MEDICAL SCIENCE MONITOR

DATABASE ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e920846
DOI: 10.12659/MSM.920846

Received: 2019.10.21
Accepted: 2019.12.18
Available online: 2020.02.01
Published: 2020.03.25

An Integrated Network Analysis of mRNA and Gene Expression Profiles in Parkinson's Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: Parkinson's disease (PD) is a degenerative neurologic disease. This study aimed to undertake bioinformatics analysis using the publicly available Gene Expression Omnibus (GEO) database to integrate mRNA expression data from patients with PD and to compare differentially expressed genes (DEGs) in tissue from the substantia nigra and whole blood from patients with PD and normal controls.

Material/Methods: Integrated network analysis included GEO datasets to identify DEGs in the substantia nigra and whole blood of patients with PD. Bioinformatics analysis was used to identify the roles of the DEGs and included the development of protein–protein interaction (PPI) networks and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment. Expression levels of DEGs were validated using GSE100054.

Results: In patients with PD, there were 1,076 upregulated DEGs and 1,075 down-regulated DEGs in the substantia nigra tissue, and 699 upregulated and 930 down-regulated DEGs in whole blood samples. The apoptotic process, the mitogen-activated protein kinase (MAPK) signaling pathway, the Wnt signaling pathway, and the Notch signaling pathway were significantly enriched in DEGs in the substantia nigra in PD. In both the substantia nigra and whole blood, the most common DEGs were significantly enriched in lysosomes, PD, Alzheimer's disease, Huntington's disease. SORT1 and CRYAB were the hub proteins in the network of the substantia nigra; PSMA1 and SDHA were the hub proteins in the network of whole blood in PD.

Conclusions: DEGs, including SORT1, CRYAB, PSMA1, and SDHA may have roles in the pathogenesis of PD through the MAPK, Wnt, and Notch signaling pathways.

MeSH Keywords: MAP Kinase Kinase Kinases • Parkinson Disease • Wnt Signaling Pathway

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/920846

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Background

Parkinson's disease (PD) is the second most common neurodegenerative disease [1,2]. PD is characterized by the loss of dopaminergic neurons in the substantia nigra in the midbrain with the development of Lewy bodies, which are intracellular inclusion bodies containing α-synuclein [3]. The clinical features of PD include tremors, rigidity, bradykinesia, and cognitive impairment.

The potential causative factors for PD include environmental toxins, drugs, pesticides, brain microtrauma, focal cerebrovascular damage, and genomic defects [4]. Cellular mechanisms involved in PD include genomic factors, oxidative stress, neuroinflammation, and cell apoptosis [5]. Currently, PD is incurable, and its etiology remains unclear, although miR-181a regulates apoptosis and autophagy by inhibiting the p38 mitogen-activated protein kinase (MAPK)/c-jun n-terminal kinase (JNK) signaling pathways in patients with PD [6]. SIRT1 is down-regulated in PD, and reduces oxidative stress-induced neural cell death and reduces the formation of α-synuclein aggregates [7]. Neuroinflammation is recognized as a pathophysiological contributor to PD. Increased levels of proinflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon gamma (IFNγ) are found in the midbrain of patients with PD, and contribute to the acceleration of nigral neuronal degeneration and reduced levels of dopamine [8,9].

Therefore, this study aimed to undertake bioinformatics analysis using the publicly available Gene Expression Omnibus (GEO) database to integrate mRNA expression data from patients with PD and to compare differentially expressed genes (DEGs) in tissue from the substantia nigra and whole blood from patients with PD and normal controls.

Material and Methods

Gene expression datasets from patients with Parkinson's disease (PD)

The expression profile datasets of patients with PD were searched from the publicly available Gene Expression Omnibus (GEO) database (*http://www.ncbi.nlm.nih.gov/geo*). The microarray datasets generated from the substantia nigra and from the whole blood of patients with PD and controls were used in the study. Following selection, 10 datasets were identified from the substantia nigra tissues, and 10 datasets were identified from whole blood samples. The details of the datasets are shown in Tables 1 and 2.

Differentially expressed genes in PD

The selected datasets were analyzed individually. To minimize the heterogeneity between different datasets enrolled in the integrated analysis, normalization and log2 transformation

Table 1. Details of the datasets from the substantia nigra tissues from patients with Parkinson's disease (PD) identified from the Gene Expression Omnibus (GEO) database.

GEO ID	Control	PD	Platform	Country	Year
GSE42966	6	9	GPL4133 Agilent-014850 Whole Human Genome Microarray 4x44K G4112F (Feature Number version)	Brazil	2018
GSE49036	8	15	GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Netherlands	2015
GSE43490	5	5	GPL6480 Agilent-014850 Whole Human Genome Microarray 4x44K G4112F (Probe Name version)	Brazil	2015
GSE54282	3	3	GPL17047 [HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array [HuGene10stv1_Hs_ENTREZG_15.0.0]	USA	2014
GSE26927	8	12	GPL6255 Illumina humanRef-8 v2.0 expression beadchip	UK	2011
GSE20164	5	6	GPL96 [HG-U133A] Affymetrix Human Genome U133A Array	USA	2011
GSE20163	9	8	GPL96 [HG-U133A] Affymetrix Human Genome U133A Array	USA	2011
GSE20292	18	11	GPL96 [HG-U133A] Affymetrix Human Genome U133A Array	USA	2010
GSE8397	11	23	GPL96 [HG-U133A] Affymetrix Human Genome U133A Array, GPL97 [HG-U133B] Affymetrix Human Genome U133B Array	UK	2008
GSE7621	9	16	GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	USA	2007
Total	**82**	**112**			

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Table 2. Details of the datasets from the whole blood samples from patients with Parkinson's disease (PD) identified from the Gene Expression Omnibus (GEO) database.

GEO ID	Control	PD	Platform	Country	Year
GSE99039	233	205	GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Israel	2017
GSE57475	49	93	GPL6947 Illumina HumanHT-12 V3.0 expression beadchip	USA	2015
GSE72267	19	40	GPL571 [HG-U133A_2] Affymetrix Human Genome U133A 2.0 Array	Italy	2015
GSE34287	12	19	GPL7884 ExonHit Human Genome Wide SpliceArray 1.0	USA	2012
GSE18838	11	17	GPL5175 [HuEx-1_0-st] Affymetrix Human Exon 1.0 ST Array [transcript (gene) version]	USA	2010
GSE6613	22	50	GPL96 [HG-U133A] Affymetrix Human Genome U133A Array	Denmark	2006
Total	**346**	**424**			

were performed for the raw data. The Meta-analysis for MicroArrays (metaMA) package in R was used to calculate the p-values of each dataset. P-values were combined to identify the differentially expressed genes (DEGs) between the patients with PD and the controls. Finally, the Benjamini-Hochberg procedure was used for multiple comparisons and correction of the false discovery rate (FDR). Genes with an FDR <0.01 were selected as DEGs. Finally, the DEGs in the substantia nigra tissue and whole blood of patients with PD were identified.

