Original Article

Screening key genes related to neuropathic pain-induced depression through an integrative bioinformatics analysis

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Background: Neuropathic pain (NP) is often accompanied by sleep disorders, anxiety, depression and other complications, and the pathogenesis is still unclear. Some drugs can relieve patients' pain, but the overall effect is not good. We screened for the key genes related to NP-induced depression based on bioinformatics.

Methods: The dataset of GSE92718 was obtained from the Gene Expression Omnibus database, data mining was conducted based on R language, the genes modules were screened by weighted correlation network analysis, Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed, a protein-protein interaction (PPI) network was constructed in the STRING database, and hub genes were screened according to degree value.

Results: Seven modules were obtained and built to identify the relationships between the NP-induced depression and the modules, weighted gene co-expression network analysis (WGCNA) was used to identify gene modules closely related to the experimental group. The GO annotations of depression-related genes mainly enriched in protein polyubiquitination, regulation of chromosome organization, mitochondrial matrix, mitochondrial protein-containing complex, etc. KEGG enrichment analysis results were: Alzheimer's disease, Huntington's disease, ribosome, thermogenesis, prion disease, non-alcoholic fatty liver disease, diabetic cardiomyopathy, oxidative phosphorylation, retrograde endocannabinoid signaling, 2-oxocarboxylic acid metabolism. PPI network analysis showed that *Polr2f*, *Rps13*, *Mrpl2*, *Mrpl40*, *Mrpl34*, and *Ndufs8* were more highly expressed in NP-induced depression. Functional analysis of key genes showed that these genes were related to mitochondrial translation termination, respiratory chain complex I, mitochondrial, mRNA Splicing (minor pathway), and of rRNA processing in the nucleolus and cytosol (major pathway).

Conclusions: The key genes of depression induced by NP are *Polr2f*, *Rps13*, *Mrpl2*, *Mrpl40*, *Mrpl34*, and *Ndufs8*.

Keywords: Bioinformatics analysis; depression; hub genes; neuropathic pain (NP)

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Introduction

Neuropathic pain (NP) is caused by functional abnormalities or diseases of the peripheral and central nervous systems (1). NP patients often have severe spontaneous pain, such as burning, pricking, electric shock, tearing, or abnormal sensory function of the skin (2). The incidence of NP in the general population is 7–10%, and for ≈60% of patients' treatment does not give effective pain relief, so NP is accompanied by different degrees of sleep disorder, anxiety, depression and other complications, resulting in a serious decline in the quality of life (3). The mechanism of NP is still unclear, and it may have a variety of causes, such as herpes zoster virus infection, spinal cord injury, diabetic neuropathy, stroke, or neurotoxicity of drugs or radiotherapy. At present, Western medicine mostly uses tricyclic antidepressants, anticonvulsants, opioid analgesics and other drugs for treatment. Although they can relieve some pain, they have many adverse side effects, and the recurrence rate is high after long-term drug use, so the overall treatment effect is not good. Although opioids can relieve pain, they are not used as first-line drugs due to their negative effects (4).

Chronic pain caused by damage or abnormal function of central neurons and surrounding fibers is characterized by abnormal pain sensation and even spontaneous pain. The formation mechanism of NP is complex (5), but based on the site of nervous system damage, NP can be divided into peripheral and central NP. The peripheral mechanism mainly includes changes in ion channels, inflammatory factors and the excitation of sympathetic nerves. The central mechanism is mainly structural plasticity of the spinal cord, central sensitization, activation of glial cells and so on. Depression is typically characterized by persistent low mood for at least 2 weeks, which is very different from what is commonly referred to as a "bad" mood. In severe cases, self-injury and suicide behavior can manifest, accompanied by delusions, hallucinations, psychotic symptoms, such as severe depressive stupor. The main clinical manifestations of depression are upset, irritability, low mood, slow thinking, loss of motivation, loss of libido, self-isolation and unwillingness to communicate with people, memory loss and other symptoms (6,7).

By reviewing relevant databases, we found that sequencing of NP has been completed and uploaded to the Gene Expression Omnibus (GEO) database, but in-depth mining of relevant data and screening of core hub genes still needs to be carried out (8). Therefore, based on the R language data mining method, we conducted deep mining of the GSE92718 dataset and obtained some valuable results, which are reported here. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5820/rc).

Highlight box

Key findings

- The key genes of depression induced by NP are *Polr2f*, *Rps13*, *Mrpl2*, *Mrpl40*, *Mrpl34*, and *Ndufs8*.

What is known and what is new?

