Identification of Hub Genes And Potential Molecular Mechanisms In Peripheral Blood Mononuclear Cells of Patients With Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease. The pathogenesis of PD remains elusive, however PD appears to be caused by a complex interaction between environmental and genetic factors affecting various biological processes. The purpose of the present study is to identify hub genes and potential molecular mechanisms in peripheral blood mononuclear cells (PBMCs) of PD patients to aid early diagnosis and start treatment promptly. Two gene expression profiles (GSE22491 and GSE100054) were obtained from the Gene Expression Omnibus (GEO) database, in which 20 PBMC samples from PD patients and 17 controls were included, and the genes were analyzed with GEO2R. 1382 and 512 differentially expressed genes (DEGs) were identified in GSE22491 and GSE100054, respectively. Additionally, a total of 80 significant DEGs were found to co-exist in the two microarray datasets via Venn diagram. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed, which showed that the DEGs were mainly enriched in platelet degranulation, blood coagulation, nitric oxide mediated signal transduction, positive regulation of GTPase activity and cellular response to lipopolysaccharide. PPI network, microRNA (miRNA) - hub gene network, and transcription factor (TF)- hub gene network were constructed. In summary, the present study provides data of potential diagnostic biomarkers and therapeutic targets for PD. SRC may be a potential target for the treatment of PD. Additionally, three TFs (HNF4A, CDX2 and FUS), three miRNAs (hsa-miR-16-5p, hsa-miR-103a-3p and hsa-miR-107), may be involved in PD.

Full Text

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Tables

Table 1 Characteristics of the microarray datasets from GEO database.

GEO Accession	PMID	Platform	n	Number of PD patients	Number of healthy controls	References
GSE22491	20096956	GPL6480	18	10	8	1
GSE100054	29223072	GPL23126	19	10	9	2

Table 2 GO analysis and KEGG pathway analysis of the DEGs

Term	Description	Gene number	<i>P</i> value
biological process			
GO:0002576	platelet degranulation	8	0.0000001
GO:0007596	blood coagulation	8	0.0000056
GO:0007263	nitric oxide mediated signal transduction	3	0.0022734
GO:0043547	positive regulation of GTPase activity	8	0.0050983
GO:0071222	cellular response to lipopolysaccharide	4	0.0087910
GO:0030168	platelet activation	4	0.0092216
GO:0050900	leukocyte migration	4	0.0108249
GO:0031623	receptor internalization	3	0.0113315
GO:0051781	positive regulation of cell division	3	0.0134357
GO:0006631	fatty acid metabolic process	3	0.0162846
GO:0007166	cell surface receptor signaling pathway	5	0.0194747
GO:0001933	negative regulation of protein phosphorylation	3	0.0219959
GO:0032496	response to lipopolysaccharide	4	0.0236951
GO:0007155	cell adhesion	6	0.0287152
GO:0060100	positive regulation of phagocytosis, engulfment	2	0.0296292
GO:0042127	regulation of cell proliferation	4	0.0322611
GO:0006930	substrate-dependent cell migration, cell extension	2	0.0332716
GO:0071404	cellular response to low-density lipoprotein particle stimulus	2	0.0332716
GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	3	0.0379707
cellular component			
GO:0031092	platelet alpha granule membrane	4	0.000017
GO:0031093	platelet alpha granule lumen	5	0.000069
GO:0005615	extracellular space	16	0.000244
GO:0005886	plasma membrane	31	0.000311
GO:0070062	extracellular exosome	22	0.002681

GO:0005925	focal adhesion	6	0.020252
GO:0005884	actin filament	3	0.027985
GO:0008074	guanylate cyclase complex, soluble	2	0.035487
GO:0031090	organelle membrane	3	0.047592
GO:0045121	membrane raft	4	0.049760
molecular function			
GO:0005543	phospholipid binding	4	0.004636
GO:0020037	heme binding	4	0.016497
GO:0004383	guanylate cyclase activity	2	0.034650
KEGG pathway			
hsa04611	platelet activation	5	0.003259
hsa00230	purine metabolism	5	0.009495

Table 3 KEGG pathway analysis of the top 3 modules from the protein-protein interaction network.

