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ORIGINAL RESEARCH

Identification of Common Genes for Neuropathic Pain and Parkinson's Disease Based on Bioinformatics Analysis and Their Potential Value in the Diagnosis of Neuropathic Pain

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Background: Parkinson's disease (PD) is a common neurodegenerative disorder of the central nervous system. Neuropathic pain (NP) is a type of symptom that is often overlooked but significantly affects the quality of life of patients. Its etiology is complex, and the specific molecular mechanism is still unclear. This study aimed to systematically identify the common genes between PD and NP, and further explore their potential diagnostic value in NP of PD.

Methods: PD- and NP-related datasets were downloaded from Gene Expression Omnibus to identify differentially expressed genes (DEGs) in each dataset. Intersection of these DEGs yielded co-DEGs. A protein-protein interaction network was established for co-DEGs, and algorithms—Matthews Correlation Coefficient, Maximal Neighborhood Component, Edge Percolated Component, and Closeness—were applied to identify hub genes, resulting in co-hub genes. Receiver operating characteristic curves were plotted to assess diagnostic efficacy of co-hub genes for PD and NP. Differences in immune cell infiltration between disease and control groups were explored, along with miRNAs of co-hub genes and their single-cell expression profiles.

Results: Three co-hub genes—*CADPS*, *GDAP1*, and *SEZ6L2*—were identified. Expression of these genes demonstrated diagnostic accuracy for PD and NP. Th2 cells and Tregs exhibited differential infiltration between disease and control groups, with Tregs showing significant infiltration in the disease group. Eight miRNAs targeting co-hub genes were predicted, including hsa-miR-330-3p, hsa-miR-7977, and hsa-miR-325-3p. All three co-hub genes were highly expressed in neurons and astrocytes.

Conclusion: In summary, we identified three co-hub genes associated with both PD and NP. These findings provide valuable insights into diagnosis and treatment of these conditions.

Keywords: Parkinson's disease, neuropathic pain, biomarkers, diagnosis, treatment

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, with its core clinical manifestations including resting tremors, bradykinesia, muscle rigidity, and postural and gait disorders.[1] Additionally, non-motor symptoms such as depression, sleep disorders, and pain are also prevalent, significantly reducing the quality of life of patients.[2] The pathological features of PD are the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain, as well as the abnormal aggregation of α-synuclein forming Lewy bodies.[3] Epidemiological data show that the number of PD patients worldwide has exceeded 6 million, and it is expected to double by 2040.[4] Notably, PD often presents significant clinical comorbidity and pathological overlap with other neurodegenerative disorders (such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)).[5] For instance, AD and PD share a high degree of overlap in key pathological mechanisms such as abnormal protein aggregation and neurotransmitter imbalance.[6–8] Additionally, both DLB and PD present with abnormal aggregation of α-synuclein (deposition of Lewy bodies) in pathology, jointly constituting the Lewy disease spectrum; both often also

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have AD-like pathologies, such as β-amyloid plaques and tau protein tangles, demonstrating significant pathological overlap with AD.[9] These suggest that different neurodegenerative diseases may share potential pathogenic molecular mechanisms, which also pose a significant challenge for the diagnosis of PD. Currently, there is a lack of biomarkers that can achieve high sensitivity and specificity in the early stages of the disease, especially in the prodromal stage.[10] Therefore, it is crucial to identify reliable biomarkers that can be used for the precise early diagnosis of PD and the assessment of disease progression.

Accumulating studies suggest that PD is not limited to damage to the motor nerve pathways; its pathogenesis also involves similar multi-factor processes to other neurodegenerative diseases, including innate immune activation and the continuous release of inflammatory mediators. For example, the activation of central microglia cells and the infiltration of peripheral immune cells (such as monocytes and macrophages) in PD patients are considered important driving factors of neurodegeneration. These cells may play a protective role in the early stage of the disease by clearing abnormally aggregated α-synuclein and inhibiting its spread, delaying neuronal damage and disease progression.[11] Therefore, on the basis of screening molecular markers for early diagnosis of PD, further exploration of their potential immunological functions is helpful for deepening the understanding of the immune-related pathogenesis of PD and providing theoretical basis for targeted intervention strategies.

Neuropathic pain (NP) is a severe and debilitating symptom that can arise from various conditions, often limiting physical function and contributing to anxiety and depression.[12] A significant proportion of PD patients experience NP, as dopamine depletion alters neurophysiology, potentially amplifying pain stimuli.[13] In PD, NP is a nonspecific yet intense and treatment-resistant symptom.[14] NP is classified as radicular or central: radicular NP involves localized sensitivity and discomfort near nerves or nerve roots, while central NP results from altered pain processing due to PD.[13,15] Prevalence of radicular pain in PD ranges from 14% to 35%, significantly higher than the 10% observed in the general population.[16–18] This high prevalence may be linked to PD's pathophysiological changes. Early PD neuropathology often begins in limbic structures such as the amygdala and thalamic intralaminar nuclei, potentially causing generalized hypersensitivity to noxious stimuli and exacerbating pain symptoms.[19] Despite progress, the shared pathological mechanisms of PD and NP remain poorly understood, necessitating further research to identify effective diagnostic methods.

This study employed bioinformatics analysis to identify co-hub genes using PD- and NP-related datasets from the GEO database. Differences in immune cell infiltration between disease and control groups were investigated, and miRNAs and single-cell expression profiles of the co-hub genes were explored. Identifying diagnostic markers and therapeutic targets for PD and NP could improve the accurate diagnosis of comorbid conditions and provide effective therapeutic avenues for patients.