Functional enrichment

Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of DEGs in PD were performed using the GeneCodis3 online enrichment analysis tool (*http://genecodis.cnb.csic.es*). An FDR <0.05 was set as the cut-off for selecting significant GO terms and for KEGG pathway analysis.

Construction of the protein–protein interaction (PPI) network

Complex cellular functions are performed through the interactions between proteins. The Biological General Repository for Interaction Datasets (BioGRID) online curated database (*https://thebiogrid.org*) was used to identify the interacting proteins. The PPI network was constructed using Cytoscape software (*http://cytoscape.org/*).

Expression levels of DEGs in the whole blood datasets from patients with PD

To determine whether the most common DEGs were dysregulated in PD, the expression level of candidate DEGs were preliminarily validated in the whole blood dataset from the GEO database. Box-plot analysis was performed to identify the expression of DEGs in the whole blood of patients with PD and normal controls.

Results

Differentially expressed genes (DEGs) in the substantia nigra tissue from patients with Parkinson's disease (PD)

In total, the mRNA expression data of 194 substantia nigra tissue generated from 112 patients with PD and 82 controls were obtained. DEGs in the substantia nigra tissue of patients with PD were identified compared with healthy controls. As shown in Figure 1, DEGs could discriminate between the patients with PD and the controls. Among the DEGs, 1,076 up-regulated and 1,075 down-regulated DEGs in the substantia nigra tissue were identified.

Dysregulated biological processes and pathways in the substantia nigra tissue in PD

The dysregulated biological processes and pathways were investigated in PD. Figure 2A shows that the biological processes related to apoptosis were significantly enriched, including the apoptotic process, cell death, and regulation of the apoptotic process. Also, the nerve growth factor receptor signaling pathway, synaptic transmission, and nervous system development were significantly enriched. As shown in Figure 2B, the enriched functional pathways identified by the Kyoto Encyclopedia of Genes and Genomes (KEGG) included oxidative phosphorylation, Parkinson's disease, the MAPK signaling pathway, the neurotrophin signaling pathway, the Wnt signaling pathway, and the Notch signaling pathway.

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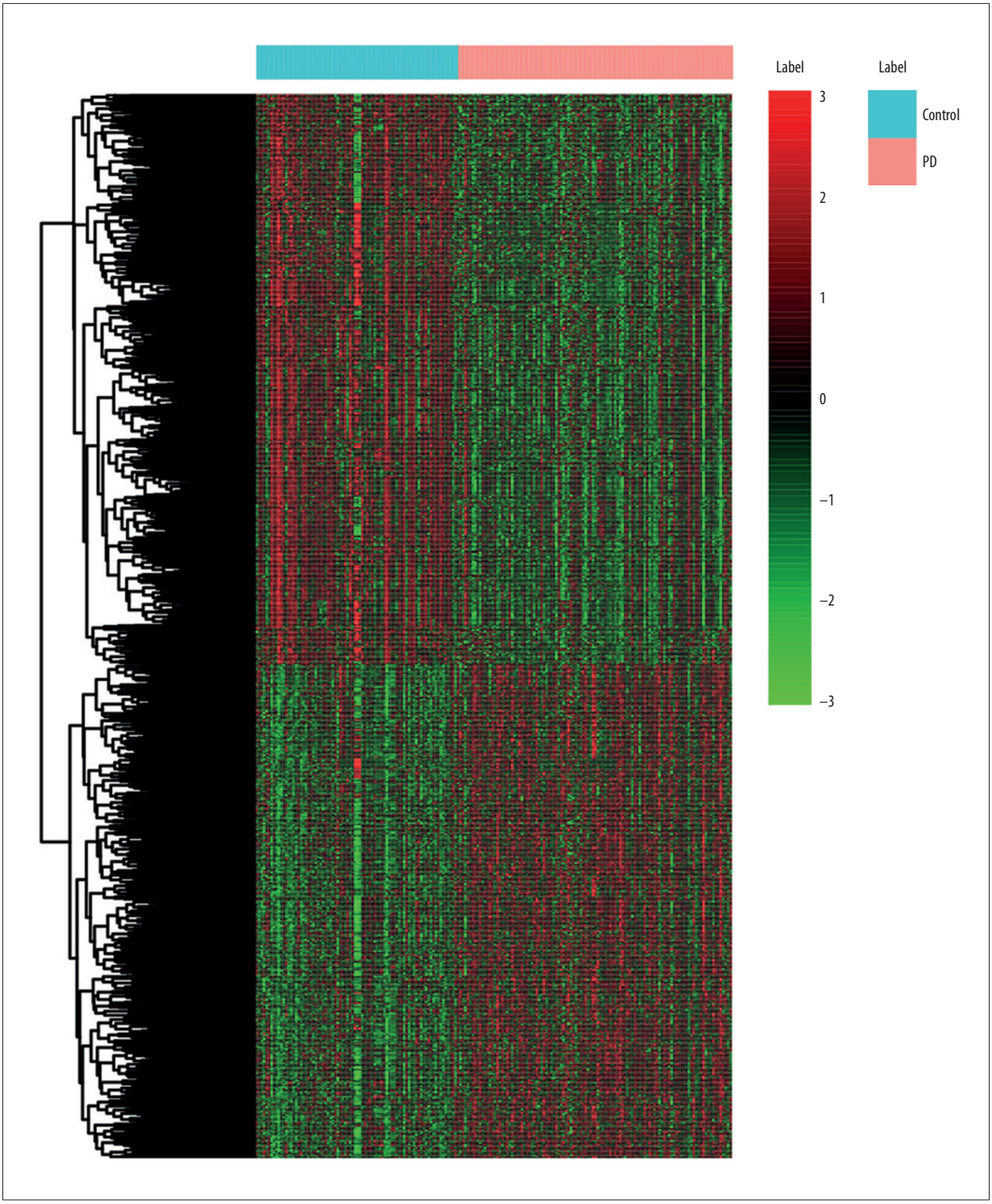

Figure 1. The heatmaps of differentially expressed genes (DEGs) in the substantia nigra of patients with Parkinson's disease (PD) compared with healthy individuals.

