Mol Neurobiol (2017) 54:4452–4465
DOI 10.1007/s12035-016-9998-8

Network and Pathway-Based Analyses of Genes Associated with Parkinson's Disease

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Received: 29 February 2016 / Accepted: 14 June 2016 / Published online: 27 June 2016
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Abstract Parkinson's disease (PD) is a major neurodegenerative disease influenced by both genetic and environmental factors. Although previous studies have provided insights into the significant impacts of genetic factors on PD, the molecular mechanism underlying PD remains largely unclear. Under such situation, a comprehensive analysis focusing on biological function and interactions of PD-related genes will provide us valuable information to understand the pathogenesis of PD. In the current study, by reviewing the literatures deposited in PUBMED, we identified 242 genes genetically associated with PD, referred to as PD-related genes gene set (PDgset). Functional analysis revealed that biological processes and biochemical pathways related to neurodevelopment, metabolism, and immune system were enriched in PDgset. Then, pathway crosstalk analysis indicated that the enriched pathways could be grouped into two modules, with one module consisted of pathways mainly involved in neuronal signaling and another in immune response. Further, based on a global human interactome, we found that PDgset tended to have more moderate degree compared with cancer-related genes. Moreover, PD-specific molecular network was inferred using Steiner minimal tree algorithm and some potential related genes associated with PD were identified. In summary, by using network- and pathway-based methods to explore pathogenetic mechanism underlying PD, results from our work may have important implications for understanding the molecular mechanism underlying PD. Also, the framework proposed in our current work can be used to infer pathological molecular network and genes related to a specific disease.

Keywords Parkinson's disease · Functional enrichment analysis · Network analysis · Pathway crosstalk

Introduction

Parkinson's disease (PD), the most common neurodegenerative movement disorder, is characterized by a number of motor symptoms such as resting tremor, rigidity, and postural instability, as well as non-motor symptoms including autonomic, psychiatric, sensory, cognitive impairments, and dementia [1]. As a complex neurological disease and the second most predominant neurodegenerative disorder after Alzheimer's disease, PD affects approximately 1 % of the population over 60 [2] and results in more than 100,000 deaths each year globally [3]. Besides the decrease of quality of life of those with the disease and their caregivers, PD also causes heavy economic burden on society. It is estimated that, in USA alone, the economic burden made by PD can be as high as $23 billion a year [4].

As a chronic and progressive disorder, the non-motor symptoms of PD often precede motor deficits by many years. Although the pathology of the disease is featured by insufficient production and activity of dopamine resulting from the degeneration of nigrostriatal dopaminergic neurons and the accumulation of α-synuclein and other proteins into Lewy

Electronic supplementary material The online version of this article (doi:10.1007/s12035-016-9998-8) contains supplementary material, which is available to authorized users.

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bodies in neurons [5–7], PD also involves neurotransmitters other than dopamine and other brain regions. Previously, Parkinson's disease was thought to be caused primarily by environmental factors, but research is revealing that the disease develops from a complicated interplay of genetic and environmental factors [8]. In the last decade, a number of studies have contributed a lot to our understanding of the pathological and molecular mechanisms of PD, from the perspective of animal models [9–11], gene expression [12–15], genome-wide association (GWA) studies [16–19], and systems biology [20–24]. The identification of the possible essential proteins such as leucine-rich repeat kinase 2 (LRRK2), PTEN-induced putative kinase 1 (PINK1), parkin (PARK2), PARK7, ubiquitin carboxyl-terminal esterase L1 (UCHL1), glucocerebrosidase (GBA), and alpha-synuclein (SNCA) has significantly accelerated the process of understanding its molecular causes. However, the molecular basis of PD remains to be unraveled.

The complexity of PD is accompanied by clinical challenges. Till now, diagnostic test for definitive diagnosis at early stages of PD does not exist, and symptomatic treatment with drugs to increase dopamine levels or directly stimulate dopamine receptors in the damaged neurons is still one of the few approaches available for PD management [8].

Dopamine-replacement therapy remains the most effective treatment for motor deficits but does not halt disease progression, and continued efficacy requires increasing doses that frequently lead to troubling side-effects (dyskinesia). Other strategies have been proposed, but disease-modifying, neuroprotective therapies that slow or halt disease progression are unmet clinical needs. An understanding of basal ganglia circuitry helps to explain how impaired motor control and cognitive function in patients with Parkinson's disease arise from an imbalance between the striatal output pathways.

Even though a number of studies have focused on elucidating the pathogenesis of PD, few endeavors are made to implement systems biology-based analyses to decode the underpinning pathological molecular mechanisms. Considering that a complicated psychiatric phenotype may be under the influence of lots of genes with small or mild effects rather than one or two major genes with large effects [25], a comprehensive analysis of potential causal genes within a pathway [26, 27] and/or a network [28, 29] framework might provide many important insights beyond the conventional single-gene analyses. In this study, we firstly conducted a comprehensive collection of genes genetically associated with PD. Then, we performed functional enrichment analyses to identify the significant biological themes within these genetic factors. To further explore the pathogenesis of the PD in a more specific manner, we analyzed the topological characteristics of these PD-related genes in the context of human protein-protein interaction network. Moreover, PD-specific molecular network was inferred using Steiner minimal tree algorithm and evaluated. This study should provide useful insights for understanding molecular mechanisms of PD at the systems biological level.

Materials and Methods

Identification of PD-Related Genes

Candidate genes associated with PD were curated by retrieving the human genetic association studies deposited in PUBMED (http://www.ncbi.nlm.nih.gov/pubmed/). Similar to refs. [18, 30, 31], we queried for reports related to PD with the term (Parkinson's disease [MeSH]) and (polymorphism [MeSH] or genotype [MeSH] or alleles [MeSH]) not (neoplasms [MeSH]). By 7 July 2015, a total of 2277 publications were retrieved for the disorder. Among the 2277 articles, there were some biochemical studies instead of genetic association studies, due to the fact that MeSH terms polymorphism, genotype, or alleles were tagged to these biochemistry-based publications and genetic association was not the main theme. Thus, the abstracts of initial publications were reviewed, and the genetic association studies of PD were selected. From the selected publications, we narrowed our selection by focusing on those reporting a significant association of one or more genes with PD. To reduce the number of false-positive findings, the studies reporting negative or insignificant associations were not included although it is likely that some genes analyzed in these studies might be associated with PD. The full reports of the selected publications were reviewed to ensure the conclusions were supported by the content. From these studies, genes reported to be associated with PD were selected for the current study. In some studies, several genes were found to act in concert to show significant association with PD, with each gene only showing a moderate effect; these genes were also included according to our inclusion criteria of gene collection. Moreover, the associated genes from several GWA studies, showing genetic association at a genome-wide significance level or strongly proposed by authors of the original reports, were included.

Functional Enrichment Analysis of PD-Related Genes

The functional features of the PD-related genes were examined by WebGestalt [32] and ToppGene [33]. WebGestalt is a Web-based system that incorporates information from different resources to detect the biological themes out of the candidate gene lists, including evaluating the enrichment significance of gene ontology (GO) terms. The notable feature of representing GO terms enrichment results in a directed acyclic graph facilitated its usage in our GO analysis. Considering the fact that GO terms with higher hierarchical level in the GO tree structure possessed more explicit biological function [34],

we adopted the criterion that in our analysis, only the leaf GO terms of biological processes with false discovery rate (FDR) value smaller than 0.05 were kept as the significantly enriched ones. Due to timely update of pathway data, ease of access, transparency of features, and visibility in publications, ToppGene was selected to analyze the biochemical pathways enriched in the candidate genes. Basically, the genes with their symbols and/or corresponding NCBI Entrez Gene IDs were uploaded into the server and compared with the genes included in each canonical pathway based on the Kyoto Encyclopedia of Genes and Genomes (KEGG; www.genome.jp/kegg) and Biocarta (www.biocarta.com) pathway databases. All the pathways with one or more genes overlapping the candidate genes were extracted, with each of them assigned a P value to denote overlap significance between the pathway and the input genes via Fisher's exact test. Thereafter, the pathways with FDR value less than 0.05 were considered to be significantly enriched.