Materials and Methods

Data Download

The transcriptome data of PD and NP (GSE8397, GSE7621, GSE148434 and GSE24982) as well as the single-cell data (GSE243639) were downloaded from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database. Among them, GSE8397 contains 58 PD brain tissue samples and 36 normal control samples; GSE7621 contains 16 PD brain tissue samples and 9 normal control samples; GSE148434 contains 6 PD brain tissue samples and 4 normal control samples; GSE24982 contains 20 mouse NP model samples and 20 control samples; GSE243639 is the preprocessed single-cell sequencing data, including 15 PD samples and 14 normal samples. Due to the limitations of the GEO database, only the NP transcriptome data from mouse sources can be obtained at present. Although there are certain species differences in the neural system structure and immune regulation mechanisms between mice and humans, cross-species analysis may bring certain biological biases. However, existing investigation has shown that integrating the expression profile data of humans and mice is feasible and has reference value in the research of neurological diseases.[20] Our study is exempt from approval based on national legislation guidelines, such as item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

Data Processing and Differential Gene Analysis

Since the PD dataset GSE8397 used two sequencing platforms (GLP96 and GPL97), we employed the combat algorithm from the "sva" R package[21] to correct the batch effects in the data obtained from the two platforms (containing 29 PD samples and 18 control samples, respectively). Subsequently, we used principal component analysis (PCA) to visualize the distribution of the data before and after correction, in order to evaluate the effectiveness of batch effect removal.

The "limma" R package[22] was utilized to perform differential analysis on disease and control groups of the PD dataset GSE8397 and the NP dataset GSE24982. Genes meeting criteria of $|\log2FC| > 0.585$ and $padj < 0.05$ were considered differentially expressed genes (DEGs) for subsequent analysis. Subsequently, the two groups of DEGs were intersected to obtain the common DEGs (Co-DEGs) related to PD and NP, which were used for subsequent analysis.

Protein-Protein Interaction (PPI) Network Construction and Co-Hub Gene Identification

STRING (https://string-db.org/), a repository for identifying known and predicted PPIs,[23] was utilized to establish a PPI network for Co-DEGs (interaction score ≥ 0.15). Network was visualized by Cytoscape. After constructing the PPI network, we used the cytoHubba plugin in Cytoscape software to score the Co-DEGs based on four commonly used network centrality algorithms: MCC (Matthews Correlation Coefficient metric), MNC (Maximal neighborhood coefficient), EPC (Edge percolated component), and Closeness. We selected the top 5 genes for each algorithm as candidate hub genes. Subsequently, we took the intersection of the four sets of candidate genes to obtain the robust hub genes (ie, Co-hub genes) that were identified by all four algorithms.

Diagnostic Performance of Co-Hub Genes

In the PD dataset (GSE8397, GSE7621 and GSE148434) as well as the NP dataset (GSE24982), we used the "pROC" R package[24] to draw the receiver operating characteristic (ROC) curves for the Co-hub genes and calculated the area under the curve (AUC) to evaluate the diagnostic significance of the Co-hub genes and to assess their diagnostic efficacy in different datasets for differentiating disease groups from normal control groups.

Immune Cell Infiltration Identification and Correlation Analysis

To accurately measure proportions of various immune cells in samples related to PD and NP, ssGSEA method from "GSVA" R package[25] was utilized to compute enrichment scores representing immune cell infiltration levels in each sample. Boxplots were generated to display changes in immune cell abundance between disease (PD/NP) and control groups. Correlation between immune cells/functions and Co-hub genes in disease samples was analyzed by combining gene expression matrices from both disease types.

Construction of Co-Hub Gene-miRNA Regulatory Network

TargetScan (https://www.targetscan.org/vert_80/) was utilized to predict miRNAs targeting Co-hub genes. Venn diagrams were created to visualize overlap of miRNAs predicted for different Co-hub genes. A regulatory network between Co-hub genes and their predicted miRNAs was constructed using Cytoscape.

Co-Hub Gene Expression Analysis Based on PD Single-Cell Data

Due to lack of single-cell datasets for NP, Co-hub gene analysis was performed only on PD single-cell dataset. RunPCA function was applied to GSE243639 dataset, with 30 dimensions selected. Cell clustering was done by implementing FindNeighbors and FindClusters functions, with a resolution set to 0.3. Uniform Manifold Approximation and Projection (UMAP) was used to visualize clustering results. Marker genes for brain tissue cell types were obtained from a previous study,[26] and cell annotation was performed using ScType. AddModuleScore function was implemented to calculate scores for all Co-hub genes, and their expression across different cell types was visualized.

Results

Identification of Co-DEFs Shared by PD and NP

Since the PD dataset GSE8397 was obtained from different sequencing platforms, we performed batch effect removal. The results of PCA showed that we successfully removed the batch effects between the datasets, and the quality of the data after removing the batch effects was good (Figure 1A). Subsequently, to screen for the Co-DEGs between PD and NP, we conducted differential expression analysis on the disease and control samples of the PD dataset GSE8397 and the NP dataset GSE24982, respectively. A total of 96 PD-related DEGs (21 upregulated and 75 downregulated) and 7365 NP-related DEGs (3649 upregulated and 3716 downregulated) were identified (Figure 1B and C). Further, by taking the intersection of the upregulated and downregulated DEGs from the two datasets, we finally obtained 22 Co-DEGs (Figure 1D and Table S1).

PPI Network Construction and Hub Gene Identification

A PPI network comprising 22 Co-DEGs was constructed using STRING database (Figure 2A). Subsequently, using the cytoHubba plugin in Cytoscape software, candidate hub genes were identified based on four network centrality algorithms (MCC, MNC, EPC, and Closeness). Specifically, the top 5 genes identified by the MCC algorithm were: *GDAP1*, *HIGD1A*, *SEZ6L2*, *CADPS*, and *FGF12*; those identified by the MNC algorithm were: *CADPS*, *GNB5*, *SEZ6L2*, *GDAP1*, and *B3GALNT1*; those identified by the EPC algorithm were: *B3GALNT1*, *UGT8*, *CADPS*, *SEZ6L2*, and *GDAP1*; and those identified by the Closeness algorithm were: *B3GALNT1*, *UGT8*, *CADPS*, *SEZ6L2*, and *GDAP1*. *CADPS*, *GDAP1*, and *SEZ6L2* were consistently identified by all four algorithms, indicating their high centrality and potential key regulatory roles in the PPI network. Therefore, these three genes were defined as Co-hub genes and were given special attention in the subsequent analysis (Figures 2B–E).