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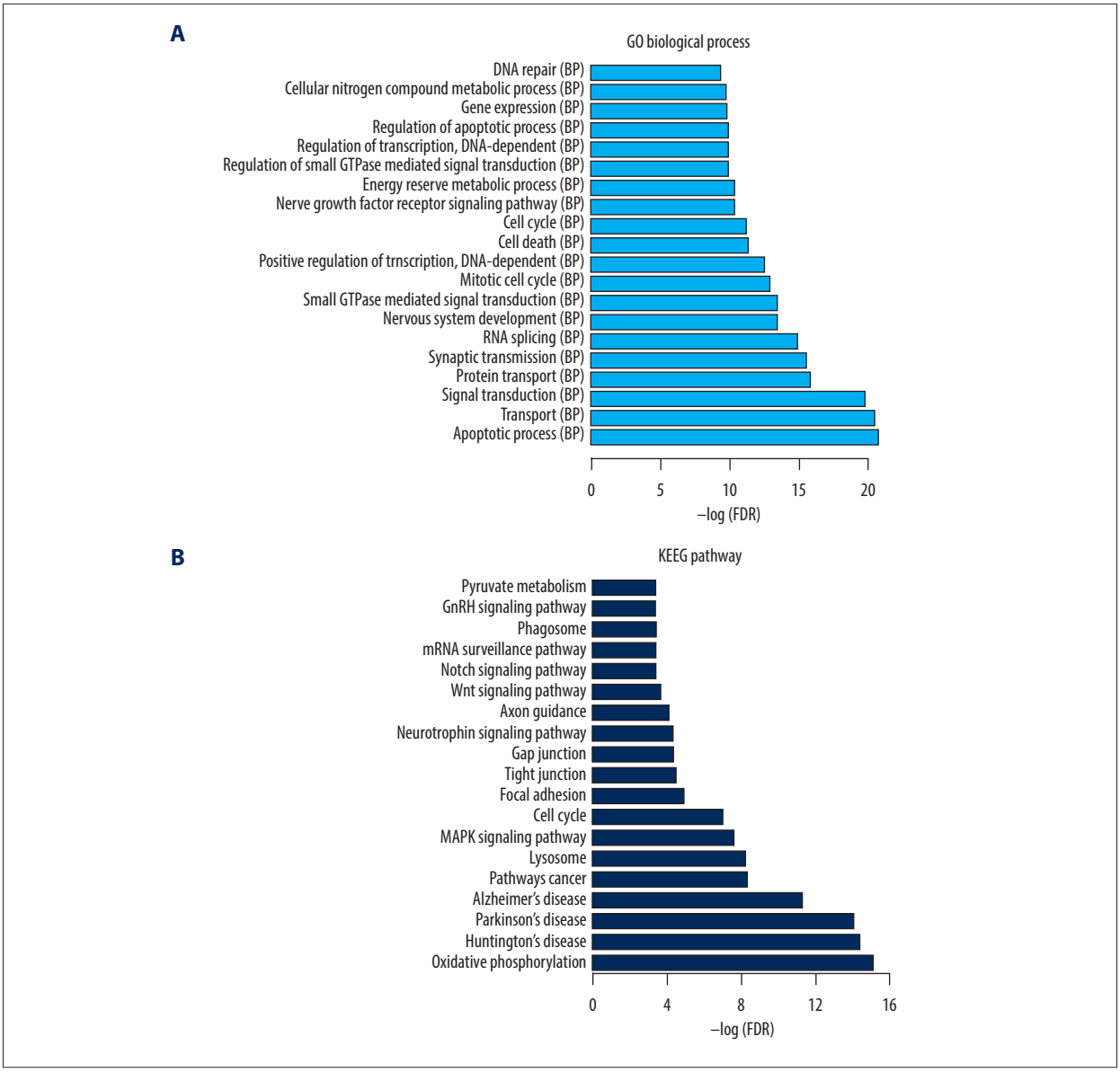

Figure 2. The enriched biological functions of differentially expressed genes (DEGs) in the substantia nigra of patients with Parkinson's disease (PD) compared with healthy individuals. (**A**) The enriched biological process of DEGs. (**B**) The enriched the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways for DEGs.

The protein–protein interaction (PPI) network in substantia nigra tissue

The protein–protein interaction (PPI) network of the top 20 upregulated and top 20 down-regulated DEGs in the substantia nigra tissue were identified. Figure 3 shows that in the PPI network, PAN2, SORT1, CRYAB, and DLK1 had the high connectivity with the DEGs, and interacted with 66, 25, 17, and 11 DEGs, respectively.

DEGs in whole blood samples from patients with PD

In total, the mRNA expression data of 770 whole blood samples generated from 424 patients with PD and 346 controls were obtained. DEGs in whole blood of patients with PD were identified compared with it in healthy controls. Figure 4 shows that the DEGs could discriminate PD from controls. Among the DEGs, 699 upregulated and 930 down-regulated DEGs in whole blood were identified.