Pathway Crosstalk Analysis

We further performed pathway crosstalk analysis to explore the interactions among significantly enriched pathways. To describe the overlap between any given pair of pathways, two measurements were computed, i.e., the Jaccard Coefficient (JC) $= \left|\frac{A \cap B}{A \cup B}\right|$ and the Overlap Coefficient (OC) $= \frac{|A \cap B|}{\min(|A|,|B|)}$, where A and B are the lists of genes included in the two tested pathways. To construct the pathway crosstalk, we implemented the following procedure:

1. Select a set of pathways for crosstalk analysis. Only the pathways with P_{BH} value less than 0.05 were used. Meanwhile, the pathways containing less than three candidate genes were removed because pathways with too few genes may have insufficient biological information.
2. Count the number of shared candidate genes between any pair of pathways. Pathway pair with less than two overlapped genes was removed.
3. Calculate the overlap of all pathway pairs and rank them. All the pathway pairs were ranked according to their JC and OC values.
4. Visualize the selected pathway crosstalk with the software Cytoscape [35].

Construction of the Human Interactome

To investigate the interaction and correlation between the genes associated with PD, we constructed a relatively comprehensive and reliable human interactome and the potential molecular network topological characteristics of gene sets related to PD were inferred and analyzed. First, we downloaded the human protein-protein interaction (PPI) data from the Protein Interaction Network Analysis (PINA) platform (release version: 21 May 2014) [36], which pooled and curated non-redundant physical interaction data from six major protein interaction databases, i.e., IntAct, BioGRID, DIP, HPRD, MINT, and MIPS/MPact. At the same time, a human interactome compiled by a recent study [37], which contained 141,296 physical interactions between 13,460 proteins, including protein-protein and regulatory interactions, metabolic pathway interactions, and kinase-substrate interactions, was adopted as another interaction data source. After excluding the redundant and self-interacting pairs and using Uniprot Retrieve/ID mapping tool (http://www.uniprot.org/uploadlists) to map these interactome data onto NCBI human protein-coding genes, we constructed a relatively comprehensive human physical interactome by merging the two data sets, which contained 16,022 nodes and 228,122 edges.

Construction of PD-Specific Network via Steiner Minimal Tree Algorithm

Disease subnetwork extraction could provide us with the hints for how the disease-related molecules react with each other. Although several methods have been developed for subnetwork extraction [38, 39], it has been shown that there is a network parsimony principle in the context of biological processes [40], i.e., underlying causal molecular pathways or/and networks are often in line with the shortest molecular paths between known disease-associated components, such as disease-related genes or proteins. Steiner minimal tree algorithm coincides with this biological principle, which uses a greedy heuristic strategy to iteratively link the smaller trees into larger ones until there is only one tree connecting all seed nodes [41]. GenRev, a tool to search the optimal additional nodes for the connection of input seed genes via the Steiner minimal tree algorithm [42], was used to extract specific potential pathological network from our human interactome by using the collected genes associated with PD as input seeds. Since the human PPI network is still far from complete, some proteins may simply have more interaction information than others because they are better studied, instead of they are biologically more important. To alleviate the influence of the genes with extremely high interactions on the network construction, the reciprocal of the degree of each node was used as its weight in building the Steiner minimal tree. To assess the non-randomness of the constructed network, we first generated 1000 random networks with the same number of vertices and interactions as the PD-specific network using Erdos-Renyi model in R igraph package [43]. Then, we calculated the arithmetic average values of the shortest-path distance and clustering coefficient. Depending on the number of random networks with average shortest-path distance (N_{D}) smaller than that of the PD-specific networks and the number of

random networks with average clustering coefficient (N_C) higher than the observed clustering coefficient, we could assess the significance level of non-randomness. Finally, we calculated the empirical P value using N_D/1000 and N_C/1000, separately.

Results

Identification of Genes Reported To Be Associated with PD

By searching PUBMED, we extracted publications on the genetic association studies related to Parkinson's disease. In this procedure, only the publications reporting a significant association of gene(s) with the disease were collected; those by the authors of original literatures reporting a negative association or insignificant result were not included. A detailed list of all genes reported to be associated with Parkinson's disease is provided in Supplemental Table 1.

Altogether, a gene set (referred to as PD-related genes gene set (PDgset)) with 242 members reported to be significantly associated with PD were collected from more than 200 studies (Supplemental Table 1). Among them were two nAChR subunit genes, i.e., CHRNA5 and CHRNB3, three dopamine receptors, i.e., DRD2, DRD3, and DRD4, and two serotonin receptors, i.e., HTR2A and HTR6. A couple of genes encoding transporters were also included, such as the dopamine transporter (SLC6A3), serotonin transporter (SLC6A4), glucose transporters (SLC2A9 and SLC2A13), as well as ion transporters (e.g., SLC11A2, SLC41A1, and SLCO3A1). The other genes were those involving the functions related to nitric oxide synthesis (NOS1, NOS2, and NOS3), peptidoglycan recognition (PGLYRP2, PGLYRP3, and PGLYRP4), immune response (e.g., IL1A, IL6, IL10, and LINGO2), as well as mitochondrial function (e.g., MT-ATP6, MT-CO1, MT-CYB, and MTIF3). The diversity of the genes significantly associated with Parkinson's disease clearly demonstrated the complexity of this disorder.

Biological Functions Enriched in PDgset

Functional enrichment analysis revealed a more specific function pattern of these genes (Supplemental Table 2). Among the GO terms significantly enriched in the candidate genes, include those associated with drug response, neurodevelopment, or synaptic transmission. GO terms related to drug response (e.g., response to amphetamine, response to nicotine, and response to alcohol) and metabolism (e.g., xenobiotic metabolic process) were enriched in genes in PDgset. These results were consistent with the findings that complicated connections existed between the pathophysiological of Parkinson's disease and drug abuse [44, 45]. Terms directly related to synaptic transmission (e.g., regulation of synaptic transmission, dopaminergic; dopamine uptake involved in synaptic transmission; and neurotransmitter secretion), dopamine metabolism (e.g., dopamine biosynthetic process and regulation of dopamine metabolic process), and other neuronal function (e.g., neuron migration, regulation of neuronal synaptic plasticity, midbrain development, and memory) were included. Also, GO terms related to immune function (e.g., positive regulation of interleukin-6 production, negative regulation of inflammatory response, and negative regulation of immune effector process) were also enriched in these genes. These results indicated the candidate genes collected were relatively reliable for following up bioinformatics analysis.

Pathway Enrichment Analysis in PDgset

Identifying the biochemical pathways enriched in the candidate genes may provide valuable hints for our understanding of the molecular mechanisms underlying PD. We searched for enriched pathways in the PDgset using ToppGene and found 44 significant enrichment pathways for PD (Table 1). Consistent with previous studies [46], several pathways related to metabolism, e.g., drug metabolism-cytochrome P450 (ranked 1st in Table 1) and metabolism of xenobiotics by cytochrome P450 (ranked 3rd in Table 1), were enriched in PDgset. Also, neurotransmitter-related pathways were identified, such as dopaminergic synapse, serotonergic synapse, tyrosine metabolism, etc., all of which were closely related to signal transduction. Moreover, immune-associated biological processes consisting of cytokines and inflammatory response, cytokine network, IL-10 anti-inflammatory signaling, IL-5 signaling, and signal transduction through IL-1R, were also significantly enriched, suggesting that the immunological system were involved in the etiology and pathological process of PD. Further, pathways related to estrogen signaling and adipocytokine signaling were also enriched in the candidate genes, which were consistent with previous studies [47, 48].