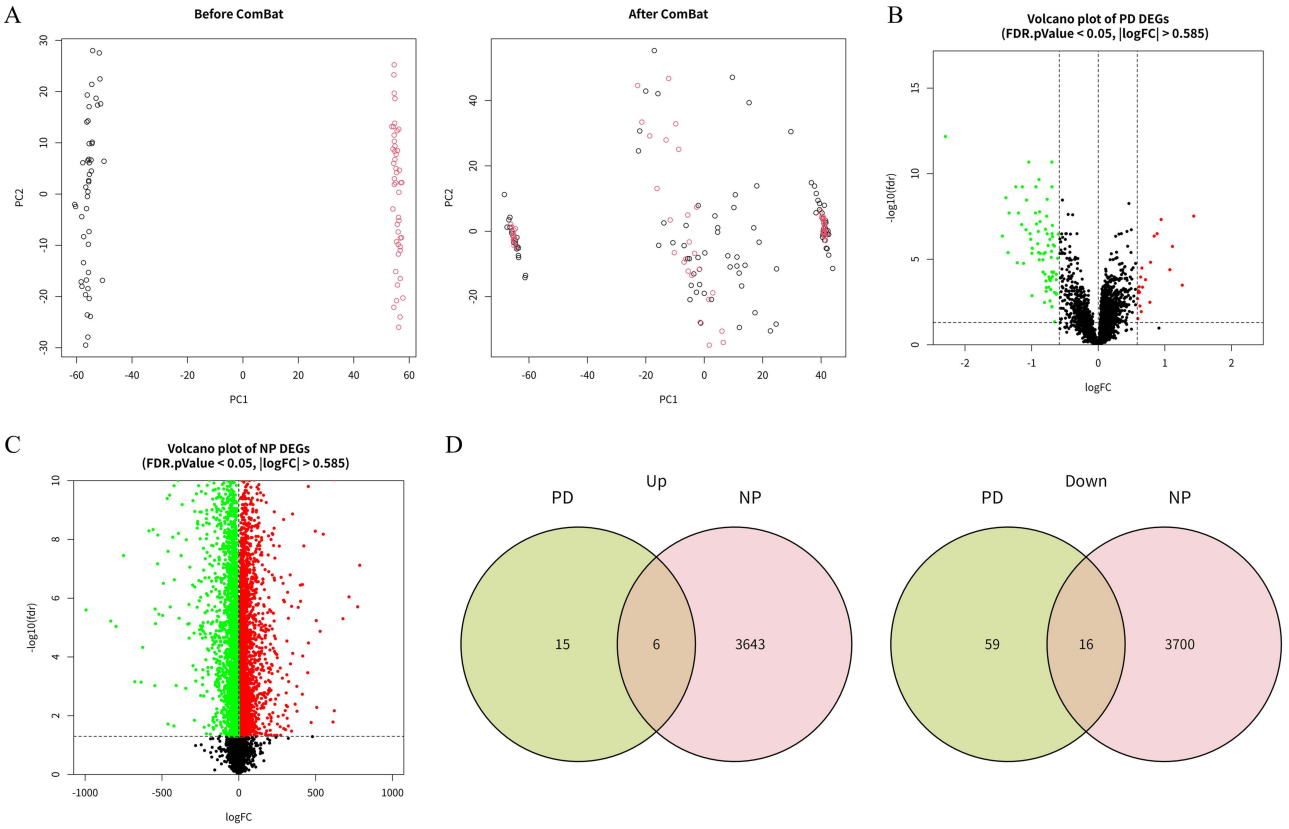

Figure 1 Identification of common DEGs shared by PD and NP. (**A**) PCA plots of the PD dataset before (left) and after (right) batch effect correction. (**B**) Volcano plot of DEGs between PD and control groups in the PD dataset. (**C**) Volcano plot of DEGs between NP and control groups in the NP dataset. (**D**) Venn diagram showing the intersection of DEGs from both datasets.