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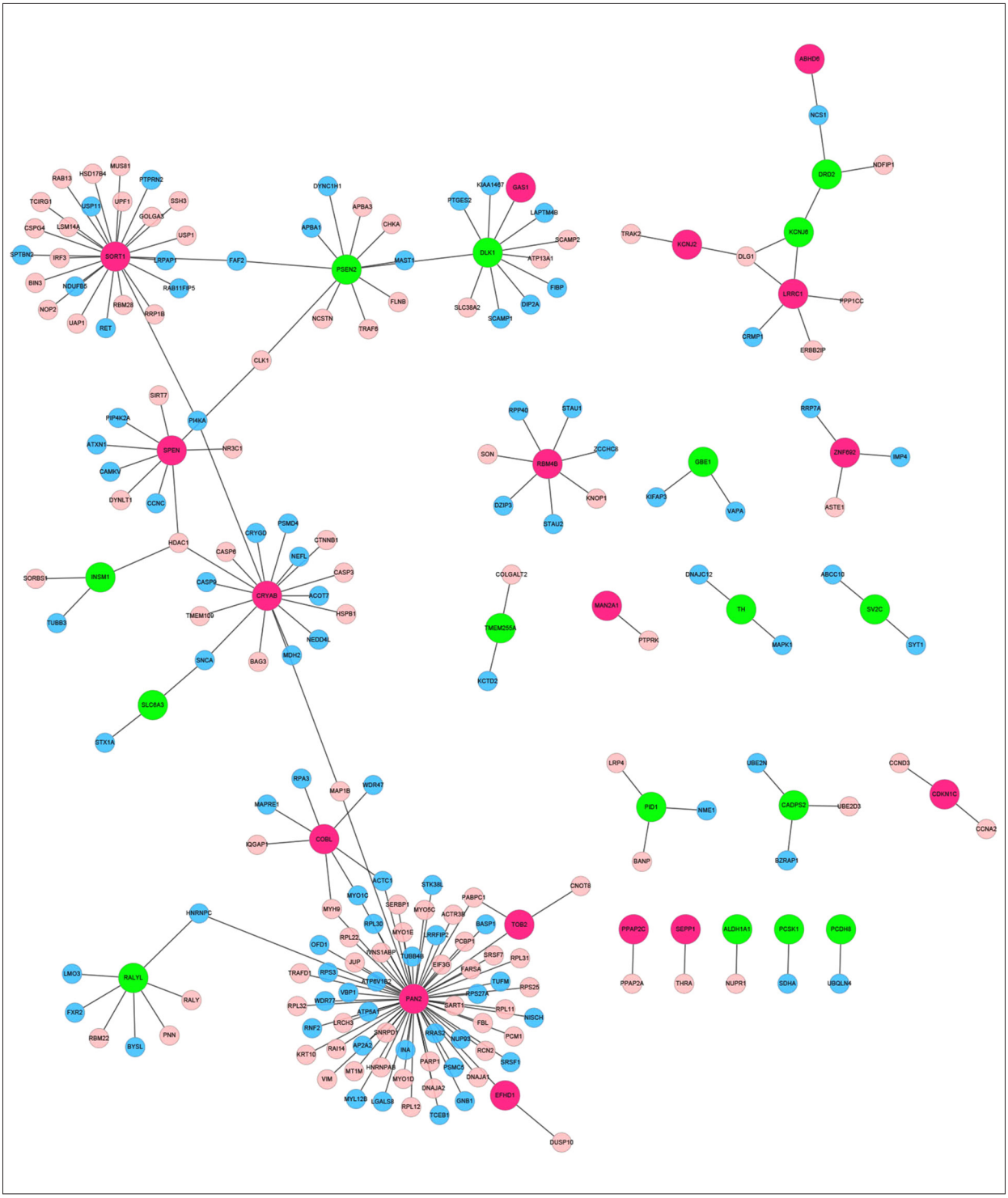

Figure 3. The protein–protein interaction (PPI) network of the top 20 upregulated differentially expressed genes (DEGs) and top 20 down-regulated DEGs in substantia nigra tissues of patients with Parkinson's disease (PD). The red and green nodes indicate the top 20 upregulated DEGs and the top 20 down-regulated DEGs in the substantia nigra.

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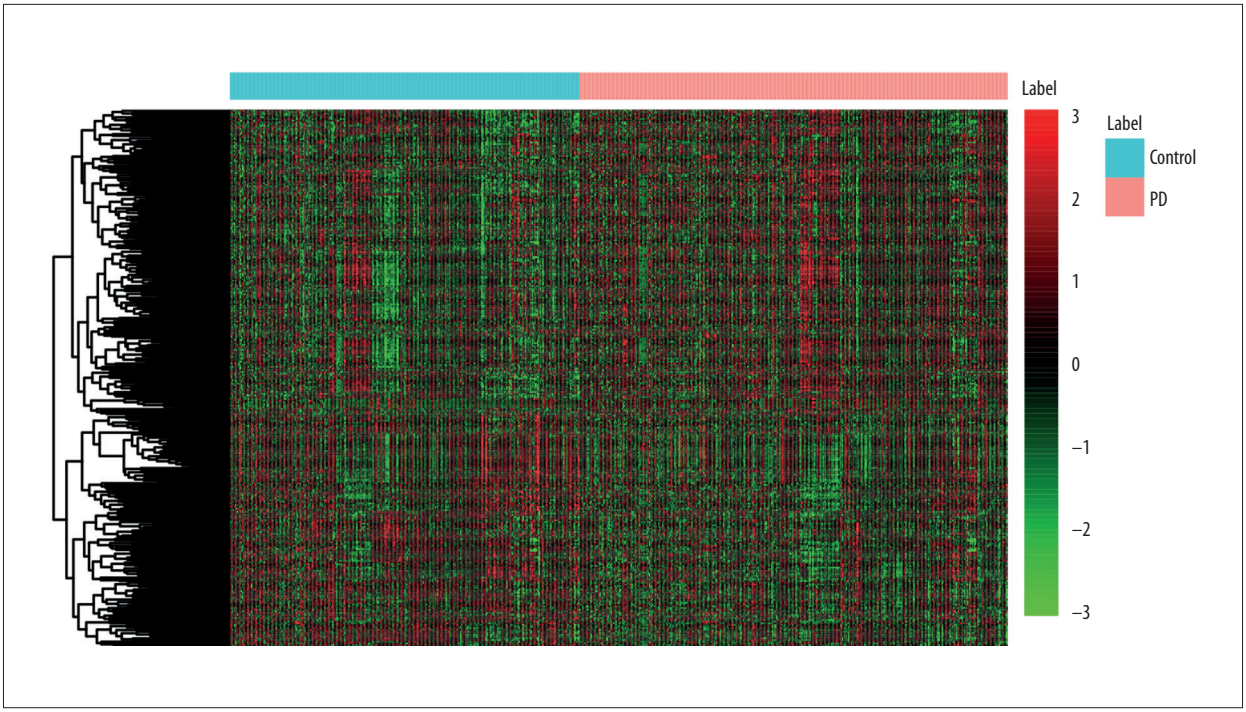

Figure 4. The heatmap of differentially expressed genes (DEGs) in the whole blood of patients with Parkinson's disease (PD) compared with healthy individuals.

Dysregulated biological process and pathways in whole blood from patients with PD

As shown in Figure 5A, in whole blood from patients with PD, the biological processes involved apoptosis, and negative regulation of cell proliferation. The KEGG pathways included the MAPK signaling pathway, the Wnt signaling pathway, the neuroactive ligand-receptor interaction, and oxidative phosphorylation, which were significantly enriched (Figure 5B).

The PPI network in whole blood

The protein–protein interaction (PPI) network of top 20 upregulated and top 20 down-regulated DEGs in whole blood of patients with PD was constructed. Figure 6 shows that in the network, PRKCD, PLAUR, GABARAPL1, and PRDX2 had high connectivity with the DEGs, and interacted with 16, 14, 13, and 12 DEGs, respectively.