- The sequencing of NP has been completed and uploaded to the Gene Expression Omnibus (GEO) database;
- We conduct in-depth mining of relevant data and screening core hub genes.

What is the implication, and what should change now?

- It is urgent to pay attention to the popularization, prevention and treatment of depression to reduce the burden of chronic pain.

Methods

Basic chip information

The bioinformatics analysis data were downloaded from the GEO database. The dataset is coded as GSE92718 and is based on the GPL6887 platform. Basic information on the dataset: anxiety-depression-like behavior in C57BL/6J male mice "Mus musculus" was induced by NP, and transcriptome analysis was performed after samples of anterior cingulate cortex were taken.

Weighted gene co-expression network analysis (WGCNA)

First, the chip data were normalized to correct any errors caused by different batches. Next, the GPL6887 platform was used to annotate the chip data and convert the gene symbols. Empty values, duplicate values, and rows with no gene symbols were removed. The R language WGCNA package was used to screen gene modules closely related to NP-induced depression, and the genes in the modules were extracted for further analysis.

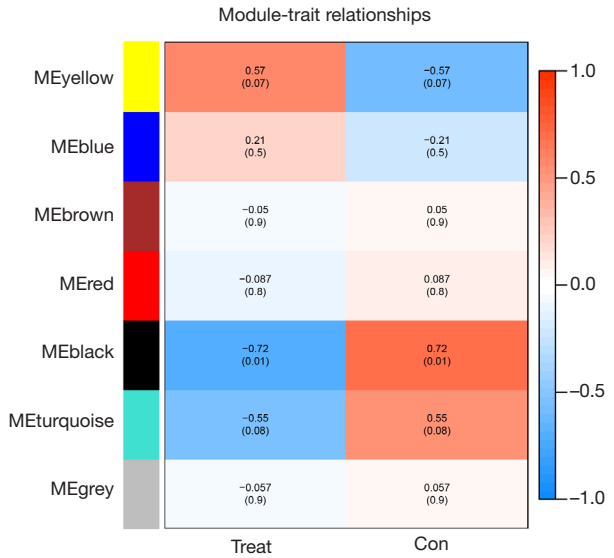

Figure 1 Correlation between the gene module and clinical traits of neuropathic pain-induced depression. The number above represents the correlation coefficient in the square, and the number in brackets represents the P value. Con, control; ME, module eigengene.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses

After obtaining the related gene modules, the genes in the modules were imported into the 'clusterProfiler' R package for GO and KEGG signaling pathway enrichment analyses. A diagram of a signal pathway closely related to NP-induced depression was obtained. These results were imported into the GGploT2 program package of R language for visualization of relevant results and data.

Protein-protein interaction (PPI) network

PPI network systematically analyzes the interaction relationship of a large number of proteins in biological systems, which is of great significance for understanding the reaction mechanism of biological signals and energy metabolism under special physiological conditions such as diseases, and understanding the functional relationship between proteins. All the screened gene modules after GO and KEGG enrichment analyses were imported into the STRING database, and corresponding species were selected for the PPI network calculation and visualization. The analysis data were downloaded and the high-frequency core gene rankings were visualized as horizontal bar graphs.

Screening of key genes

We performed PPI network analysis again on the top 30 gene screened by the first PPI network analysis, so as to clearly show the interaction between key genes, and carefully identify the genes with the highest value. At the same time, we analyzed the functions and pathways of the above top 30 core genes through the online gene enrichment analysis tool Metascape, and the enrichment analysis results of functions and pathways were obtained, with a statistical significance of $P<0.05$.

Statistical analysis

Measurement data are expressed as the addition and subtraction of statistical standard deviation, and the mean between two groups was used for the independent sample *t*-test. Standard statistics are reported, and differences between groups of the two samples were analyzed: mean scores of the samples before and after treatment were compared, and conditions and data levels were estimated between the two counts. Where possible, the structure ratio and average rank (R) are expressed. Compared with Fisher X survey percentages, there are two different types of percentages. All data were calculated in R language.

Results

Screening related gene modules by WGCNA

We used WGCNA to identify gene modules with highly synergistic changes. Finally, 7 modules were built to identify the relationships between the NP-induced depression and the modules (*Figure 1*). The genes in the black module were highly correlated with the traits of NP-induced depression (P=0.01), which were selected for further analysis.