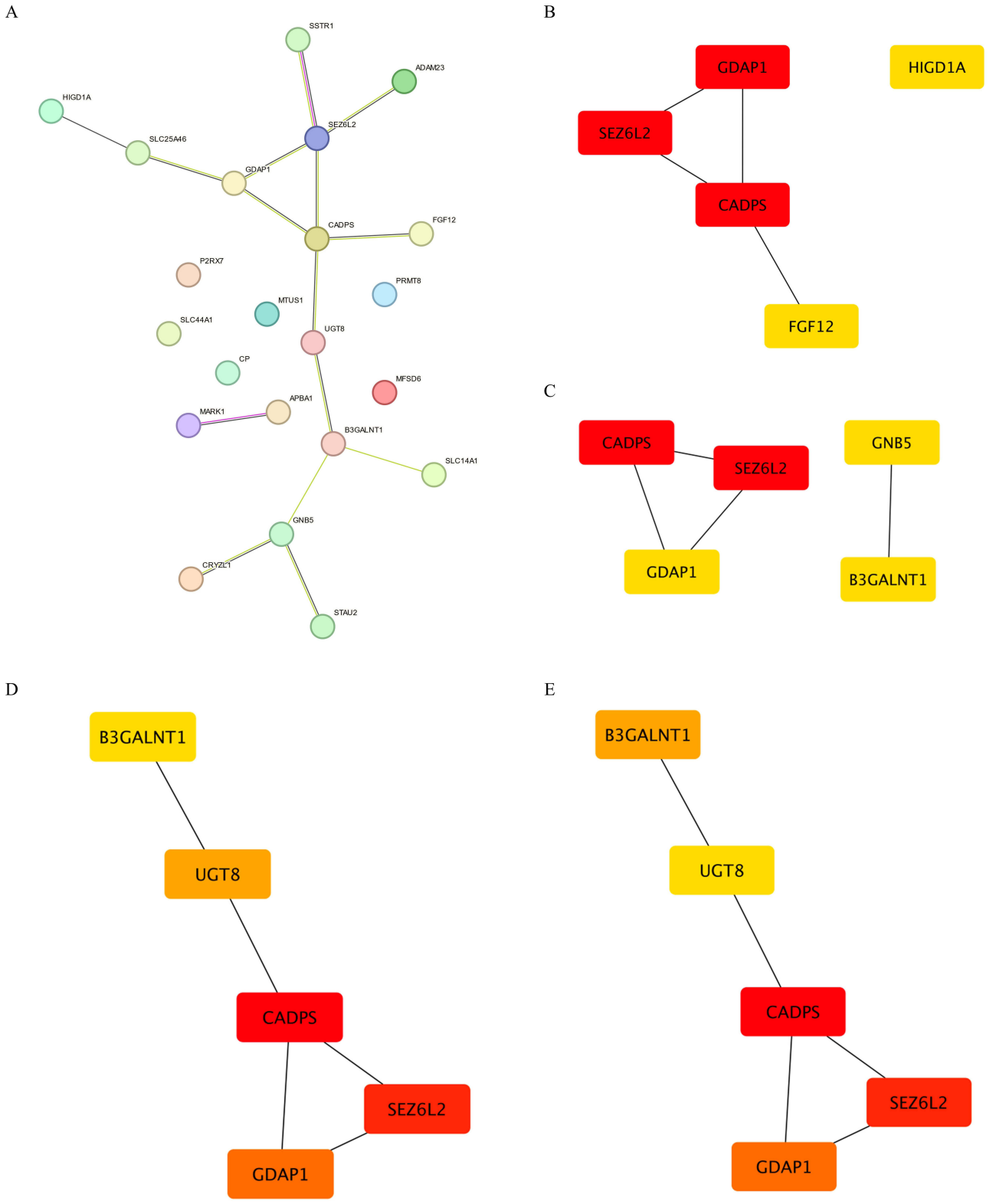

Figure 2 Construction of the Co-DEGs PPI network and identification of hub genes. (**A**) PPI network of Co-DEGs based on the STRING database. (**B**–**E**) Top 5 node networks identified by the MCC (**B**), MNC (**C**), EPC (**D**), and Closeness (**E**) algorithms.

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Diagnostic Performance of Co-Hub Genes

Furthermore, we plotted the ROC curves for three co-hub genes (CADPS, GDAP1, and SEZ6L2) in the PD dataset (GSE8397, GSE7621, and GSE148434) and the NP dataset (GSE24982). The results showed that the expressions of *CADPS*, *GDAP1*, and *SEZ6L2* in diagnosing PD diseases all had high accuracy (with AUC values greater than 0.68) (Figure 3A–C). Additionally, *CADPS*, *GDAP1*, and *SEZ6L2* also demonstrated certain accuracy in diagnosing NP diseases (with AUC values greater than 0.7) (Figure 3D).

Immune Characteristic Differences Between PD and NP Datasets

ssGSEA algorithm was implemented to determine relative infiltration levels of immune cells and functional differences between disease (PD/NP) and control groups. In PD dataset, Th2 cell levels were significantly higher in control group compared to PD group, while regulatory T cells (Tregs) were more abundant in PD group ($p < 0.05$) (Figure 4A). CCR and checkpoint scores were significantly higher in PD group ($p < 0.05$) (Figure 4A). In NP dataset, macrophage infiltration was significantly higher in control group, while dendritic cells, neutrophils, NK cells, Th1 cells, Th2 cells, TILs, and Tregs were more abundant in the NP group ($p < 0.05$) (Figure 4B). CCR, checkpoint, and T cell co-inhibition scores were significantly higher in NP group ($p < 0.05$) (Figure 4B). Statistically significant differences in Th2 cells, Tregs, CCR and checkpoint were observed in PD and NP groups compared to control groups ($p<0.05$). Correlation analysis revealed that expression of the three Co-hub genes (CADPS, GDAP1, and SEZ6L2) tended to be negatively correlated with immune cells and functions in PD dataset (Figure 4C). In NP dataset, these immune cells and functions showed significant negative correlations with Co-hub gene expression, with fewer positive correlations ($p < 0.05$) (Figure 4D).

Construction of miRNA-Co-Hub Gene Regulatory Network

Using TargetScan, we predicted miRNAs targeting three Co-hub genes. A total of 274 miRNAs interacting with *CADPS*, 787 miRNAs interacting with *GDAP1*, and 256 miRNAs interacting with *SEZ6L2* were identified (Figure 5A and B). Among these, eight miRNAs were predicted to target all three Co-hub genes: hsa-miR-330-3p, hsa-miR-7977, hsa-miR-325-3p, hsa-miR-4433a-5p, hsa-miR-137, hsa-miR-4433b-5p, hsa-miR-3613-3p, and hsa-miR-1183, suggesting their potential role as common regulatory nodes in PD and NP (Figure 5B).

Expression Analysis of Co-Hub Genes in PD Single-Cell Dataset

To determine expression of Co-hub genes across different cell types, we visualized Co-hub genes on single-cell datasets. However, due to data limitations, we were only able to obtain single-cell datasets for PD. UMAP visualization of dimensionality-reduced data identified 24 cell clusters (Figure 6A). These clusters were annotated into seven cell types: Astrocytes, Microglia, Neurons, Oligodendrocytes, OPCs, T cells, and Vascular cells (Figure 6B). Co-hub gene scores and individual gene expression analysis revealed that Co-hub genes were highly expressed in Neurons and Astrocytes (Figure 6C). Specifically, CADPS was highly expressed in Neurons, Astrocytes, and OPCs; GDAP1 was highly expressed in Neurons, Oligodendrocytes, Astrocytes, and OPCs; and SEZ6L2 was highly expressed in Neurons and Astrocytes (Figure 6D).