The most common DEGs identified in substantia nigra tissue and whole blood from patients with PD

The common DEGs overlapped with DEGs in the substantia nigra tissue and DEGs in the whole blood of patients with PD. As shown in Figure 7A, the 169 common DEGs included 80 that were upregulated and 89 that were down-regulated. These DEGs were significantly enriched in the apoptotic process, programmed cell death, and negative regulation of programmed cell death of biological process (Figure 7B). Also, the most common DEGs were significantly enriched in the KEGG pathways, including oxidative phosphorylation, lysosomes, Parkinson's disease, Alzheimer's disease, and Huntington's disease (Figure 7C). In the PPI network, the common DEGs included PSMA1 and SDHA that interacted with the four common DEGs (Figure 7D).

Detection of expression levels of common DEGs in substantia nigra tissue and whole blood of patients with PD

The GSE22491 dataset, containing whole blood mRNA expression profiles of patients with PD, was used to investigate the expression levels of 169 common DEGs preliminarily. The expression of 36 out of 80 upregulated common DEGs, and 45 out of 89 down-regulated common DEGs in GSE22491 was used in the integrated analysis. Also, 21 out of 36 DEGs were significantly upregulated and 14 out of 45 DEGs were significantly down-regulated in GSE22491. As shown in Figure 8, CENPB, COL9A1, DMPK, and FCGRT were significantly upregulated (Figure 8A–8D), and ATP6V1H, PIP4K2A, PSMA1, and TRIM58 were significantly down-regulated in GSE22491 (Figure 8E–8H).

Discussion

This study used bioinformatics analysis of data from the publicly available Gene Expression Omnibus (GEO) database to

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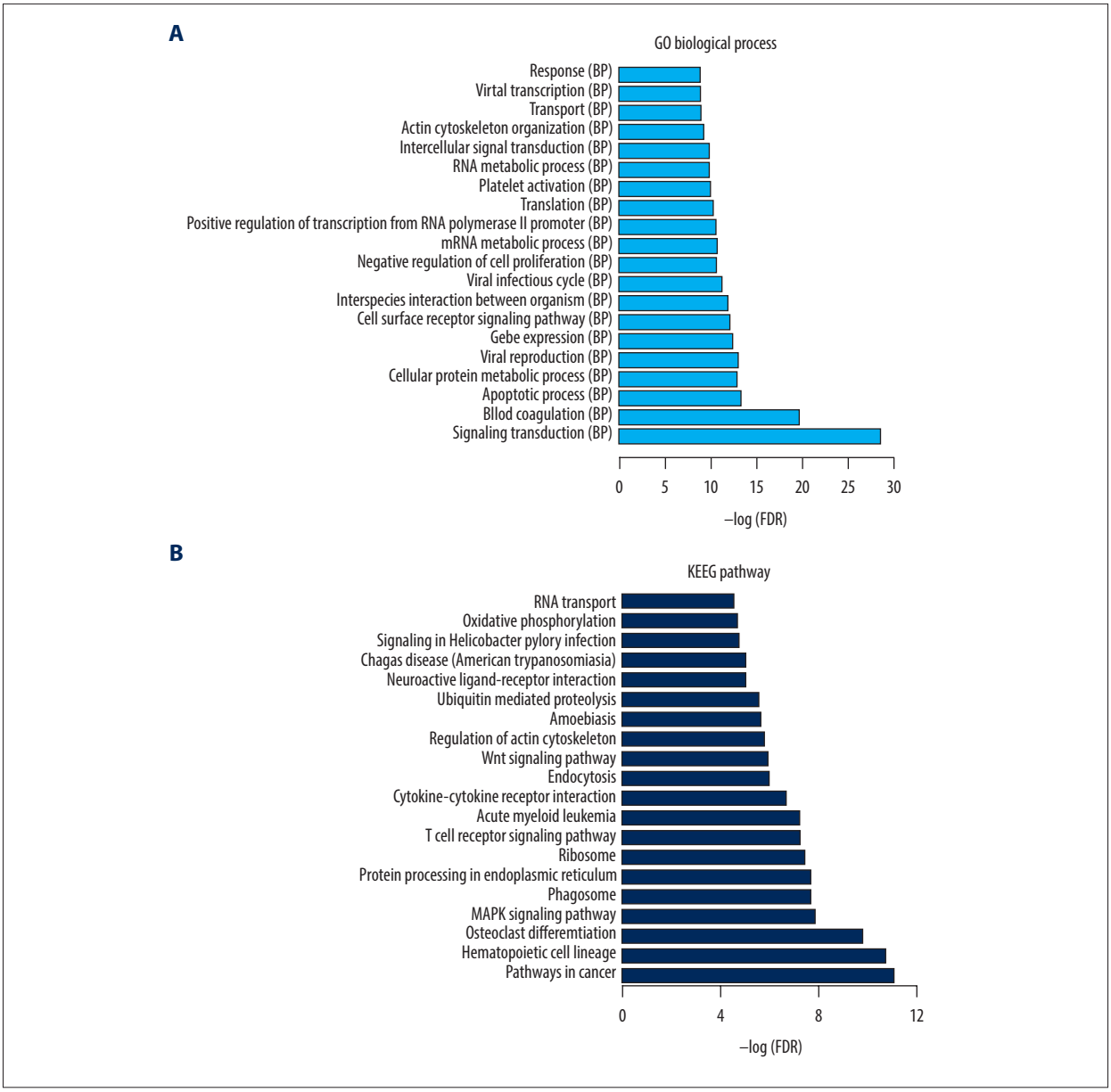

Figure 5. The enriched biological functions of the differentially expressed genes (DEGs) in the whole blood of patients with Parkinson's disease (PD). (**A**) The enriched biological process of DEGs. (**B**) The enriched the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the most common DEGs.

integrate mRNA expression data from patients with Parkinson's disease (PD), and compared the differentially expressed genes (DEGs) in tissue from the substantia nigra and from whole blood in patients with PD and normal controls. The MAPK signaling pathway, the Wnt signaling pathway, and the Notch signaling pathway were significantly enriched in patients with PD in this study.