Crosstalk Among Significantly Enriched Pathways

To take a further step beyond identifying lists of significantly enriched pathways and to understand how they interact with each other, we performed a pathway crosstalk analysis among the 44 significantly enriched pathways. The approach was based on the assumption that two pathways were considered to crosstalk if they shared a proportion of PDgset [28]. There were 39 pathways containing three or more members in PDgset, of which, 36 pathways met the criterion for crosstalk analysis, i.e., each pathway shared at least two genes with one or more other pathways. All the pathway pairs (edges) formed by these pathways were utilized to build the pathway crosstalk, and the overlapping level between two pathways was measured according to the average scores of coefficients

Table 1 Pathways enriched in PDgset

Pathways	*P* value[a]	P_{BH} value[b]	Genes included in the pathway[c]
Drug metabolism-cytochrome P450	2.20×10^{-7}	9.79×10^{-6}	ADH1C, ADH7, CYP2D6, CYP2E1, GSTM1, GSTO1, GSTP1, GSTT1, MAOA, MAOB
Cytokines and inflammatory response	4.54×10^{-7}	1.26×10^{-5}	CXCL8, HLA-DRA, HLA-DRB1, IL10, IL1A, IL6, TNF
Metabolism of xenobiotics by cytochrome P450	4.97×10^{-7}	1.26×10^{-5}	ADH1C, ADH7, CYP1A1, CYP2D6, CYP2E1, EPHX1, GSTM1, GSTO1, GSTP1, GSTT1
Cytokine network	1.05×10^{-6}	2.05×10^{-5}	CXCL8, IL10, IL18, IL1A, IL6, TNF
Dopaminergic synapse	2.53×10^{-6}	4.15×10^{-5}	AKT1, COMT, DRD2, DRD3, DRD4, GRIN2A, GSK3B, MAOA, MAOB, SLC18A2, SLC6A3, TH
Tyrosine metabolism	3.87×10^{-6}	6.03×10^{-5}	ADH1C, ADH7, COMT, DBH, MAOA, MAOB, TH
IL-10 anti-inflammatory signaling pathway	7.51×10^{-6}	1.11×10^{-4}	HMOX1, IL10, IL1A, IL6, TNF
IL-5 signaling pathway	1.65×10^{-5}	2.24×10^{-4}	HLA-DRA, HLA-DRB1, IL1B, IL6
Antigen processing and presentation	7.98×10^{-5}	8.59×10^{-4}	HLA-C, HLA-DQA2, HLA-DQB1, HLA-DRA, HLA-DRB1, HLA-DRB5, HSPA1A, TNF
Hematopoietic cell lineage	1.32×10^{-4}	1.37×10^{-3}	CD14, HLA-DRA, HLA-DRB1, HLA-DRB5, IL1A, IL1B, IL6, TNF
Cells and molecules involved in local acute inflammatory response	1.70×10^{-4}	1.71×10^{-3}	CXCL8, IL1A, IL6, TNF
Signal transduction through IL-1R	2.30×10^{-4}	2.18×10^{-3}	IL1A, IL1B, IL1RN, IL6, TNF
NOD-like receptor signaling pathway	4.21×10^{-4}	3.75×10^{-3}	CXCL8, IL18, IL1B, IL6, NOD2, TNF
HIF-1 signaling pathway	4.76×10^{-4}	4.12×10^{-3}	AKT1, ERBB2, HMOX1, IL6, INS, NOS2, NOS3, TF
Antigen-dependent B cell activation	9.86×10^{-4}	6.99×10^{-3}	HLA-DRA, HLA-DRB1, IL10
Calcium signaling pathway	1.14×10^{-3}	7.76×10^{-3}	ADORA2A, BST1, ERBB2, GRIN2A, HTR2A, HTR6, NOS1, NOS2, NOS3, P2RX7
Prolactin signaling pathway	1.47×10^{-3}	9.73×10^{-3}	AKT1, ESR1, ESR2, GSK3B, INS, TH
Adhesion and diapedesis of granulocytes	1.59×10^{-3}	1.01×10^{-2}	CXCL8, IL1A, TNF
Mineral absorption	1.77×10^{-3}	1.11×10^{-2}	HMOX1, HMOX2, SLC11A2, TF, VDR
Oxidative phosphorylation	2.09×10^{-3}	1.28×10^{-2}	MT-ATP6, MT-CO1, MT-CYB, MT-ND1, MT-ND3, MT-ND4, MT-ND5, NDUFV2
Catecholamine biosynthesis, tyrosine => dopamine => noradrenaline => adrenaline	2.85×10^{-3}	1.62×10^{-2}	DBH, TH
TNF signaling pathway	2.87×10^{-3}	1.62×10^{-2}	AKT1, IL1B, IL6, MMP9, NOD2, TNF, TNFRSF1A
Arginine and proline metabolism	2.91×10^{-3}	1.62×10^{-2}	MAOA, MAOB, NOS1, NOS2, NOS3
Mechanism of gene regulation by peroxisome proliferators via PPARa(alpha)	3.14×10^{-3}	1.72×10^{-2}	HSPA1A, INS, NOS2, PPARGC1A, TNF
Serotonergic synapse	3.51×10^{-3}	1.85×10^{-2}	CYP2D6, HTR2A, HTR6, MAOA, MAOB, SLC18A2, SLC6A4
Chaperones modulate interferon signaling pathway	3.97×10^{-3}	2.00×10^{-2}	HSPA1A, TNF, TNFRSF1A
Th1/Th2 differentiation	3.97×10^{-3}	2.00×10^{-2}	HLA-DRA, HLA-DRB1, IL18
Biosynthesis of neurotransmitters	4.23×10^{-3}	2.09×10^{-2}	DBH, TH
One carbon pool by folate	4.62×10^{-3}	2.25×10^{-2}	MTHFR, MTR, SHMT1
NF-kappa B signaling pathway	4.78×10^{-3}	2.27×10^{-2}	CD14, CXCL8, IL1B, PARP1, TNF, TNFRSF1A
Tryptophan metabolism	4.80×10^{-3}	2.27×10^{-2}	ACMSD, CYP1A1, MAOA, MAOB
Lysosome	5.09×10^{-3}	2.37×10^{-2}	CTSD, GBA, GLA, LAMP3, SCARB2, SLC11A2, SMPD1
MAPK signaling pathway	5.18×10^{-3}	2.38×10^{-2}	AKT1, BDNF, CD14, FGF20, HSPA1A, IL1A, IL1B, MAPT, RRAS2, TNF, TNFRSF1A
Phagosome	5.97×10^{-3}	2.70×10^{-2}	CD14, HLA-C, HLA-DQA2, HLA-DQB1, HLA-DRA, HLA-DRB1, HLA-DRB5, NOS1
Adipocytokine signaling pathway	7.04×10^{-3}	3.09×10^{-2}	AKT1, POMC, PPARGC1A, TNF, TNFRSF1A
Estrogen signaling pathway	7.53×10^{-3}	3.26×10^{-2}	AKT1, ESR1, ESR2, HSPA1A, MMP9, NOS3
Neuroactive ligand-receptor interaction	8.02×10^{-3}	3.38×10^{-2}	ADORA2A, CHRNA5, CHRNB3, CRHR1, DRD2, DRD3, DRD4, GRIN2A, HTR2A, HTR6, P2RX7

Table 1 (continued)