Discussion

PD ranks the second most common inflammatory neurodegenerative disorder following Alzheimer's disease, with its prevalence rising alongside population aging, making it a leading cause of neurological disability.[27,28] Pain is a recognized and significant non-motor symptom of PD, with some pain classified as NP.[13] However, NP in PD remains incompletely understood, often overlooked, and affected patients frequently receive inadequate pain management. Therefore, determining whether PD and NP share common pathological and molecular mechanisms is crucial for diagnosis and treatment. This study employed bioinformatics analysis of PD and NP datasets to identify key genes and analyze immune microenvironment characteristics, aiming to find fresh diagnostic biomarkers and treatment targets.

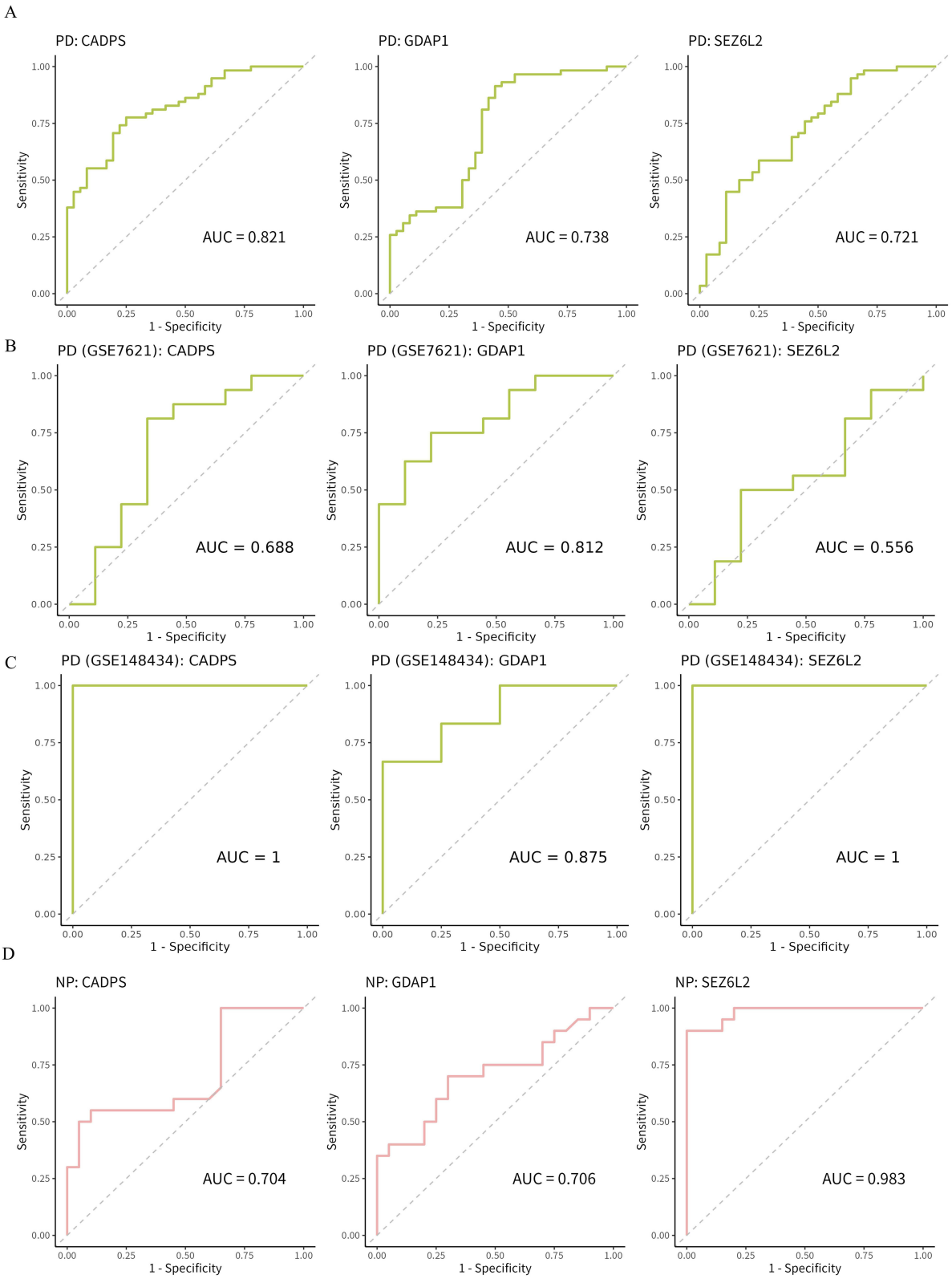

Figure 3 Evaluation of the diagnostic value of Co-hub genes in the PD and NP datasets. (**A**–**C**) ROC curves of the Co-hub genes (*CADPS*, *GDAP1*, and *SEZ6L2*) in the PD datasets GSE8397 (**A**), GSE7621 (**B**), and GSE148434 (**C**). (**D**) ROC curves of the Co-hub genes (*CADPS*, *GDAP1*, and *SEZ6L2*) in the NP dataset.