GO and KEGG enrichment analyses

GO covers three aspects of biology: cell component, molecular function and biological process. Each node in the annotation system is a description of a gene or protein, and each node represents a basic description unit (Term). The relationship between nodes is strictly maintained. The main GO enrichment analysis results were: protein polyubiquitination, regulation of chromosome organization, mitochondrial matrix, mitochondrial protein-containing complex, organellar ribosome, mitochondrial ribosome, organellar large ribosomal, mitochondrial large ribosomal

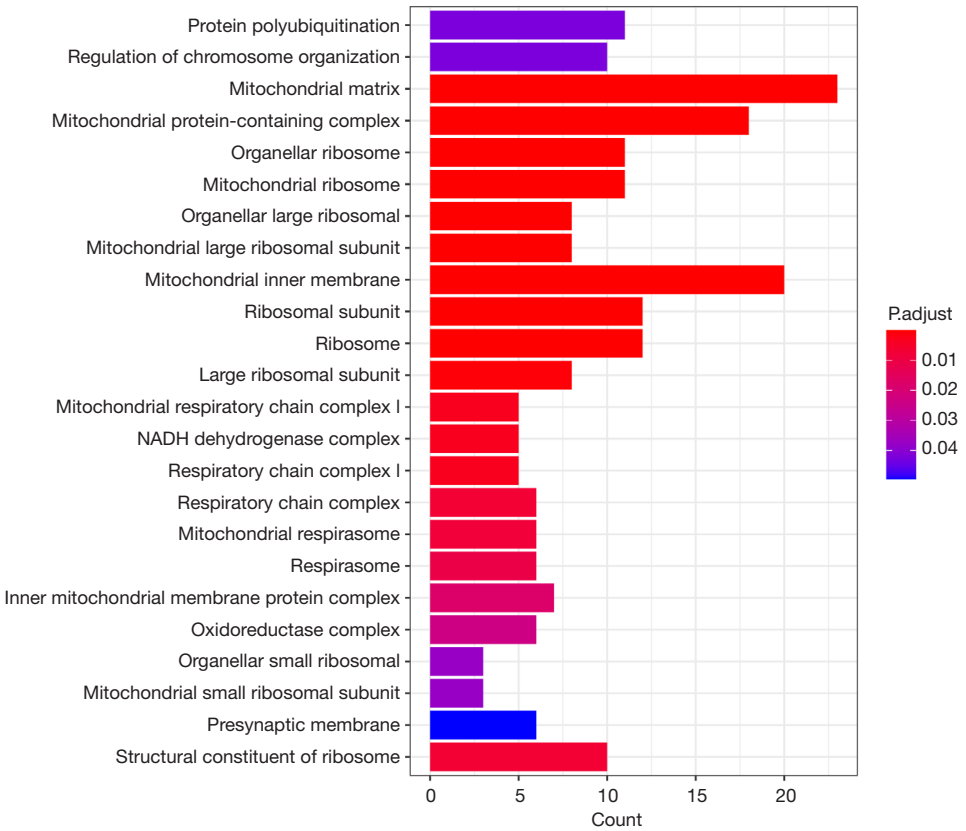

Figure 2 Gene ontology enrichment analysis of genes in the black module. GO, Gene Ontology.

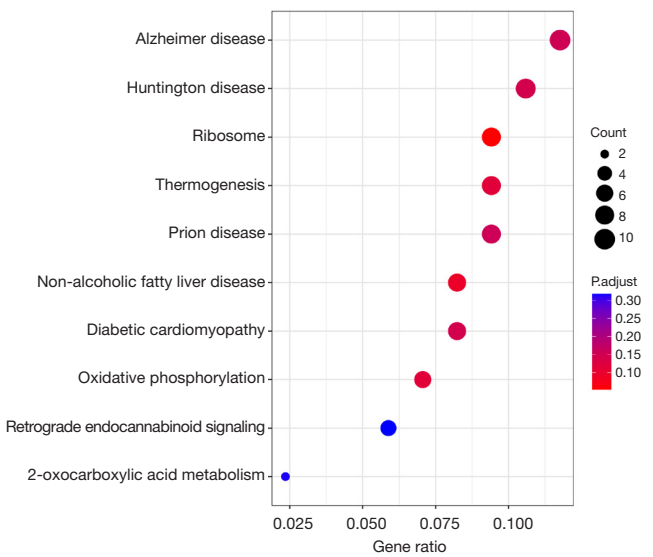

Figure 3 KEGG enrichment analysis of genes in the black module. KEGG, Kyoto Encyclopedia of Genes and Genomes.

subunit, mitochondrial inner membrane, ribosomal subunit, etc. (*Figure 2*).