Pathways	*P* value[a]	P_{BH} value[b]	Genes included in the pathway[c]
GABA biosynthesis, eukaryotes, putrescine => GABA	9.81×10^{-3}	4.07×10^{-2}	MAOA, MAOB
Toll-like receptor signaling pathway	9.91×10^{-3}	4.07×10^{-2}	AKT1, CD14, CXCL8, IL1B, IL6, TNF
Glutathione metabolism	1.13×10^{-2}	4.48×10^{-2}	GSTM1, GSTO1, GSTP1, GSTT1
Histidine metabolism	1.20×10^{-2}	4.61×10^{-2}	HNMT, MAOA, MAOB
Free radical-induced apoptosis	1.21×10^{-2}	4.61×10^{-2}	CXCL8, TNF
SODD/TNFR1 signaling pathway	1.21×10^{-2}	4.61×10^{-2}	TNF, TNFRSF1A
TNFR1 signaling pathway	1.32×10^{-2}	4.97×10^{-2}	PARP1, TNF, TNFRSF1A

PDgset Parkinson's disease-related genes gene set

[a] *P* values were calculated by Fisher's exact test

[b] P_{BH} values were adjusted by Benjamini and Hochberg (BH) method

[c] Two hundred forty-two PD-related genes included in the pathway

JC and OC. Based on their crosstalk, the pathways could be roughly grouped into two major modules, with each module including pathways shared more interactions compared with other pathways and may likely be involved in the same or similar biological process (Fig. 1). One module mainly consisted of neuronal signaling-related pathways, such as calcium signaling, dopaminergic synapse, and seotonergic synapse, as well as the metabolic pathways of neurotransmitters or drug, such as tryptophan metabolism and tyrosine metabolism. The second module was primarily dominated by immune system-related pathways, including role of cytokines in mediating communication between immune cells, toll-like receptor signaling, and others. At the same time, the two modules were not independent, instead, they were connected via a couple of pathway interactions.

Network Topological Characteristics of PDgset

Analyzing the topological properties of nodes and interactions between nodes via PPI-based analysis can help to reveal the underpinning biological-related mechanisms associated with the network [49]. To delineate the network topological characteristics of PDgset, the degree of the constructed network was analyzed in the context of our constructed human interactome. For comparison, the network features of two other gene sets, i.e., a list of nicotine addiction-related genes (NAGenes) with 220 members [18] and a list of cancer-related genes (CAgenes) with 569 genes (Cancer Gene Census database; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/) were also analyzed. Nicotine addiction can evoke the dysfunction of neuronal

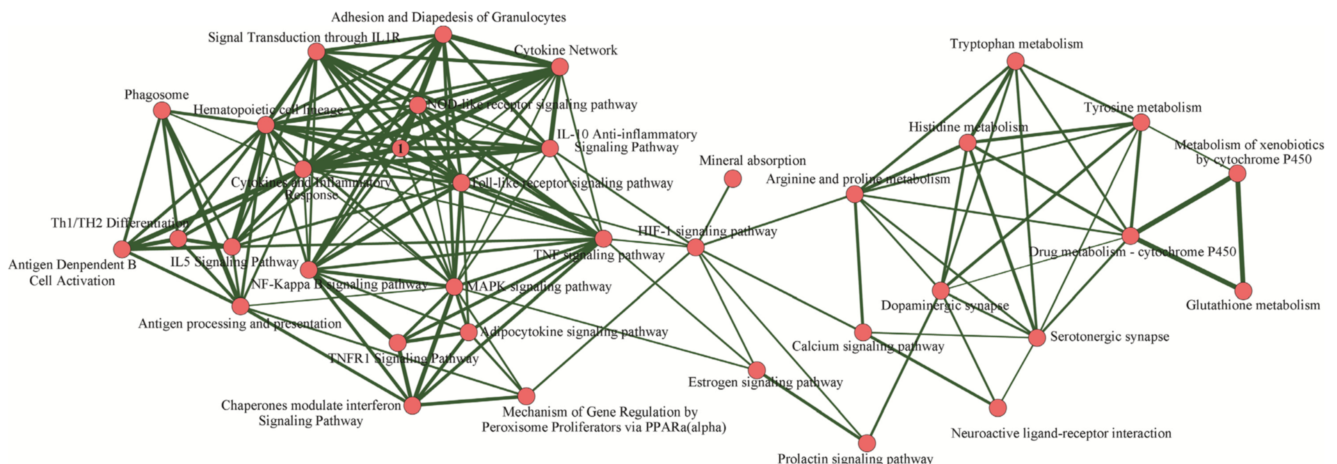

Fig. 1 Pathway crosstalk among PDgset-enriched pathways. *Nodes* represent pathways, and *edges* represent crosstalk between pathways. Edge-width corresponds to the score of specific pathway pair. Larger edge-width indicates higher score. *Node marked with bold number 1* represents the pathway "cells and molecules involved in local acute inflammatory response"

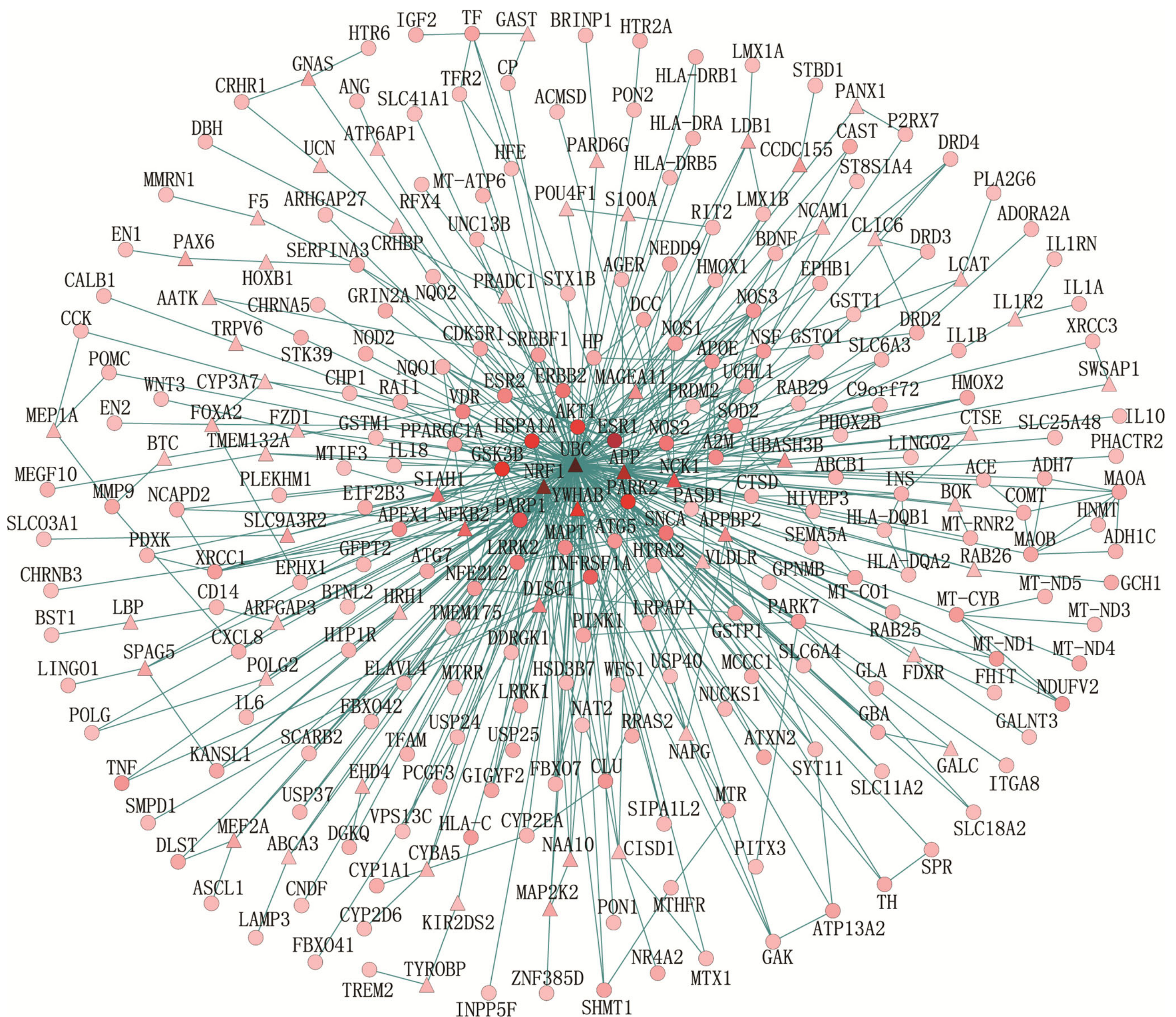

Fig. 2 Parkinson's disease-specific network. PD-specific network was constructed via node-weighted Steiner minimal tree algorithm, with 276 nodes and 522 edges. *Ellipse nodes* are genes of PDgset, and *triangular nodes* are non-original/extended genes. *Node color* corresponds to its degree in the human interactome. *Darker color* indicates higher degree