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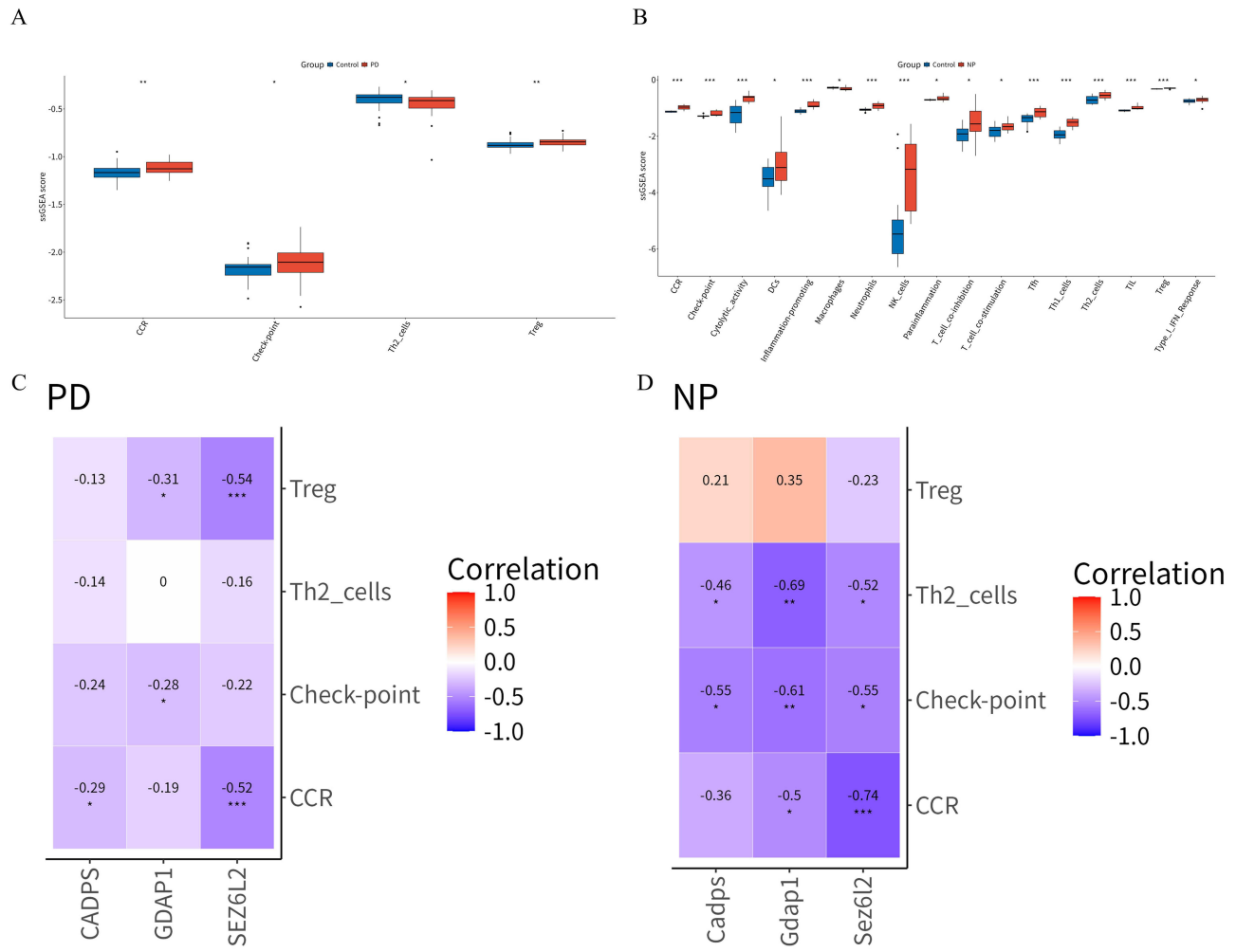

Figure 4 Immune characteristic analysis. (**A and B**) Differences in immune cell infiltration and functional scores between control and disease groups in the PD dataset (**A**) and NP dataset (**B**). (**C and D**) Heatmaps showing correlations between immune cells/functions and Co-hub gene expression in PD disease samples (**C**) and NP disease samples (**D**). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Based on PD and NP datasets, we identified three Co-hub genes—*CADPS*, *GDAP1*, and *SEZ6L2*—using differential expression analysis, PPI network construction, and algorithms (MCC, MNC, EPC, and Closeness). ROC curves demonstrated that these three Co-hub genes could accurately diagnose PD and NP. Furthermore, these three genes are highly expressed in neurons and astrocytes. These results suggest that *CADPS*, *GDAP1*, and *SEZ6L2* may not only demonstrate diagnostic efficacy in PD and NP, but also play a crucial regulatory role in neurological diseases. PD is considered an age-related neurodegenerative disease caused by vesicle transport dysfunction and abnormal neurotransmitter secretion.[29] In neuroendocrine cells, the exocytosis of secretory granules is regulated by Ca^{2+}, and *CADPS*, as a key regulatory factor, participates in regulating this process.[30] PD-related proteins *LRRK2* and α-synuclein abnormally regulate the transcriptional activity of *CADPS*, revealing its important role in synaptic dysfunction, and thereby promoting the occurrence of PD.[31] Additionally, *CADPS* has been confirmed as one of the core genes of PD. This finding is highly consistent with our results.[32] However, no studies have explored the association between *CADPS* and NP so far. Our research has shown for the first time that *CADPS* has high diagnostic accuracy in both PD and NP, suggesting that it may play a role in both diseases through a common vesicle transport mechanism. *GDAP1* (Ganglioside-induced differentiation-associated protein 1) is another key gene we identified. *GDAP1* is mainly expressed in the outer mitochondrial membrane of neurons and participates in regulating various mitochondrial functions.[33] Additionally, *GDAP1* has also been reported to participate in the metabolic disorder process of Osthole alleviating NP through metabolic pathways and gut microbiota.[34] Although there are no studies directly establishing the connection between