KEGG is a database for genome deciphering. One of the major challenges in the post-genetic era is how to fully express and deduce cells and organisms on computers, so that genetic information can be used to make computational predictions about higher and more complex cellular activities and biological behaviors. The results of KEGG enrichment analysis were: Alzheimer's disease, Huntington's disease, ribosome, thermogenesis, prion disease, non-alcoholic fatty liver disease, diabetic cardiomyopathy, oxidative phosphorylation, retrograde endocannabinoid signaling, 2-oxocarboxylic acid metabolism (*Figure 3*).

The processing of proteins by the endoplasmic reticulum includes glycosylation, hydroxylation, acylation, disulfide bond formation, etc., the most important being glycosylation. Almost all proteins synthesized by the endoplasmic reticulum are finally glycosylated.

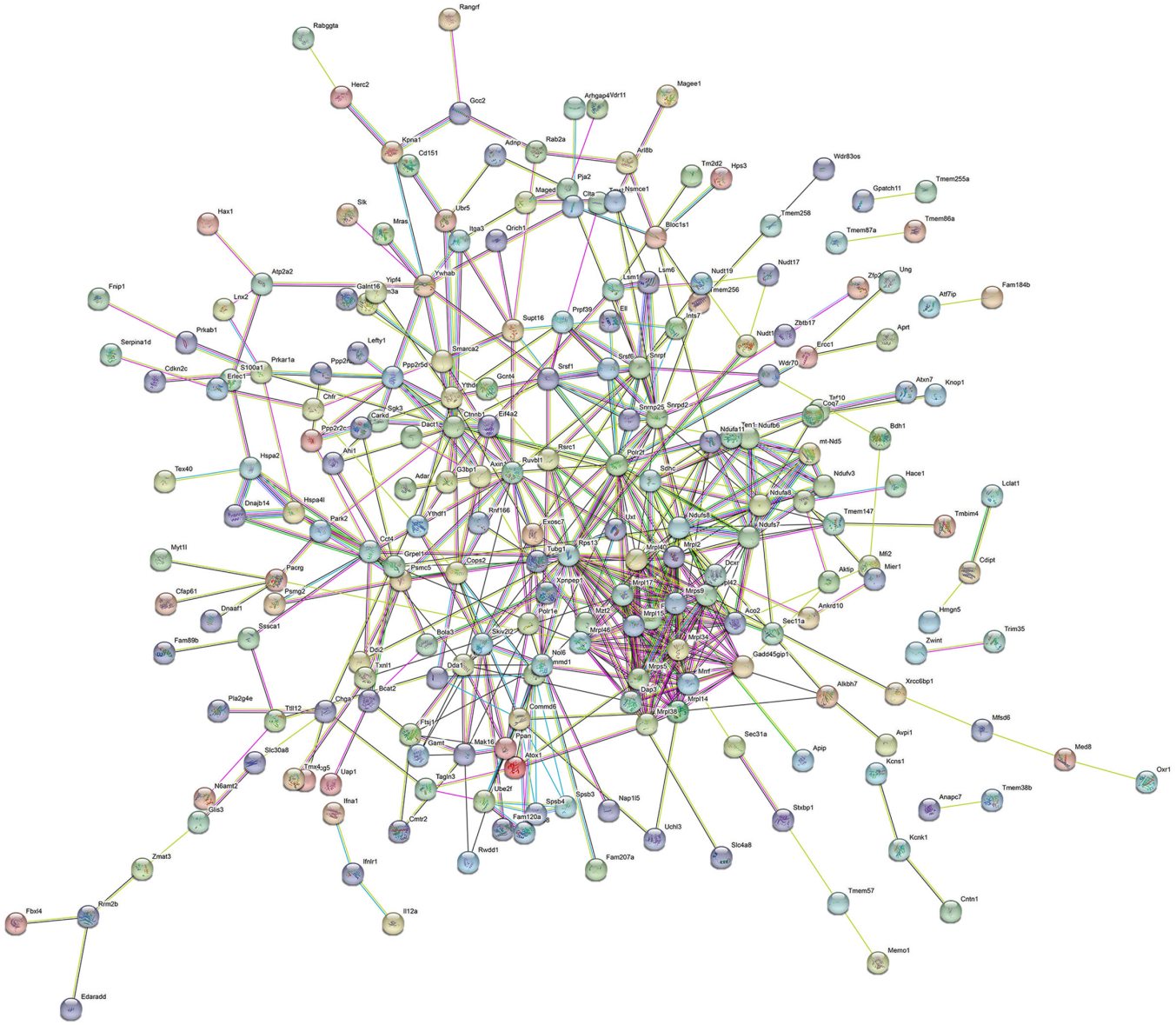

Figure 4 PPI network construction of key genes using STRING database. PPI, protein-protein interaction; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.

