symptoms.^{12,38} Such as, some studies have found that depression can affect changes in multiple brain regions, most commonly in areas such as prefrontal cortex(PFC), anterior cingulate cortex (ACC), hippocampus and amygdala, where gray matter volume loss and alterations in activity similar to those that occur in chronic pain.^{38,39}Neuroimaging

studies have also revealed the close relationship between brain regions (somatosensory, IC ACC, PFC and thalamus) involved in the integration of pain sensation and emotions and the regions regulated by depression.⁴⁰ These common influencing factors may cause differences in pain susceptibility genes between depression patients and the general population. However, to our knowledge, studies exploring the genetic mechanisms of pain in patients with depression are limited, and the corresponding susceptibility genes remain unclear. Therefore, we conducted GWAS studies on different pain phenotypes in patients with depression, and identified three candidate genes associated with different pain phenotypes. These candidate genes not only have multiple functions affecting psychiatric disorders, nervous system development and neurogenesis, but it is noteworthy that some genes are also involved in physiological processes affecting pain symptoms, such as *ADGRF1* identified for neck or shoulder pain, *SLC9A9* gene for MCP and *TRIOBP* for stomach or abdominal pain.

ADGRF1 (adhesion G protein-coupled receptors) is a group of specific target receptors for synaptic amides that are highly expressed in neural stem cells and the brain during development.⁴¹ Its ligand, N-Docosahexaenoylamine (Synaptamide), is an endocannabinoid metabolite. This signaling pathway can not only by influencing the neurogenic and synaptic genes expression, induction of neurogenesis of hippocampus and cortex neurons and synapses, and the neuronal differentiation of neural stem cells, can also ring through cyclic adenosine monophosphate (cAMP) to transmit anti-inflammatory signals, inhibiting the expression of pro-inflammatory genes and pro-inflammatory cytokines.^{41,42} Because of these biological functions, synaptamide play a role in improving cognitive function and neuronal plasticity in neuropathic pain.⁴³ What's more, Park et al. demonstrated the immunomodulatory effects of *ADGRF1* in the brain and in the periphery, and jointly promoted the anti-neuroinflammatory effects of synaptamide in systemic inflammatory conditions. These results suggest that *ADGRF1* mediated inhibition of innate immune cell activation may be a novel therapeutic strategy for controlling brain and/or peripheral inflammation and related diseases.⁴⁴

SLC9A9 (solute carrier family 9, member A9) mainly encodes sodium/proton exchanger 9 (NHE9), It is expressed in many brain tissues and modulates luminal pH of circulating endosomes, which are important organelles for synaptic transmission and plasticity.⁴⁵ And *SLC9A9* pathway is associated with long-term potentiation, which underlies cognitive functions that are frequently disrupted in learning and memory, ADHD, and ASD.⁴⁶ Previous studies have found that changes in *SLC9A9* gene expression and protein function are associated with a variety of human diseases, such as ADHD, ASD et al.⁴⁷ In addition, a protein-protein interaction network pathway analysis showed that *SLC9A9* is also involved in oxidative stress, nociception and other functions.⁴⁶ Since there are multiple overlapping factors between the functions involved in *ADGRF1* and *SLC9A9* and the influencing factors of pain symptoms, we speculate that two genes are associated with the pain in patients with depression by influencing the factors of pain symptoms. Further studies are still needed to verify our speculation.

TRIOBP gene primarily encodes TRIO and F-actin binding proteins, which are involved in neural tissue development and control actin cytoskeleton organization, cell motility and cell growth.⁴⁸ Among them, several studies have implicated that *TRIOBP-1* is involved in schizophrenia by forming protein aggregates in the brain.⁴⁹ At present, studies of *TRIOBP* gene are limited, and further studies are needed to confirm its possible etiological association with pain symptoms.