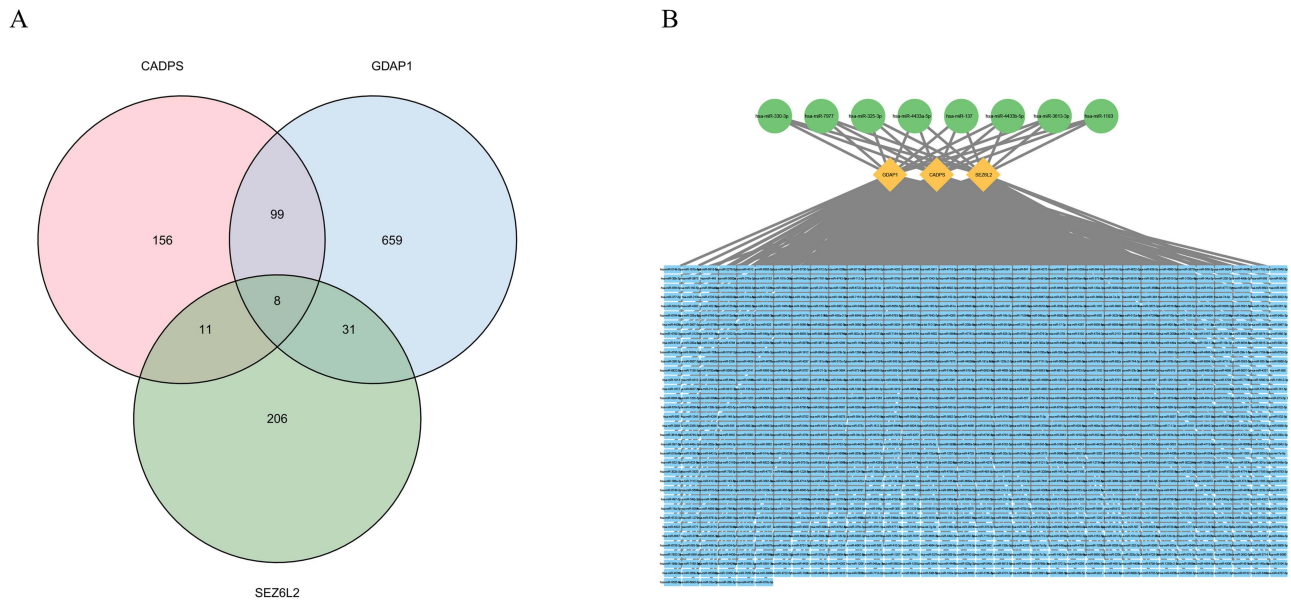

Figure 5 Construction of the miRNA-Co-hub gene regulatory network. (**A**) Venn diagram showing miRNAs shared by the three Co-hub genes. (**B**) miRNA-gene regulatory network based on Co-hub genes.

GDAP1 and PD, given that mitochondrial dysfunction is a core pathological mechanism of various neurodegenerative diseases including PD,[35] we speculate that the function of *GDAP1* in neurons may be an important pathway for mediating PD and related neurological pathologies. *SEZ6L2* is a member of the Sez6 protein family and is widely expressed in the brain. As a novel complement regulatory factor, it participates in regulating the complement-mediated immune response in the nervous system and affects synaptic formation and neural development by inhibiting C3 convertase activity and promoting C3b degradation.[36,37] Currently, there are very limited studies on *SEZ6L2* in PD or NP, and there is no direct evidence to clearly demonstrate its role in the pathological mechanism of PD or NP. However, given its role in the nervous system, combined with the high expression level of *SEZ6L2* in neurons and astrocytes as discovered in our study, as well as its performance as a potential diagnostic marker for PD and NP, we speculate that *SEZ6L2* may regulate neuroinflammation and complement system activity, participating in the pathogenesis of PD and NP, and becoming an important target for future exploration of the common mechanisms of these two diseases.

Immune infiltration results revealed that immune cells are linked to development and progression of PD and NP, consistent with earlier studies.[38,39] Substantial differences in immune cell infiltration were observed between disease and control groups in both PD and NP datasets, including Th2 cells and Tregs. Treg infiltration was significantly elevated in PD and NP disease groups. Th2 cell infiltration was significantly reduced in PD disease group but enhanced in NP disease group. Th2 cells, a subset of $CD4^+$ T cells, primarily regulate humoral immunity by secreting cytokines (IL-4, IL-5, IL-10, IL-13), facilitating B cell activation and antibody production while repressing Th1 cell proliferation.[40] $CD4^+$ and $CD8^+$ T cells in PD patients' peripheral circulation produce Th1/Th2 cytokines in response to α-synuclein, with Th2 cytokines exhibiting neuroprotective effects.[41,42] In NP, a sudden Th2 cell phenotype with high interleukin-6 (IL-6) levels has been linked to bortezomib-induced NP.[43] Somatosensory cortex and central amygdala projections to the spleen via the vagus nerve can modulate peripheral Th2 immune responses mediated by NP.[44] Tregs regulate body's immune response to hurtful invaders and prevent overreactions. Their deficiency, reduction, dysfunction, transformation, or instability can cause autoimmune diseases.[45] In NP patients, an imbalance in TH17/Treg ratio and elevated FoxP3 and TGF-β mRNA expression associated with Tregs have been observed, leading to a significant increase in Tregs.[46] Tregs prevent pain-induced hypersensitivity mediated by microglia.[47] In PD patients, enhanced Treg responses are associated with clinical improvement.[48] These findings align with our results, suggesting that changes in Treg quantity and function may be involved in shared pathophysiology of PD and NP. Based on the literature and our data, we hypothesize that in PD, the immunosuppressive environment (increased Tregs and decreased Th2) may inhibit the secretion of protective