PPI network

The PPI network diagram obtained from the STRING database was shown in *Figure 4*. Each point represented a protein corresponding to a gene, and the interacting points were connected by lines. The more lines around the dot, the greater the chance of interaction. According to the analysis results, we obtained the genes with the highest degree values: *Commd1*, *Srsf1*, *Skiv212*, *Nol6*, *Pum3*, *Ruvbl1*, *Ndufa11*, *Ndufs7*, *Mrrf*, *Ndufa8*, *Mrpl42*, *Gadd45gip1*, *Aco2*, *Snrpf*, *Mrps5*, *Mrpl38*, *Mrps9*, *Mrpl17*, *Mrpl15*, *Dap3*, *Snrpd2*, *Mrpl46*, *Mrpl14*, *Ctnnb1*, *Ndufs8*, *Mrpl34*, *Mrpl40*, *Mrpl2*, *Rps13*, *Polr2f*, and their respective degree values were 20, 22, 22, 22, 24, 26, 26, 28, 28, 30, 30, 30, 30, 32, 32, 32, 34, 34, 34, 34, 36, 36, 36, 36, 38, 40, 44, 46, 50, 50 (*Figure 5*).

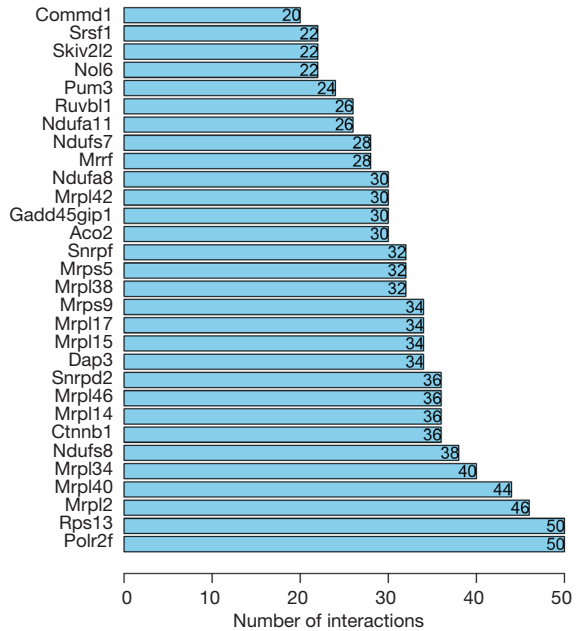

Figure 5 Rank and degree value of high-frequency genes in the PPI network. PPI, protein-protein interaction.

Screening of key genes

We performed PPI network analysis again on the key 30 genes, which was displayed in *Figure 6*. STRING was also used to verify protein interactions between key genes, and the results showed that *Polr2f*, *Rps13*, *Mrpl2*, *Mrpl40*, *Mrpl34*, and *Ndufs8* were significantly correlated with most of the key genes.

The above 30 key genes highly expressed in NP-induced depression were analyzed online by Metascape to obtain enrichment analysis of functions and pathways, mainly in mitochondrial translation termination, respiratory chain complex I, mitochondrial, mRNA splicing (minor pathway), and of rRNA processing in the nucleolus and cytosol (major pathway) (*Figure 7*).

Discussion

In the research, we recognize seven modules between the NP-induced depression group and control group. PPI network was used to identify core genes related with NP-