system, and some biological mechanisms may be related to PD. Cancer has been well studied and is expected to have substantially different pathological characteristics from PD. Of all three gene sets, the nodes with specific degrees (number of genes connecting with a given gene) were scattered in a range from 1 to more than 1000. For the PDgset, 215 of 242 genes could be mapped onto the human interactome network, with a mean degree of 37.1 (i.e., each gene connected with 37.1 other genes on average); for the NAGenes, 210 of 220 genes could be mapped onto the human interactome, with an average degree of 46.1; for the cancer genes, 551 out of 569 had the corresponding nodes in our interactome, with an average degree of 74.5. Further, for PDgset and NAGenes, 57.9 % (140/242) and 56.8 % (125/220) genes fell in the degree interval of 1–20, respectively, while only 30 % of the cancer genes were included in this range. Thus, PDgset and NAgenes tended to have lower or moderate links than the cancer genes and their degree distributions appeared to be closer to each other, indicating obvious distinctions between neurological disorders and cancer, at least from the aspect of network.

PD-Specific Molecular Network Inference

To unravel the possible pathological molecular network of PDgset, we extracted the specific network for PD from the

human interactome network using the Steiner minimal tree algorithm. Basically, this approach linked maximal members of a list of genes with the minimal intermediate nodes. As shown in Fig. 2, the network of PD contained 276 nodes and 522 edges. To check the non-randomness of the extracted network, 1000 random networks were created using Erdos-Renyi model and their corresponding average shortest-path distance and average clustering coefficient were compared with the corresponding values of the PD-specific network. For these random subnetworks, the mean shortest-path distance was 4.3, significantly larger than that of the PD-related network (shortest-path distance, 2.9; empirical $p < 0.001$). The average clustering coefficient of the random networks was 0.01, statistically significantly less than that of the PD distinctive network (clustering coefficient, 0.25; empirical $p < 0.001$). Thus, our extracted PD-specific network is a non-random network.

As specified, 215 of the 242 genes in PDgset were included in human interactome network and the extracted PD-specific network, which accounted for 88.8 % of the genes in PDgset and 77.9 % of 276 genes in the PD-specific network, indicating a high coverage of PDgset in the subnetwork. On the other hand, 61 genes in the PD-specific network were not included in PDgset (Table 2). These genes had close interaction with genes known to be related to the biological processes involved in Parkinson’s disease, they may also be involved in the pathological condition of this disorder. Of note, some of the genes, e.g., nuclear respiratory factor 1 (NRF1), cathepsin E (CTSE), neural cell adhesion molecule 1 (NCAM1), and coagulation factor V (F5), had been purportedly associated with PD in previous studies [24, 50–53]. Some of these genes may have not been found to be directly involved in the pathogenesis of PD, but genes interacting with them or other members from the same family have been demonstrated to play a role in such procedure. For example, Solute carrier family 9 subfamily A member 3 regulator 2 (SLC9A3R2), encoding a member of the NHERF family of PDZ scaffolding proteins that mediate many cellular processes by binding to and regulating the membrane expression and protein-protein interactions of membrane receptors and transport proteins, was included in the PD-specific network. It can interact with serum and glucocorticoid-regulated kinase 1 (SGK1), an important player in cell death processes underlying neurodegerative diseases including PD [54–56]. 14-3-3 protein beta/alpha (YWHAB), a member of the highly conserved 14-3-3 family whose members are involved in mediating signal transduction by binding to phosphoserine-containing proteins, was also included in the PD-specific network. YWHAZ, another member from the same family, has been found to play a key role in a number of neurodegenerative disorders [57]. Thus, these genes provided a list of potential candidates for further exploration.

Discussion

In the past decades, much has been learnt about the molecular mechanisms underlying Parkinson’s disease from studies on human subjects, animals, or cell models. Although with the development of high-throughput technology more and more genes/proteins have been identified to be related to this disorder, a thorough understanding of the biological processes related to pathogenesis of PD at the molecular level is still far from complete. So, there is a need for decoding the potential pathogenesis of PD at systems biology level. In this study, by collecting the genes genetically associated with PD, systematically exploring the interaction of these genes using pathway and network analyses, we provided a comprehensive and systematic framework to delineate related biochemical processes.

Although candidate gene-based genetic association and biochemical studies have provided us with the knowledge about factors involving PD, a systematic approach described in our study has significant advantages. First, in this work, we conducted a comprehensive collection of the genes potentially genetically associated with PD, which provided valuable sources for further analysis. Moreover, as many diseases are caused by the altered expression of many genes, each with a small to moderate effect, which act in concert to influence several biological pathways that eventually leads to the clinical phenotype [58], we retrieved several genes collectively showing association with PD, which supplies a high coverage of related genes. In addition, pathway analysis taking account of the biological relevance of genes can be more robust to possible false positives caused by various genes in different studies, and coupling with network analysis, it might provide a more comprehensive view of the molecular mechanisms underlying PD.

Biological function enrichment analysis identified the specific biological processes involved by PDgset. Our GO enrichment analysis indicated that these genes for PD participated in drug response processes, immune system, metabolic process, and neurodevelopment. For instance, terms such as response to ethanol, positive regulation of interleukin-6 production, xenobiotic metabolic process, and neurotransmitter biosynthetic process were significantly enriched in PD-related genes, indicating the importance of these activities in the pathologic processes of PD. Of significance, we found that the GO biological process terms of visual learning, sleep, and memory were also in the enriched list, in line with previous findings of various

Table 2 Genes included in PD-specific network but not in PDgset

Gene symbol	Gene name
AATK	Apoptosis-associated tyrosine kinase
ABCA3	ATP-binding cassette, subfamily A (ABC1), member 3
APP	Amyloid beta (A4) precursor protein
APPBP2	Amyloid beta precursor protein (cytoplasmic tail) binding protein 2
ARFGAP3	ADP-ribosylation factor GTPase activating protein 3
ATP6AP1	ATPase, H+ transporting, lysosomal accessory protein 1
BOK	BCL2-related ovarian killer
BTC	Betacellulin
CCDC155	Coiled-coil domain containing 155
CISD1	CDGSH iron sulfur domain 1
CLIC6	Chloride intracellular channel 6
CRHBP	Corticotropin releasing hormone binding protein
CTSE	Cathepsin E
CYB5A	Cytochrome b5 type A (microsomal)
CYP3A7	Cytochrome P450, family 3, subfamily A, polypeptide 7
DISC1	Disrupted in schizophrenia 1
EHD4	EH-domain containing 4
F5	Coagulation factor V (proaccelerin, labile factor)
FDXR	Ferredoxin reductase
FOXA2	Forkhead box A2
FZD1	Frizzled class receptor 1
GALC	Galactosylceramidase
GAST	Gastrin
GNAS	GNAS complex locus
HOXB1	Homeobox B1
HRH1	Histamine receptor H1
IL1R2	Interleukin 1 receptor, type II
KIR2DS2	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 2
LBP	Lipopolysaccharide binding protein
LCAT	Lecithin-cholesterol acyltransferase
LDB1	LIM domain binding 1
MAGEA11	Melanoma antigen family A11
MAP2K2	Mitogen-activated protein kinase kinase 2
MEF2A	Myocyte enhancer factor 2A
MEP1A	Meprin A, alpha (PABA peptide hydrolase)
NAA10	*N*(alpha)-acetyltransferase 10, NatA catalytic subunit
NAPG	*N*-ethylmaleimide-sensitive factor attachment protein, gamma
NCAM1	Neural cell adhesion molecule 1
NCK1	NCK adaptor protein 1
NFKB2	Nuclear factor of kappa light polypeptide gene enhancer in B cells 2 (p49/p100)
NRF1	Nuclear respiratory factor 1
PANX1	Pannexin 1
PARD6G	Par-6 family cell polarity regulator gamma
PAX6	Paired box 6
POLG2	Polymerase (DNA directed), gamma 2, accessory subunit
POU4F1	POU class 4 homeobox 1
PRADC1	Protease-associated domain containing 1
RAB26	RAB26, member RAS oncogene family