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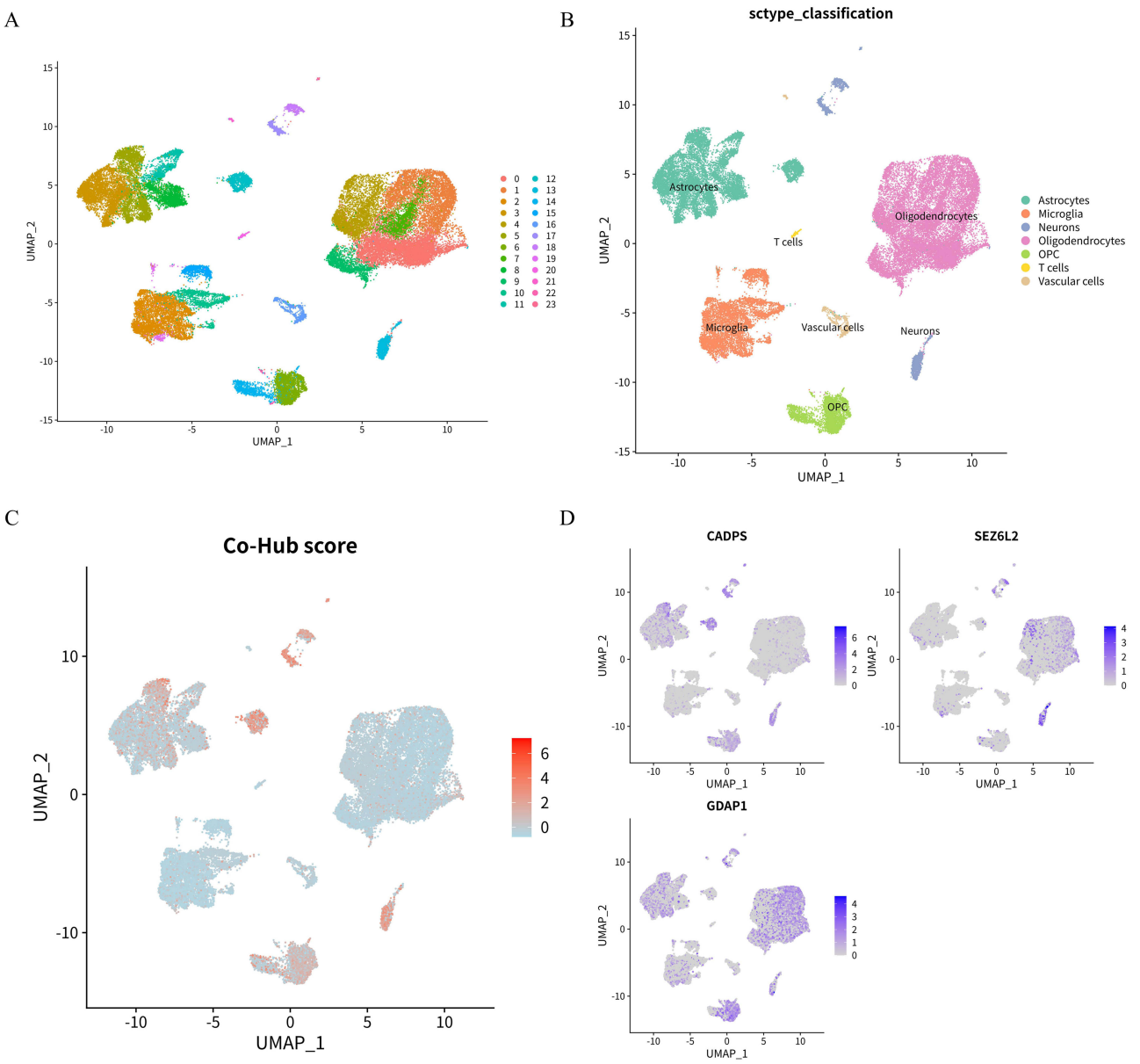

Figure 6 Expression of Co-hub genes in the PD single-cell dataset. (**A**) UMAP visualization of cell clustering results. (**B**) Annotation of cell types in all PD cell clusters. (**C**) UMAP visualization of Co-hub gene expression across cell types. (**D**) Expression of individual Co-hub genes in various cell types.

Th2 factors (such as IL-4 and IL-10), promoting neuroinflammatory damage; while in NP, although the activation of Th2 cells provides some neuroprotection, their combined action with Tregs may lead to an imbalance in immune regulation, thereby maintaining the chronic pain state. However, due to the limitations of current research, this hypothesis still needs to be further verified through cell co-culture experiments, animal models, etc.

MicroRNAs (miRNAs) are a class of important non-coding RNAs that can regulate the expression of target mRNAs by binding to them. Studies have shown that miRNAs play a crucial role in the pathogenesis of NP and PD.[49,50] Therefore, exploring the miRNA network that may be regulated by Co-hub genes can help reveal their upstream regulatory mechanisms and provide a theoretical basis for subsequent intervention targets. In this study, we predicted a total of 1170 miRNAs that may target the three Co-hub genes (*CADPS*, *GDAP1*, and *SEZ6L2*). Among them, hsa-miR-330-3p, hsa-miR-7977, hsa-miR-325-3p, hsa-miR-4433a-5p, hsa-miR-137, hsa-miR-4433b-5p, hsa-miR-3613-3p, and hsa-miR-1183 simultaneously target the three Co-hub genes. Therefore, they are also considered to be one of the common regulatory nodes for PD and NP. Although there is currently a lack of experimental verification on the direct

regulatory relationship between the above miRNAs and the target genes, the results of this study provide a new research direction for in-depth understanding of the co-morbidity molecular mechanism of PD and NP, as well as the development of miRNA-targeted therapeutic strategies.

In summary, this study identified three key Co-hub genes (*CADPS*, *GDAP1*, and *SEZ6L2*) between PD and NP for the first time, and multiple data levels (bulk RNA, ROC diagnostic ability, immune infiltration, miRNA regulation, single-cell expression) systematically verified the key roles of *CADPS*, *GDAP1*, and *SEZ6L2* in PD and NP. These findings not only improve the reference for revealing the possible common molecular mechanisms of PD and NP, but also provide new directions for the early identification and mechanism research of the two diseases. However, although our research has made some progress, it is not to be ignored that this study still has some limitations. Firstly, due to the scarcity of human data on NP in existing public databases, the NP data used in this study mainly comes from mouse models. This limitation may affect the cross-species generalizability of the results. Therefore, although we found the same Co-hub genes in PD and NP in the mouse NP model, these results are currently only applicable for theoretical research and need further validation for their applicability in actual clinical populations. Secondly, although this study used bioinformatics methods to conduct a preliminary exploration of the association between PD and NP, our research still relies on and is limited by public databases. Therefore, in the future, it is necessary to collect larger sample sizes and more diverse clinical data, especially multi-omics information from human NP patients, and introduce experimental verification to enhance the translational potential of the results. Although the three Co-hub genes and immune cells identified in this study show potential for PD and NP diagnosis and treatment, further research is needed to confirm their roles as diagnostic markers or therapeutic targets.

Data Sharing Statement

The data and materials in the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Our study is exempt from approval based on national legislation guidelines, such as item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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