It has previously been reported that the MAPK signaling pathway is involved in the pathogenesis of PD. Activation of the apoptosis signaling cascade involving apoptosis signal-regulating kinase 1 (ASK1)[2] results in the destruction of dopaminergic neurons in the substantia nigra in PD [10]. Also, p38, MAPK, and PI3K/AKT signaling contribute to the imbalance between pro-apoptotic and anti-apoptotic pathways in PD [11]. Liu et al. reported that miR-181a regulates cell apoptosis and cell autophagy by inhibiting the p38/MAPK/JNK pathway in PD [6]. Also, miR-96 has been shown to inhibit dopaminergic neuronal apoptosis through the blockade of the MAPK signaling pathway by upregulating the expression of the calcium voltage-gated channel auxiliary subunit gamma 5 (CACNG5) gene in a mouse model of PD [12]. Simvastatin inhibits the activation

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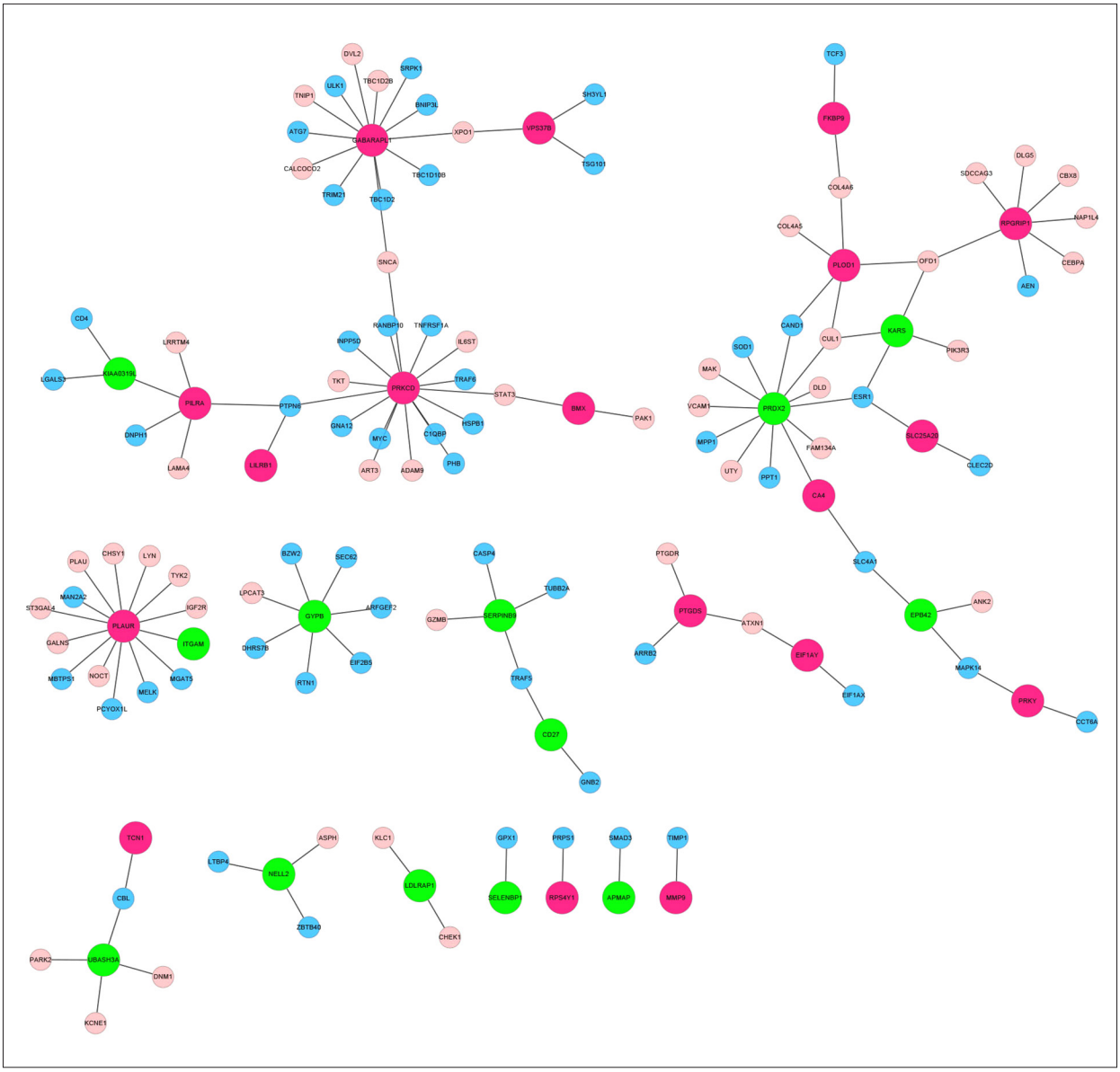

Figure 6. The protein–protein interaction (PPI) network of the top 20 upregulated and top 20 down-regulated differentially expressed genes (DEGs) in the whole blood and substantia nigra tissue of patients with Parkinson's disease (PD). The red and green nodes indicate the top upregulated DEGs and the top down-regulated DEGs in the whole blood of patients with PD. The red and green nodes indicate the top upregulated DEGs and the top down-regulated DEGs in the substantia nigra tissue of patients with PD.

of the NADPH oxidase/p38 MAPK pathway, enhances the expression of antioxidant proteins, and protects against oxidative stress in animal models of PD [13].

In this study, the Wnt pathway and the Notch signaling pathway were also significantly enriched in PD. The essential roles of the Wnt pathway and the Notch signaling pathway have been previously reported. Glycogen synthase kinase-3β contributes to the balance between neurogenesis and gliosis in a rat model of PD through the Wnt pathway and the Notch signaling pathway [14]. Leucine-rich repeat kinase 2 (LRRK2) is a key molecule in the pathogenesis of familial and idiopathic PD, which may negatively regulate the Notch signaling pathway, accelerate neural stem cell differentiation, and modulate the function and survival of differentiated dopaminergic neurons in PD [15]. Also, a previous study showed that osthole, a natural coumarin compound, reduced MPTP-induced PD in a mouse model by inhibiting the Notch signaling pathway [16].