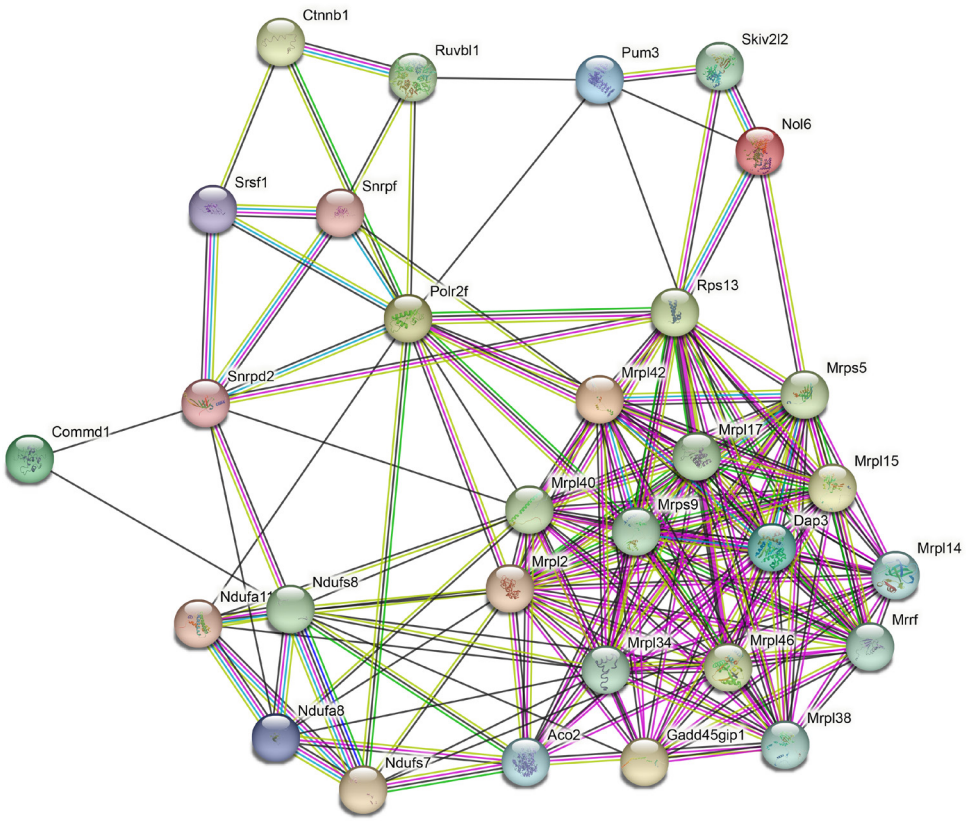

Figure 6 The PPI network of top 30 key genes. PPI, protein-protein interaction.

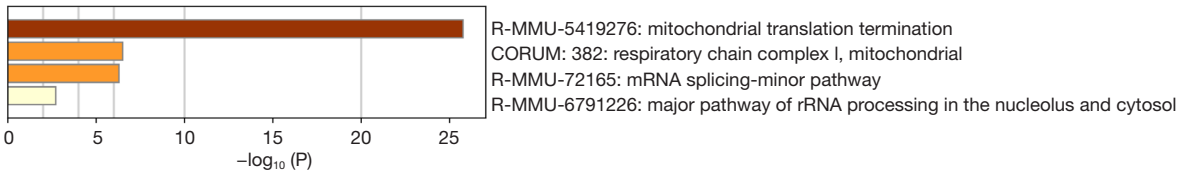

Figure 7 Function and pathway enrichment analysis results of top 30 key genes.

induced depression. NP (i.e., pain caused by overexcitation of nerves, regardless of the type of stimulation) is a subjective sensation (9-11). Pain itself is not a disease, but a signal from the nervous system (peripheral, central or local nerves) after some adverse stimulation. Pain is essentially a protective mechanism, a signal that can express very complex information (12). Based on the site of the pain, the nature of the pain and its severity, and the patient's perception, the diagnosis and treatment are selected (13-15).

Neuralgia often occurs with functional diseases or organic lesions such as early cancer. Patients have headaches, nerve pain or feel uncomfortable in a part of the body or it manifests as a somatization disorder, such as angina pectoris, gastrointestinal pain and other symptoms. The pain results directly from damage to the somatosensory system or from disease damage to the peripheral nerves, posterior roots of the spinal cord, and certain parts of the spinal cord and to the central nervous system. Clinically common diseases include trigeminal neuralgia, greater occipital neuralgia, glossopharyngeal neuralgia, sciatic neuralgia, etc. Only by assessing the etiology, lesion location and type, neurogenesis symptoms and signs can the correct conclusion be drawn (16). For example, if the pain is affecting the head and face, it is recommended to perform nuclear magnetic resonance imaging, because the early stage of certain craniocerebral tumors can manifest as nerve pain. Oral nutrition, such as B vitamins, may also assist with pain management (17), and conventional pain relievers such as carbamazepine and pregabalin can be given when the pain is severe and frequent.

The symptoms of NP are usually intermittent, burning, pinching, cutting, or even tearing pain distributed along the line of the nerve (18). The pain is often severe, with a short duration ranging from a few seconds to a few minutes. It can occur dozens or even hundreds of times per day. NP is not uncommon and although its etiology is still unclear, damage to a peripheral nerve in the excited state is considered as a major factor (19). Hyperexcitability changes in primary afferent neurons may be long-lasting.

Depression is generally believed to involve psychological, genetic, social and other factors, which are interconnected (20). According to the World Health Organization, there are more than 300 million patients with depression worldwide, and nearly 800,000 people commit suicide due to depression every year. Depression accounts for 10% of the total global burden of nonfatal diseases and causes more years of disability loss worldwide than other diseases (21).