Among the candidate genes associated with different pain phenotypes identified by PWAS, several candidate genes, such as *P2RX7* and *SIRPA*, are associated with biological mechanisms that influence pain symptoms or participate in the pain process. *P2RX7* (purinergic receptor P2X 7) is a non-selective cationic channel activated by extracellular ATP. It is mainly expressed in the peripheral and central nervous system and immune system. Activation of *P2RX7* not only contributes to pro-inflammatory response to injury or bacterial invasion and mediates apoptosis, but also plays a role in chronic inflammation and neuropathic pain.⁵⁰ Such as, an animal study revealed that *P2RX7* may promote pain modulation through its effect on peripheral tissue damage and altered central nervous system processing in clinical pain states.⁵¹ Kambur's study reinforces this evidence and suggests that *P2RX7* gene and genetic variants may be involved in regulating human pain sensitivity.⁵⁰ In addition, previous studies have found that the *P2RX7* variant is associated with a higher risk of psychiatric disorders such as bipolar disorder and depression, and that the *P2RX7* receptor is involved in psychosis related pathways, such as synaptic plasticity, neurotransmission, and immune regulation.⁵²

It is worth noting that *SIRPA* gene was overlapping genes in two PWAS studies with different reference weights. *SIRPA* gene mainly encodes proteins that are members of the signal-regulatory-protein (SIRP) family, which are involved in signal transduction mediated by various growth factor receptors. Previous studies have found that cleavage of signal-regulatory-protein α (SIRP α) is related to enhanced inflammatory signaling,⁵³ CD47 is a demonstrated ligand for this receptor protein, and its signaling pathway, CD47-SIRP α , is involved in the regulation of immune homeostasis and neuronal networks.⁵⁴ What's more, Haiyue Zhang et al revealed the importance of CD47 and SIRP α in the neuroinflammatory process of central nervous system diseases.⁵⁵ Overall, *P2RX7* has been shown to be directly involved in the regulation of chronic pain, while *SIRPA* is mainly involved in the biological process of influencing factors of pain symptoms, so it can be speculated that they may influence pain symptoms by regulating and participating in inflammatory responses. Further studies are needed to confirm our speculation. In addition, among the numerous candidate genes identified in the PWAS study, many genes are also associated with psychiatric disorders, nervous system development, and neuronal conduction. For example, *PPM1F*⁵⁶ and *GSTM3*⁵⁷ et al.

In the calculation results of genetic correlation with different psychiatric disorders, we found that ADHD, and PTSD were significantly positively correlated with different pain phenotypes, reflecting the possible common genetic structure. It is particularly noteworthy that the genetic positive correlation between ADHD and MCP phenotype was consistent with the significant association gene (*SLC9A9*) identified in the GWAS of MCP. *SLC9A9* gene pathway is associated with long-term potentiation, which is the basis of cognitive functions that are frequently disrupted in ADHD.⁴⁶ This further indicates that ADHD and MCP phenotype share the common genetic structure, and also reflects pleiotropy, in which specific genetic alleles may increase the risk of both phenotypes.⁵⁸

In addition, enrichment analysis revealed that significant genes were associated with multiple biological processes and functional pathways. Some of these related biological processes and functional pathways can directly or indirectly affect pain symptoms. For example, sulfur compound metabolism process,

previous studies have found that sulfur compounds (such as hydrogen sulphide) can relieve pain symptoms and inflammation⁵⁹, so significant genes may regulate the pain of patients with depression by participating in sulfur compound metabolism process, What's more, some studies have also found that signal release and chemical synaptic transmission are involved in the biological process of pain symptoms⁶⁰, and the biological relationship between other pathways and pain symptoms needs to be further studied.

Overall, one advantage of our study is the use of a large sample size from the UK Biobank, which can eliminate statistical noise by overcoming potential confounding factors such as selection biases and heterogeneity. In addition, compared with previous pain GWAS studies, our research focused more on multiple pain phenotypes in patients with depression. Based on GWAS, PWAS study and LDSC analysis were further used to explore the potential biological mechanisms related to pain in patients with depression from the perspective of protein expression level and genetics.