Table 2 (continued)

Gene symbol	Gene name
S100P	S100 calcium binding protein P
SIAH1	Siah E3 ubiquitin protein ligase 1
SLC9A3R2	Solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 2
SPAG5	Sperm associated antigen 5
SWSAP1	SWIM-type zinc finger 7 associated protein 1
TMEM132A	Transmembrane protein 132A
TRPV6	Transient receptor potential cation channel, subfamily V, member 6
TYROBP	TYRO protein tyrosine kinase binding protein
UBASH3B	Ubiquitin associated and SH3 domain containing B
UBC	Ubiquitin C
UCN	Urocortin
VLDLR	Very low-density lipoprotein receptor
YWHAB	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta

PD Parkinson's disease, *PDgset* PD-related genes gene set

physiological processes, including learning, sleep, and memory [59–61], involved in PD.

Pathway analysis revealed that immunologic system-related pathways were enriched in PDgset, which further consolidates ties between the pathology of PD and immune-specific activities. Numerous studies have confirmed the role of neuroinflammation in the PD pathology, with inflammatory cytokines playing a central role [62–64]. In the meantime, three pathways related to monoamine neurotransmitters were found to be enriched in the PDgset, consistent with their indispensable roles in the pathogenesis and pathological development of PD [65, 66]. Dopamine and serotonin are separately major excitatory and inhibitory neurotransmitter, and both of them exert critical effects in the development of PD. These neurotransmitters interact with the corresponding receptors, thus triggering a series of neural signaling pathways, and then ultimately modulate various physiological processes. They could directly or indirectly act in the impairing course of synaptic plasticity such as long-term potentiation and long-term depression of animal models or PD patients [67–69], subsequently damaging several synapse-based biological functions such as cognition and memory. Therefore, these neurotransmitter-associated pathways might be involved in the early developmental stages of neurodegeneration and facilitate the emergence of dopamine neuron losses and impaired cognitive and memory activities. We found out that the adipocytokine signaling was in the enriched pathway list for PD-related genes. Inside the pathway, leptin, as the key protein, was dissected to exert neuroprotective effects on specific neuronal cells and reduce the risk of PD, strengthening the notion that there might be a link between neurodegeneration and abnormal or disrupted adipocytokine signaling [70]. As indicated by these results, the molecular mechanisms underlying PD are so complex and further thorough studies are needed to decipher their underlying pathologic mechanisms.

Of significance, in pathway crosstalk analysis, we identified two main modules. One module was mainly dominated by the pathways associated with the activity of the nervous system. Among these pathways, dopaminergic synapse, serotonergic synapse, calcium signaling pathway, and neuroactive ligand-receptor interaction have been well studied to be involved in neuron or central nervous system, as well as the progress of Parkinson's disease [71–73]. For another module, the pathways were mainly involved in immune response or related functions. Subsequently, we collected the genes contributing to the crosstalk, and the most frequently shared genes included dopamine receptors (e.g., DRD2, DRD3, and DRD4), monoamine oxidase A (MAOA), and B (MAOB), tumor necrosis factor (TNF), interleukins (e.g., IL-6, IL-10, and IL-18), suggesting these genes might be more potential targets in the development of PD. Furthermore, the two modules were connected into a larger interacting profile via multiple edges formed by pathways, suggesting that these modules, as well as the pathways included, function in a concerted manner, instead of in separate ways. Based on such information, the major pathways involved in Parkinson's disease can be summarized into a schematic representation (Fig. 3). In earlier work [17], a set of genes related to nicotine dependence (ND) was analyzed by similar approach and three major functional modules were revealed from the pathway

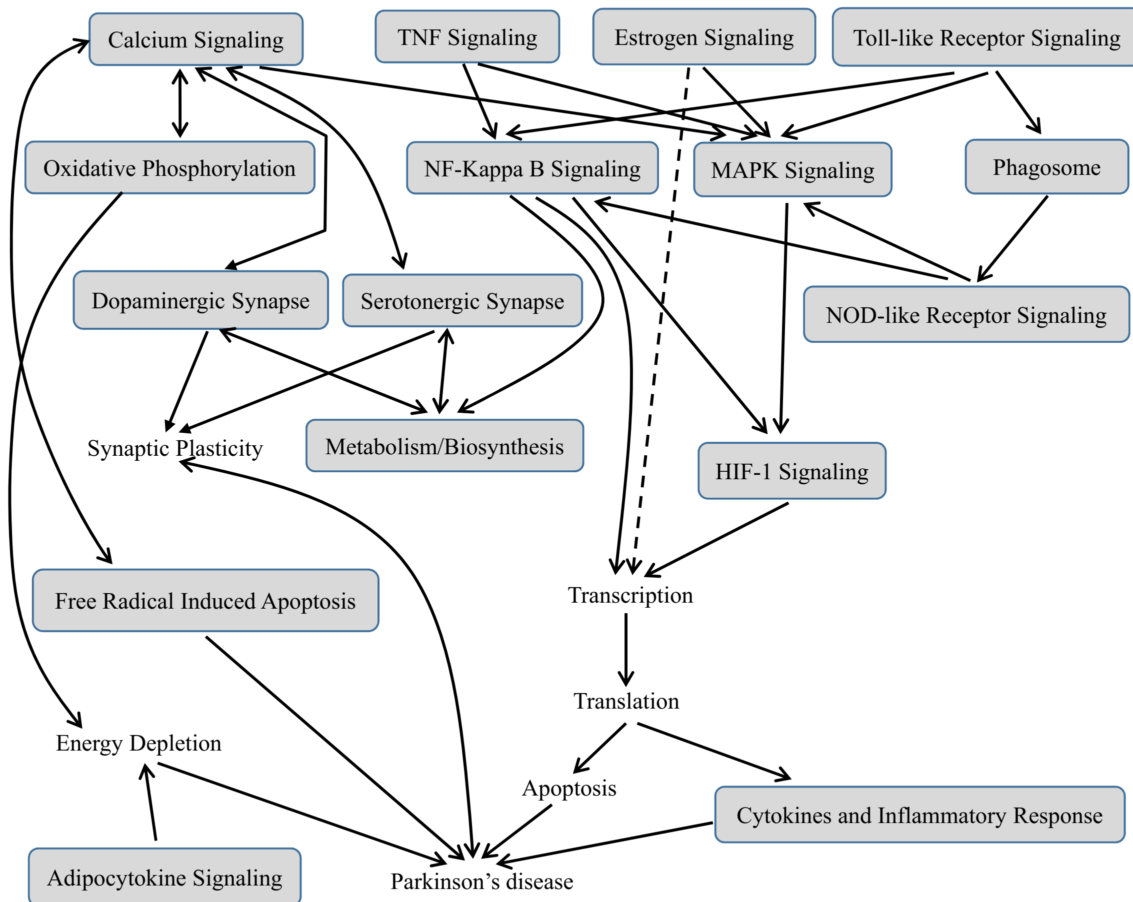

Fig. 3 Schematic representation of the major pathways involved in Parkinson's disease. Genetic studies have indicated that Parkinson's disease is a complex disorder. These main pathways were connected on the basis of their biological relations