Conventional Western medical and nursing interventions are the mainstay of the treatment of depression. With increasing research into traditional Chinese medicine (TCM) in recent years, it has begun to play an important therapeutic role. The TCM category is "depressive syndrome" depression "insomnia" and by adjusting qi activity, it can promote sleep quality, and improve the overall quality of life of the patient. Combined with Western therapeutic approaches, patients can experience humanistic, integrated, harmonious and comfortable treatment (22).

Many in-depth studies (23-25) have investigated depression, but the exact pathogenesis is still unclear. Depression is not a simple functional mental disorder, but a disease involving genetic, psychological, biochemical, social environment and other factors (26). Hypotheses to explain the pathogenesis of depression include the monoamine neurotransmitter hypothesis proposed by Schildkraut *et al.* (27), in which it is believed that the decline in monoamine neurotransmitter in the brain leads to depression. Each hypothesis has different entry points and different pathogenic mechanisms, but all of them potentially explain the pathogenesis of depression.

Treatment methods based on current research and theories are briefly described. Monoamine neurotransmitters are mainly secreted in the brain and adrenal gland, and include 5-hydroxytryptamine, norepinephrine and dopamine. They play a core role in brain development, emotion regulation and stress response (28). The antihypertensive drug reserpine can lead to severe depression in a small

number of patients, and isoniazid, a drug for the treatment of tuberculosis, can significantly improve depression. Reserpine will deplete monoamine neurotransmitters in the brain, and isoniazid is a monoamine oxidase inhibitor, which can improve the systemic function of serotonin and norepinephrine. At present, most antidepressants, including monoamine oxidase inhibitors, tricyclic and selective serotonin reuptake inhibitors, are derived from Schildkraut's hypothesis. However, this hypothesis has great limitations. For example, it cannot explain why patients can show an increase in the level of monoamine neurotransmitters in the brain after taking drugs for a few minutes, while the antidepressant effect only appears after a few weeks, and such antidepressants are only effective for 60–70% of patients. The pathogenesis of depression is far more complex than the monoamine hypothesis. It has been found that the expression of serotonin receptors in the hippocampus is decreased and that the noradrenergic neurons are presynaptic β (29). The downregulation of these two receptors is closely related to the occurrence of depression. The number and sensitivity of monoamine neurotransmitter receptors will also affect neurotransmission function, leading to depression. Because the monoamine neurotransmitter hypothesis was the first to be proposed and is the theoretical basis for most antidepressants, it still occupies an important position.

The hypothalamic pituitary adrenal (HPA) axis comprises the hypothalamus, pituitary, adrenal gland and downstream target organs. It is the regulatory hub of the human neuroendocrine immune network and plays an important role in maintaining homeostasis. When the human body is subjected to external pressure, the HPA axis, which is the main regulatory system of the stress response, will be activated, increasing the secretion of corticotropin-releasing hormone and glucocorticoids (GCs). Excessive GCs creates negative feedback to inhibit the activity of the HPA axis, and maintain the homeostatic level of the body's hormones. If the body is subjected to chronic, sustained stress, the level of GCs remains high, leading to desensitization of GCs receptors, further stimulating the HPA axis, and finally leading to obstacles in the negative feedback regulation between GCs and receptors (30). The HPA axis function continues to be hyperactive, forming a vicious cycle, and eventually leading to depression. In addition, if the secretion of neurotransmitters such as 5-hydroxytryptamine and acetylcholine in the human body decreases, the HPA axis function also decreases, leading to depression, violent impulses and other symptoms. Therefore, HPA axis hyperactivity is not only a prominent feature of patients with depression, but also a key factor in the pathogenesis and progression of depression.

The neuroplasticity hypothesis is a major breakthrough in the understanding of the etiology of depression. There is an inevitable relationship between neuroplasticity disorder and depression, with the occurrence of depression a result of changing the hippocampal structure, reducing the regeneration or increasing the apoptosis, of neurons, blocking the signal transduction pathway and impairing synaptic plasticity. The hippocampal volume of patients with depression is significantly smaller than that of unaffected people, and the degree of atrophy is directly proportional to the duration and severity of depression. The degree of hippocampal atrophy of patients receiving antidepressant treatment is significantly improved. The reduction in the hippocampal volume may be caused by excessive apoptosis of hippocampal neurons, the difficulty of regeneration and a decrease in synaptic plasticity. In addition, when the HPA axis is in a hyperactive state, high levels of GCs will also damage the hippocampus, causing degenerative changes in the pyramidal cells of the hippocampal neurons, resulting in the reduction of hippocampal volume and synaptic plasticity. The decreased synaptic plasticity may eventually lead to damage of neural circuits, which may lead to depression. Therefore, dysregulation of neuroplasticity is considered to be a key factor in the occurrence of depression.