Nevertheless, it is worth noting that our research has some limitations. First, all data in our research were derived from the UK Biobank, and the research participants were limited to depression patients of European descent. When applying the research results to different populations, the impact of genetic backgrounds differences on the results should be considered, Secondly, because the phenotyping of pain in the UK Biobank was based on a specific non-standard pain-related questionnaire, it may result in pain phenotypes being broadly defined and not filtered by other potentially relevant information about the nature, duration or intensity of pain. Finally, genes significantly associated with pain symptoms were identified in our study, and while previous studies have suggested that they play a role in neurological function and disease, there is no direct evidence that they are involved in pain symptoms, and further research is needed to confirm this.

In summary, through GWAS and PWAS analysis, we found several susceptibility genes significantly associated with pain phenotype in patients with depression, What's more, LDSC analysis found that there was a significant genetic correlation between different pain phenotypes and ADHD and PTSD, suggesting that there may be a common genetic structure. These findings contribute to the understanding of the biological mechanism of pain phenotype in patients with depression and provide new clues for the study of its pathogenesis.

Declarations

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Institutional Review Board Statement: This study has been approved by UK Biobank (Application 46478) and obtained participants' health-related records.

Data Availability Statement: The UK Biobank data are available through the UK Biobank Access Management System <https://www.ukbiobank.ac.uk/> (accessed on 20 December 2020). We will return the derived data fields following UK Biobank policy, in due course, they will be available through the UK Biobank Access Management System.

Author Contributions: Z.Z. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y.W., Y.J. and F.Z. conceptualized and designed the study. All authors contributed in acquisition, analysis, and interpretation of the data. Z.Z. drafted the manuscript. F.Z., L.L. helped with critical revision of the manuscript for important intellectual content. H.Z. performed statistical analysis. Y.W., Y.J. and F.Z. provided administrative, technical, or material support. F.Z. supervised the study. All authors have read and agreed to the published version of the manuscript.

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Figures

Figure 1

Manhattan plot of different pain phenotypes in patients with depression. (a) Multisite chronic pain, a SNP allele was found to be significantly associated with MCP (b) Stomach or abdominal pain phenotype, four independent SNP alleles were significantly associated with stomach pain or abdominal pain phenotype. (c) Neck or shoulder pain phenotype, three independent SNP alleles were significantly associated with Neck or shoulder pain phenotype. Biobank Genomic coordinates are displayed along the X-axis, with the negative logarithm of the association P value for each SNP displayed on the Y-axis, meaning that each dot on the Manhattan plot signifies a SNP. The red line indicates the P-value threshold for genome-wide significance ($P_{\text{GWS}} < 5 \times 10^{-8}$) while the blue line indicates P-value threshold for suggestive significance ($P_{\text{GWS}} < 1 \times 10^{-5}$).

Figure 2

PWAS results of Banner reference weights for different pain phenotypes in patients with depression. (a) Multisite chronic pain, 17 candidate genes were found to be significantly associated with MCP. (b) Stomach or abdominal pain phenotype, 16 candidate genes were significantly associated with stomach pain or abdominal pain phenotype. (c) Neck or shoulder pain phenotype, 8 candidate genes were significantly associated with Neck or shoulder pain phenotype. The results of the PWAS study are shown through the Manhattan plot. These candidate genes may contribute to the biological mechanisms of pain in depressed patients through their cis-regulated brain protein abundance. The red line indicates the P-value threshold for Proteome-wide significance ($P < 0.05$).

Figure 3

PWAS results of Rosmap reference weights for different pain phenotypes in patients with depression. (a) Multisite chronic pain, 22 candidate genes were found to be significantly associated with MCP. (b) Stomach or abdominal pain phenotype, 15 candidate genes were significantly associated with stomach pain or abdominal pain phenotype. (c) Neck or shoulder pain phenotype, 14 candidate genes were significantly associated with Neck or shoulder pain phenotype. The results of the PWAS study are shown through the Manhattan plot. These candidate genes may contribute to the biological mechanisms of

pain in depressed patients through their cis-regulated brain protein abundance. The red line indicates the P-value threshold for Proteome-wide significance ($P < 0.05$).

Figure 4

Bubble plot of enrichment analysis. This bubble plot showed biological processes or functional pathways of the 16 clusters in the enrichment analysis results.

Supplementary Files

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