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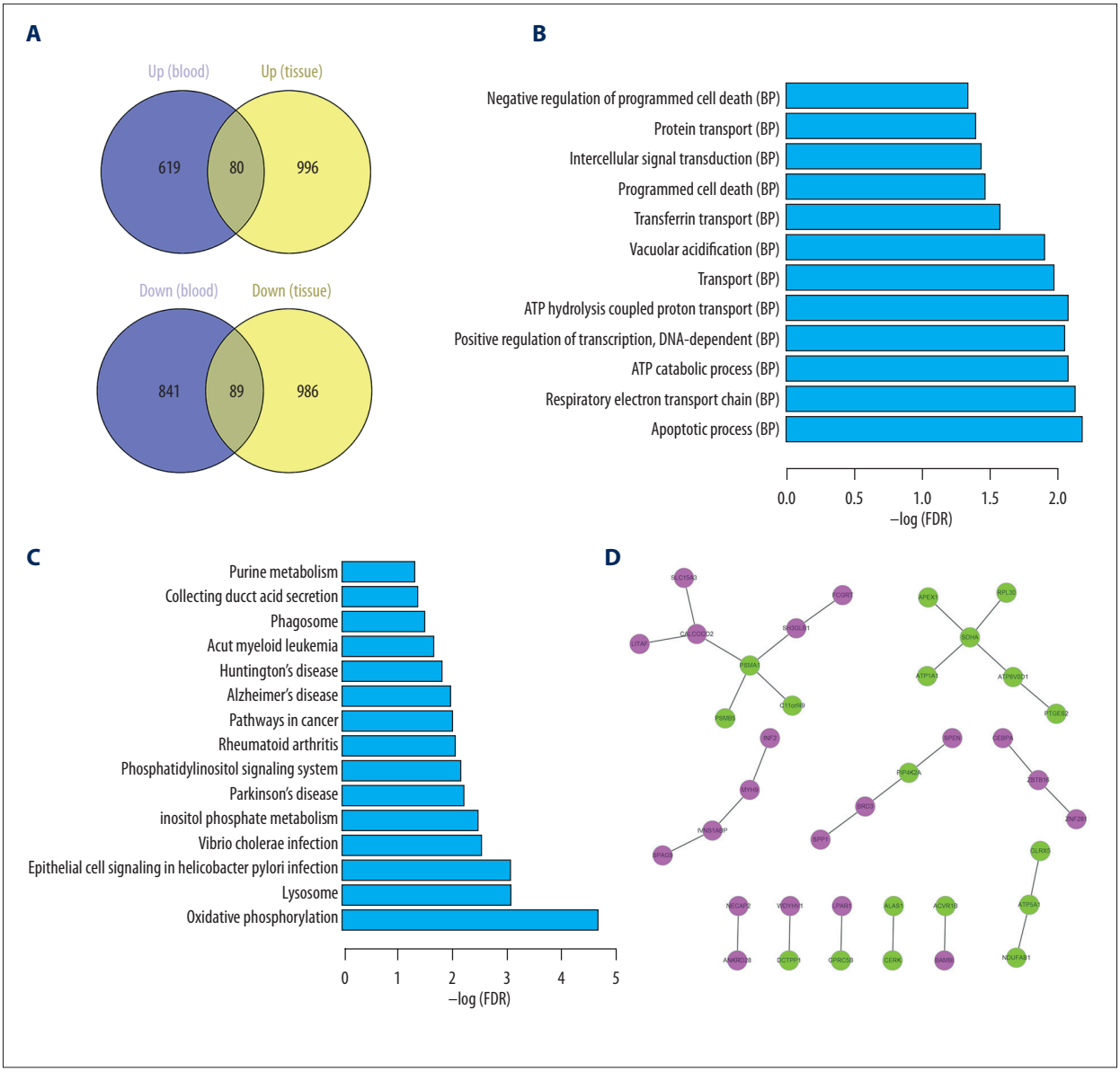

Figure 7. The common differentially expressed genes (DEGs) in the substantia nigra tissue and whole blood of patients with Parkinson's disease (PD). (**A**) The overlapping DEGs in the substantia nigra and whole blood in PD. (**B**) The enriched biological process of common DEGs. (**C**) The enriched the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the most common DEGs. (**D**) The protein–protein interaction (PPI) network of the common DEGs. The red and blue nodes indicate the upregulated and down-regulated DEGs, respectively.

Wnt proteins are required for basic cell developmental processes, including cell senescence, cell proliferation, and cell division. The Wnt signaling pathway is involved in the pathogenesis of PD as targeted methylation sequencing showed that Wnt signaling was dysregulated in PD [17]. Curcumin showed protective effects against oxidative stress-induced injury in a rat model of PD via the Wnt/β-catenin signaling pathway [18]. The Wnt/β-catenin signaling pathway could regulate dopaminergic neuronal survival, recovery, regeneration in the MPTP mouse model of PD [19].

In the present study, PSMA1 and SDHA were the hub proteins in the PPI network and the most common DEGs identified in the substantia nigra tissue and whole blood of patients with PD. In 2013, Cron et al. reported that inducible PSMA1 that was knocked down with short-hairpin RNA (shRNA) combined with irradiation in mouse xenografts of human non-small cell lung cancer (NSCLC) significantly increased the survival of mice when compared with radiation treatment alone [20]. SDHA encodes succinate dehydrogenase complex flavoprotein subunit A, which is a complex of the mitochondrial respiratory

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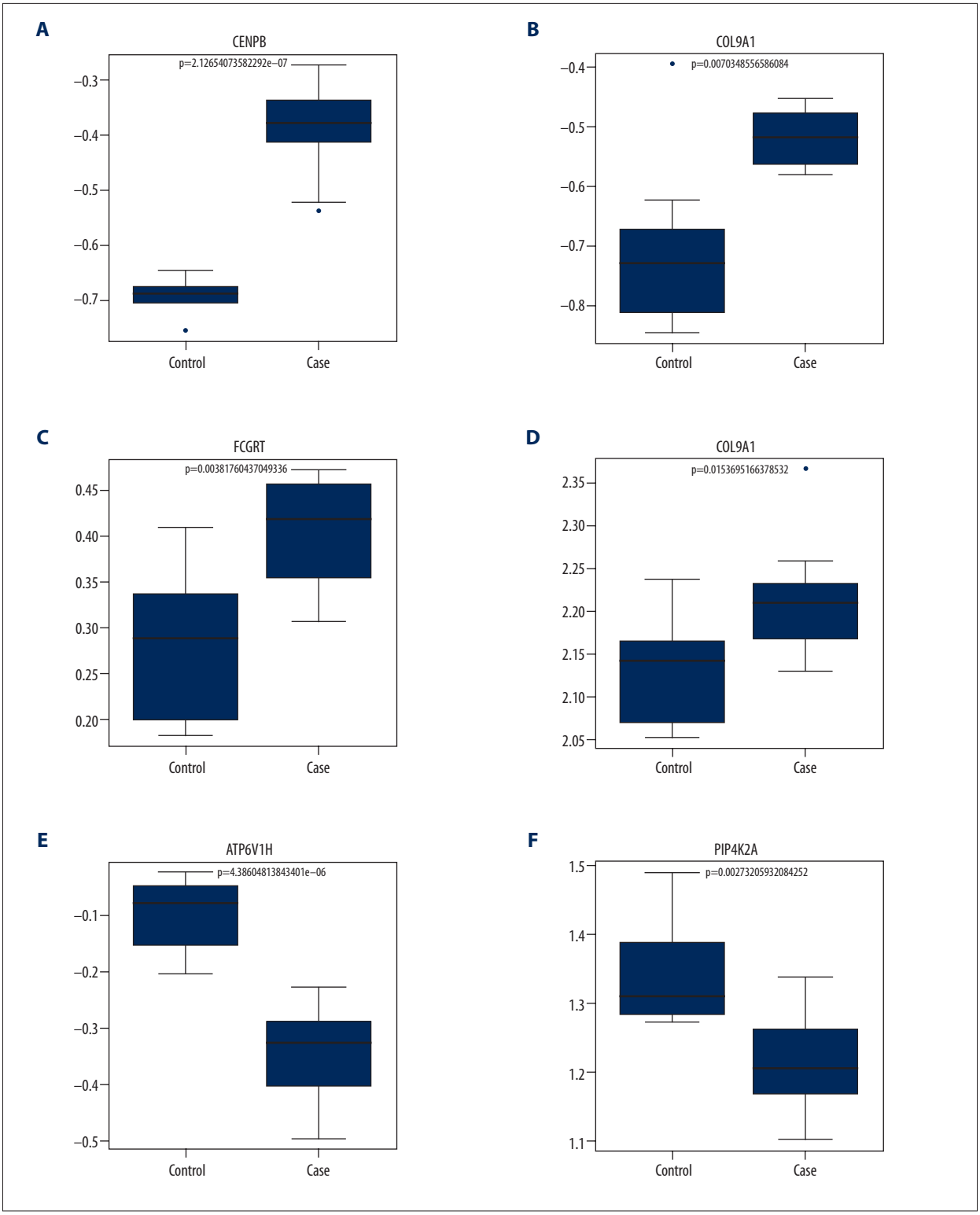