The neurotrophic factor hypothesis, which is closely related to the neuroplasticity hypothesis, holds that the downregulation of the expression and function of neurotrophic factors, especially brain-derived neurotrophic factor (BDNF), is likely to lead to emotional depression, and thus trigger depression. BDNF is an important neurotrophic factor in the central nervous system, and essential for the growth and survival of neurons. A study found that the level of BDNF in the hippocampus of suicide victims with depression was significantly lower than normal, and the expression of BDNF in the brains of suicidal patients who had received antidepressant treatment was significantly higher than that of those who had not received treatment (31). The use of antidepressants can promote adult hippocampal neurogenesis and increase the expression of BDNF. Overall, BDNF may play an antidepressant role by regulating the growth, differentiation, injury, apoptosis of neurons and regulating the neuroendocrine network. Therefore, BDNF is also an important target in the study of the pathogenesis of depression.

Neurons are closely related to the pathogenesis and

treatment of depression, so more and more studies are focusing on the neuronal cascade signaling pathway. A study found that there were abnormalities in the molecular level of neuronal signal transduction in patients with depression, suggesting that the signal transduction process may play an important role in the pathogenesis of depression (32). The phosphatidylinositol-3-kinase protein kinase B signaling pathway is an important pathway that mediates the promotion of survival by a variety of growth factors, and it is an important connection for the treatment of depression (33).

Neuronal apoptosis, promoting BDNF release and enhancing synaptic plasticity delay the development of depression. According to previous studies, the hypothesis of a cellular molecular mechanism and the hypothesis of neuroplasticity are closely related and affect each other (34,35). The inflammation hypothesis speculates that the onset of depression may be related to the inflammatory state of the body. It holds that when the body is in an inflammatory state, proinflammatory cytokines were released (36). At present, patients with depression often show dysfunction of the immune system, impaired immune function of peripheral cells, and increased expression of interleukin-1, interleukin-6, and tumor necrosis factor-α. The levels of other proinflammatory cytokines are significantly lower than in unaffected people. Proinflammatory cytokines play an important role in the pathogenesis of depression by affecting monoamine neurotransmitters, the HPA axis and reducing BDNF. At present, increased proinflammatory cytokines is a marker to judge the onset of depression. Finding biomarkers and therapeutic targets of depression through the anti-inflammatory pathway has also become a new research strategy.

To sum up, depression is not only related to the nervous system, but also closely related to the immune and endocrine systems. Depression may be the result of the joint action of multiple systems and factors. The excitatory amino acid system may be involved in the pathogenesis of depression, especially the metabotropic glutamate receptor system and γ-aminobutyric acid receptor system. Glutamate is an important excitatory amino acid in the central nervous system and an important neurotransmitter in the hippocampus. The levels of metabotropic glutamate in the plasma and cerebrospinal fluid of patients with depression are significantly increased. The pathogenic mechanism may be that the high level of metabotropic glutamate activates the N-methyl-D-aspartate receptor located on the cell membrane of neurons, resulting in the opening of calcium channels, causing a large influx of calcium, intracellular calcium overload, and neuronal degeneration and even death. γ-Aminobutyric acid is an important inhibitory neurotransmitter in nerve tissue, and functional changes play a leading role in potential depressive mental diseases, Levels of γ-aminobutyric acid in the cerebrospinal fluid and plasma of depressed patients are decreased, which suggests that the excitatory amino acid system plays an important role in the course of depression and may be related to the balance between excitatory and inhibitory neurotransmitters. Protein interactions can usually be divided into physical and genetic interactions. Physical interaction refers to the binding or chemical reaction between proteins through spatial conformation or chemical bonds, which is the main research object of protein interaction. Genetic interaction refers to the interaction between proteins or coding genes influenced by other proteins or genes under special circumstances, often manifested as phenotypic changes. The protein interaction network applied the protein interaction detection technology based on protein interaction database (37).

Conclusions

The rate of recognition of depression by hospitals is less than 20%, and less than 10% of patients have received relevant drug treatment. At the same time, the occurrence of depression has begun to trend younger. Therefore, it is urgent to pay attention to the popularization, prevention and treatment of depression to relieve the burden of chronic pain, and this has been listed as the focus of national mental health research.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5820/rc

Conflicts of Interest: All authors have completed the

ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5820/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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