Category	Term	Description	Gene number	<i>P</i> value
Module 1	hsa04062	Chemokine signaling pathway	10	2.77E-11
	hsa04727	GABAergic synapse	7	1.36E-08
	hsa05032	Morphine addiction	7	2.06E-08
	hsa04713	Circadian entrainment	7	2.68E-08
	hsa04723	Retrograde endocannabinoid signaling	7	3.88E-08
Module 2	hsa04260	Cardiac muscle contraction	4	1.23E-05
	hsa04261	Adrenergic signaling in cardiomyocytes	4	7.67E-05
	hsa05410	Hypertrophic cardiomyopathy (HCM)	3	0.001242
	hsa05414	Dilated cardiomyopathy	3	0.001439
Module 3	hsa04144	Endocytosis	5	1.61E-04
	hsa04510	Focal adhesion	4	0.0019454
	hsa05100	Bacterial invasion of epithelial cells	3	0.0043399

Table 4 Functional roles of 10 hub genes

Gene symbol	Full name	Function
VWF	von Willebrand factor	Pathways: PI3K-Akt signaling pathway and Focal adhesion; GO: immunoglobulin binding and protease binding
SRC	SRC proto-oncogene	Pathways: GABAergic synapse and Chemokine signaling pathway; GO: kinase activity and protein binding
ACTN2	actinin alpha 2	Pathways: Arrhythmogenic right ventricular cardiomyopathy; GO: identical protein binding and ion channel binding
F2	coagulation factor II	Pathways: Platelet activation and Phospholipase D signaling pathway; GO: heparin binding and signaling receptor binding
KDR	kinase insert domain receptor	Pathways: MAPK signaling pathway and PI3K-Akt signaling pathway; GO: protein tyrosine kinase activity and vascular endothelial growth factor binding
PPBP	pro-platelet basic protein	Pathways: Cytokine-cytokine receptor interaction and Chemokine signaling pathway; GO: CXCR chemokine receptor binding and chemokine activity
PRKACA	protein kinase cAMP-activated catalytic subunit alpha	Pathways: Dopaminergic synapse and Wnt signaling pathway; GO: cAMP-dependent protein kinase activity and ubiquitin protein ligase binding
SELP	selectin P	Pathways: Cell adhesion molecules; GO: calcium ion binding and protein binding
PF4	platelet factor 4	Pathways: Cytokine-cytokine receptor interaction and Chemokine signaling pathway; GO: CXCR chemokine receptor binding and chemokine activity
CCL5	C-C motif chemokine ligand 5	Pathways: Chemokine signaling pathway and TNF signaling pathway; GO: CCR chemokine receptor binding and chemokine activity

Figures

Figure 1

Identification of differentially expressed genes. a Volcano plot of GSE22491 data, b Volcano plot of GSE100054 data. Red points, significantly upregulated genes. Green points, significantly downregulated genes. Black points, genes with no significant difference, c Venn diagram of DEG selection in microarray datasets

Figure 2

Enriched Gene Ontology terms of differentially expressed genes obtained from the Database for Annotation. a biological process (BP), b cellular component (CC), c molecular function (MF)

a **b** **c** **Figure 4**

Top 3 modules from the PPI network. a module 1: Score = 11.125, b module 2: Score = 6.667, c module 3: Score = 4.286

Figure 5

The biologic process analysis of the top 3 modules. a module 1, b module 2, c module 3. Different colors of nodes refer to the functional annotation of ontologies

Figure 6

Interaction network and analysis of the hub genes. a PPI network of top 10 hub genes, b The biologic process analysis of hub genes. Different colors of nodes refer to the functional annotation of ontologies. $P < 0.05$ was considered statistically significant

Figure 7

MiRNA-target networks of hub genes. Blue circles represent miRNAs, and green rectangles represent hub genes