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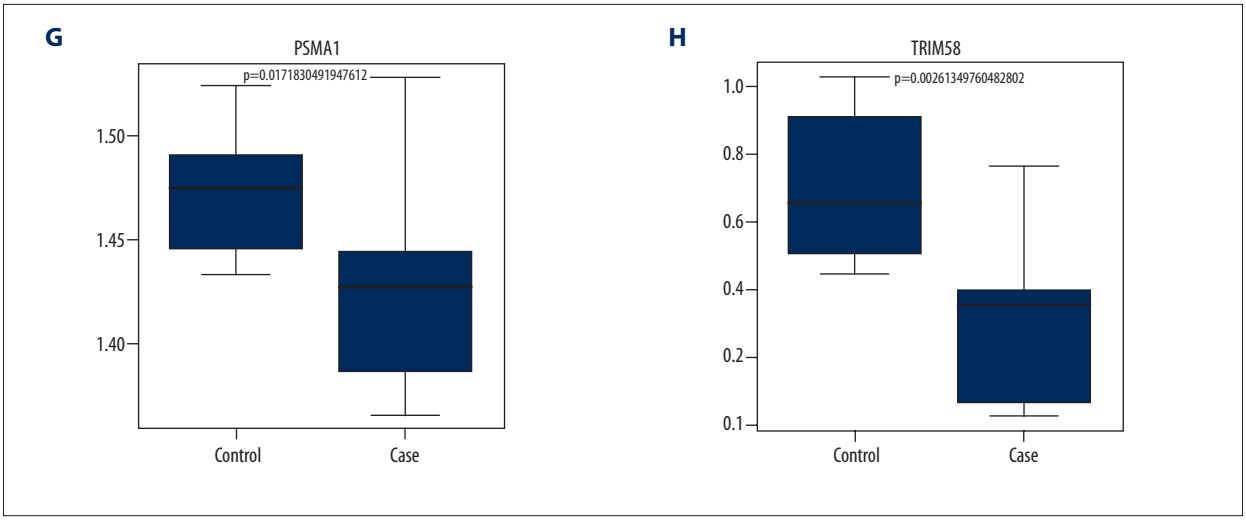

Figure 8. Box plot analysis of the expression of differentially expressed genes (DEGs) in the GSE22491 dataset. (**A**) CENPB. (**B**) COL9A1. (**C**) DMPK. (**D**) FCGRT. (**E**) ATP6V1H. (**F**) PIP4K2A. (**G**) PSMA1. (**H**) TRIM58.

chain. SDHA mutations and dysregulation are associated with the progression of diseases that include leukodystrophy, bladder paragangliomas, pituitary adenoma, and gastrointestinal stromal tumors [21]. SDHA mutations result in complex II deficiency with the development of ocular movement disorder [21]. Germline SDHA mutation and the loss of SDHA protein expression is associated with pituitary adenoma [22]. However, the biological roles of PSMA1 and SDHA in PD have not been identified. Further studies are proposed to identify the biological roles of PSMA1 and SDHA in the progression of PD using *in vivo* and *in vitro* studies.

In the present study, SORT1 and CRYAB were the hub proteins in the PPI network of substantia nigra tissue in PD. A Swedish case-control cohort study showed that the SORT1 rs17646665 gene polymorphism was significantly associated with a reduced risk of Alzheimer's Disease [23]. In a European study, SORT1 was found to be associated with an increased risk for frontotemporal dementia [24]. The CRYAB gene encodes crystallin alpha B. CYRAB is highly expressed in substantia nigra tissue and was shown to be upregulated in reactive astrocytes and microglia in a neurotoxin-induced mouse model of PD model [25]. In the present study, CRYAB was significantly upregulated in the substantia nigra in PD, which supports the findings from the previous studies. CRYAB is associated with cellular processes that include neuroinflammation and cell apoptosis. Overexpression of CRYAB has previously been reported to regulate the cell cycle and to prevent caspase-mediated apoptosis in H9C2 cardiomyocytes [26]. In mouse neonatal cardiomyocytes studied *in vitro*, exposure to H_2O_2 resulted in an increase in the expression levels of CRYAB, and CRYAB gene silencing resulted in increased levels of apoptosis after exposure to H_2O_2 [27]. However, the biological roles of SORT1 and CRYAB in the pathogenesis of PD remain to be determined by future studies.

Conclusions

This study aimed to undertake bioinformatics analysis using the publicly available Gene Expression Omnibus (GEO) database to integrate mRNA expression data from patients with PD and to compare differentially expressed genes (DEGs) in tissue from the substantia nigra and whole blood from patients with PD and normal controls. The DEGs identified included SORT1, CRYAB, PSMA1, and SDHA, which may have roles in the pathogenesis of PD through the MAPK, Wnt, and Notch signaling pathways.

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