crosstalk analysis, i.e., one module mainly consisting of neurodevelopment-related signaling pathways, one module including the immune system-related pathways, and a third one mainly including metabolic pathways of neurotransmitters or drug. As we know, ND is a neuronal disorder stemming from dysregulated neuronal activities triggered by chronic nicotine exposure, and PD is a neurodegenerative disease due to genetic reasons and/or various environmental factors. However, it has been observed that there is a close relationship between smoking and PD [74] as nicotine may act as a potential neuroprotective agent for PD, which means the two diseases may have some overlaps in their molecular mechanisms. Thus, the functional modules, as well as the pathways included, detected for ND and PD, may represent the major biological procedures involved in each disease, and the difference of the functional modules may indicate the difference in molecular mechanisms underlying the two diseases. Of course, the identification of genes related to ND and PD is still an ongoing task. We still do not have a complete gene list for either disease yet, and it is also possible that some genes in the lists may prove to be false positives in the future. Thus, the pathways and their connections related to each disease may also be subjected to change when more evidences are obtained.

We further inferred the PD-specific network from our human reference interactome network. It was noteworthy that some extended genes not included in the PDgset but appearing in the human interactome were plausible ones reported to be associated with PD. For example, NRF1 was identified as a potential PPARGC1A target gene in PD, which was downregulated by PARIS accumulation in the nigrostriatal pathway [51]. TYROBP, a transmembrane signaling polypeptide, was identified by our network analysis. It has been demonstrated that the TYROBP-deficient mouse bore the impaired synaptic function in the microglial [75], suggesting a potential pathological role of TYROBP in PD. FOXA2, a specifically expressed protein in adult dopamine neurons, is required to generate dopaminergic neurons in the period of fetal development, which exerts a clue to its correlation with PD [76]. To investigate the protection mechanisms of glial cell line-derived neurotrophic factor (GDNF) preventing the dopaminergic neurons from degeneration, through establishing early PD rat models, Cao et al. indicated that NFKB2, the transcription factor complex nuclear factor (NF)-kappaB, as part of

NF-kappaB signaling pathway, was involved in the effects of GDNF on dopamine neurons [77]. As demonstrated by the results elaborated above, our network-inferring method could not only provide meaningful inferred network of PDgset for PD but also have the promise to identify potential related genes.

There have been several studies devoted to the curation of PD-related genes. By incorporating genetic variation, population studies, literature evidence, and gene sequences, Tang et al. developed The Mutation Database for Parkinson's Disease (MDPD) [78]. By collecting 6130 substantia nigra (SN)-expressed sequenced tags from normal SN tissues and PD patients' SN tissues, Yang et al. [79] constructed a database, namely PDbase, which contains 2698 PD-related genes, genetic variation, and functional elements. The most widely used PD-related genes are from PDGene database, built by Lill et al. [80] and Nalls et al. [20], mainly based on results pertaining to the meta-analysis for 15 independent GWAS datasets of European descent. Among these databases, only PDGene is still available now. Compared with PDGene, last updated on 19 August 2014, our data set PDgset included the more recent studies. Also, PDgene analyzed all the included datasets with a single criterion and ranked the polymorphisms according to their significance. On the other hand, in PDgset, we utilized a unified gene symbol standard to collect genes reported to be significantly associated with PD by the original authors. Since most of the genes were from association studies on individual genes, some of the genes may only have moderate *P* values, but they concerted with other genes to show a significant association with PD, which made PDgset a more comprehensive dataset for PD exploration. Thus, PDgset should provide a useful complement for PDGene.

Undeniably, there are several limitations of this study. First, our pathway and network analysis results depend entirely on genes in the retrieved literatures purported to be associated with PD. Given that identification of risk genes for PD is an ongoing process, the genes, GO biological process terms, pathways, and results from the network analysis identified in this study should be treated in the same way. Second, we accepted the results drawn by the original authors of each retrieved study in our analysis, which surely bias our results because of the imbalance and incomprehensiveness of those current available studies. Thirdly, to reduce the false-positive rate of genes, we excluded publications with negative or insignificant results. However, we cannot deny that some genes from these studies may be associated with our interested phenotype. This is largely due to the small sample size or heterogeneity or any other factors. In addition, although the number and data quality of PPI databases have been significantly improved, the human interactome is still incomplete. At the same time, owing to the limitation of current technology, some false-positive data may exist in the PPI [81]. To some extent, the incompleteness of human interactome network may affect our results [37, 82]. For example, our proposed node-weighted Steiner minimal tree algorithm should have avoided genes/proteins with fundamental biological function, such as ubiquitin C (UBC); however, due to the partialness of human interactome network, these genes/proteins are the only linkers between our collected genes. With improvement of coverage for PPI, the real molecular network will be discovered and these fundamental genes/proteins will certainly be prevented from appearing in our inferred network.

Conclusion

In this study, we adopted a systems biology framework for a comprehensive and systematic biological function- and network-based analysis of PD using associated genes compiled from selective literatures deposited in PUBMED. Through integrating the information from GO, pathway and pathway crosstalk analysis, we found that biological processes and biochemical pathways related to immunological system and neurodevelopment were enriched in PDgset and examined the inner relations among these significant pathways. Moreover, PD-specific pathological molecular network was created using Steiner minimal tree algorithm and some potential related genes associated with PD were identified. Such a systematic and comprehensive exploration of the genes involved in PD will not only improve our understanding of the contribution of genetic factors and their interaction with environmental factors to the pathogenesis of Parkinson's disease but will also help us to identify potential biomarkers for further exploration. Meanwhile, the framework proposed in our current paper can be transplanted to infer pathological molecular network and genes related to a specific disease.

Acknowledgments This project was supported in part by grants from the National Natural Science Foundation of China (grant no. 31271411, no. 61202379) and Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry of China.

Compliance with Ethical Standard

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Volta M, Milnerwood AJ et al (2015) Insights from late-onset familial parkinsonism on the pathogenesis of idiopathic Parkinson's disease. Lancet Neurol 14(10):1054–1064
2. Samii A, Nutt JG et al (2004) Parkinson's disease. Lancet 363(9423):1783–1793
3. GBD 2013 Mortality and Causes of Death Collaborators (2015) Global, regional, and national age-sex specific all-cause and

cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 385(9963):117–171
4. Findley LJ (2007) The economic impact of Parkinson's disease. Parkinsonism Relat Disord 13(Suppl):S8–S12
5. Cookson MR (2009) α-synuclein and neuronal cell death. Mol Neurodegener 4(1):9
6. Guttmacher AE, Collins FS et al (2003) Alzheimer's disease and Parkinson's disease. N Engl J Med 348(14):1356–1364
7. Langston JW (2006) The Parkinson's complex: parkinsonism is just the tip of the iceberg. Ann Neurol 59(4):591–596
8. Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386(9996): 896–912
9. Chin MH, Qian WJ et al (2008) Mitochondrial dysfunction, oxidative stress, and apoptosis revealed by proteomic and transcriptomic analyses of the striata in two mouse models of Parkinson's disease. J Proteome Res 7(2):666–677
10. Gstir R, Schafferer S et al (2014) Generation of a neuro-specific microarray reveals novel differentially expressed noncoding RNAs in mouse models for neurodegenerative diseases. RNA 20(12): 1929–1943
11. Yokoyama H, Uchida H et al (2011) Role of glial cells in neurotoxin-induced animal models of Parkinson's disease. Neurol Sci 32(1):1–7
12. Botta-Orfila T, Tolosa E et al (2012) Microarray expression analysis in idiopathic and LRRK2-associated Parkinson's disease. Neurobiol Dis 45(1):462–468
13. Dumitriu A, Latourelle JC et al (2012) Gene expression profiles in Parkinson disease prefrontal cortex implicate FOXO1 and genes under its transcriptional regulation. PLoS Genet 8(6):e1002794
14. Simunovic F, Yi M et al (2009) Gene expression profiling of substantia nigra dopamine neurons: further insights into Parkinson's disease pathology. Brain 132(7):1795–1809
15. Sun A-G, Wang J et al (2014) Identifying distinct candidate genes for early Parkinson's disease by analysis of gene expression in whole blood. Neurosci Lett 35(5):398–404
16. Do CB, Tung JY et al (2011) Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. PLoS Genet 7(6):e1002141
17. Liu M, Fan R et al (2015) Pathways and networks-based analysis of candidate genes associated with nicotine addiction. PLoS One 10(5):e0127438
18. Liu X, Liu M et al (2015) Prioritizing genes related to nicotine addiction via a multi-source-based approach. Mol Neurobiol 52(1):442–455
19. Liu ZH, Guo JF et al (2015) Analysis of several loci from genome-wide association studies in Parkinson's disease in mainland China. Neurosci Lett 587:68–71
20. Nalls MA, Pankratz N et al (2014) Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 46(9):989–993
21. Rakshit H, Rathi N et al (2014) Construction and analysis of the protein-protein interaction networks based on gene expression profiles of Parkinson's disease. PLoS One 9(8):e103047
22. Riley BE, Gardai SJ et al (2014) Systems-based analyses of brain regions functionally impacted in Parkinson's disease reveals underlying causal mechanisms. PLoS One 9(8):e102909
23. Zhang B, Xia C et al (2012) Identification of key pathways and transcription factors related to Parkinson disease in genome wide. Mol Biol Rep 39(12):10881–10887
24. Zhang X, Yin X et al (2012) Quantitative proteomic analysis of serum proteins in patients with Parkinson's disease using an isobaric tag for relative and absolute quantification labeling, two-dimensional liquid chromatography, and tandem mass spectrometry. Analyst 137(2):490–495
25. Tandon K, McGuffin P (2002) The genetic basis for psychiatric illness in man*. Eur J Neurosci 16(3):403–407
26. Glazko GV, Emmert-Streib F (2009) Unite and conquer: univariate and multivariate approaches for finding differentially expressed gene sets. Bioinformatics 25(18):2348–2354
27. Goeman JJ, Bühlmann P (2007) Analyzing gene expression data in terms of gene sets: methodological issues. Bioinformatics 23(8): 980–987
28. Jia P, Kao C-F et al (2011) A comprehensive network and pathway analysis of candidate genes in major depressive disorder. BMC Syst Biol 5(Suppl 3):S12
29. Jia P, Zheng S et al (2011) dmGWAS: dense module searching for genome-wide association studies in protein–protein interaction networks. Bioinformatics 27(1):95–102
30. Sullivan PF, Neale BM et al (2004) Candidate genes for nicotine dependence via linkage, epistasis, and bioinformatics. Am J Med Genet B Neuropsychiatr Genet 126(1):23–36
31. Wang J, Li MD (2010) Common and unique biological pathways associated with smoking initiation/progression, nicotine dependence, and smoking cessation. Neuropsychopharmacology 35(3): 702–719
32. Zhang B, Kirov S et al (2005) WebGestalt: an integrated system for exploring gene sets in various biological contexts. Nucleic Acids Res 33(suppl 2):W741–W748
33. Chen J, Bardes EE et al (2009) ToppGene Suite for gene list enrichment analysis and candidate gene prioritization. Nucleic Acids Res 37(suppl 2):W305–W311
34. Jain S, Bader GD (2010) An improved method for scoring protein-protein interactions using semantic similarity within the gene ontology. BMC Bioinf 11:562
35. Shannon P, Markiel A et al (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13(11):2498–2504
36. Cowley MJ, Pinese M et al (2012) PINA v2.0: mining interactome modules. Nucleic Acids Res 40(Database issue):D862–865
37. Menche J, Sharma A et al (2015) Disease networks. Uncovering disease-disease relationships through the incomplete interactome. Science 347(6224):1257601
38. Lemetre C, Zhang Q et al (2013) SubNet: a Java application for subnetwork extraction. Bioinformatics 29(22):2958
39. Zhang X, Zhang Z et al (2014) Extracting the globally and locally adaptive backbone of complex networks. PLoS One 9(6):e100428
40. Barabasi AL, Gulbahce N et al (2011) Network medicine: a network-based approach to human disease. Nat Rev Genet 12(1): 56–68
41. Klein P, Ravi R (1995) A nearly best-possible approximation algorithm for node-weighted Steiner trees. J Algorithms 19(1):104–115
42. Zheng S, Zhao Z (2012) GenRev: exploring functional relevance of genes in molecular networks. Genomics 99(3):183–188
43. Erdös P, Rényi A (1960) On the evolution of random graphs. Publ Math Inst Hungar Acad Sci 5:17–61
44. Atmaca M (2014) Drug-induced impulse control disorders: a review. Curr Clin Pharmacol 9(1):70–74
45. Curtin K, Fleckenstein AE et al (2015) Methamphetamine/amphetamine abuse and risk of Parkinson's disease in Utah: a population-based assessment. Drug Alcohol Depend 146:30–38
46. Mann A, Miksys SL et al (2012) The neuroprotective enzyme CYP2D6 increases in the brain with age and is lower in Parkinson's disease patients. Neurobiol Aging 33(9):2160–2171
47. Martins M, Rosa A et al (2011) Convergence of miRNA expression profiling, alpha-synuclein interacton and GWAS in Parkinson's disease. PLoS One 6(10):e25443
48. Ragonese P, D'Amelio M et al (2006) Implications for estrogens in Parkinson's disease. Ann N Y Acad Sci 1089(1):373–382
49. Barabasi A-L, Oltvai ZN (2004) Network biology: understanding the cell's functional organization. Nat Rev Genet 5(2):101–113

50. Pan C, Zhou Y et al (2014) Targeted discovery and validation of plasma biomarkers of Parkinson's disease. J Proteome Res 13(11): 4535–4545
51. Shin JH, Ko HS et al (2011) PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. Cell 144(5):689–702
52. Thomas RR, Keeney PM et al (2012) Impaired complex-I mitochondrial biogenesis in Parkinson disease frontal cortex. J Parkinsons Dis 2:67–76
53. van Dijk KD, Persichetti E et al (2013) Changes in endolysosomal enzyme activities in cerebrospinal fluid of patients with Parkinson's disease. Mov Disord 28(6):747–754
54. Chun J, Kwon T et al (2002) The Na(+)/H(+) exchanger regulatory factor 2 mediates phosphorylation of serum- and glucocorticoid-induced protein kinase 1 by 3-phosphoinositide-dependent protein kinase 1. Biochem Biophys Res Commun 298(2):207–215
55. Schoenebeck B, Bader V et al (2005) Sgk1, a cell survival response in neurodegenerative diseases. Mol Cell Neurosci 30(2):249–264
56. Yun CC, Chen Y et al (2002) Glucocorticoid activation of Na(+)/H(+) exchanger isoform 3 revisited. The roles of SGK1 and NHERF2. J Biol Chem 277(10):7676–7683
57. Joo Y, Schumacher B et al (2015) Involvement of 14-3-3 in tubulin instability and impaired axon development is mediated by Tau. FASEB J 29(10):4133–4144
58. Williams-Skipp C, Raman T et al (2009) Unmasking of a protective tumor necrosis factor receptor I-mediated signal in the collagen-induced arthritis model. Arthritis Rheum 60(2):408–418
59. Kensinger EA, Shearer DK et al (2003) Working memory in mild Alzheimer's disease and early Parkinson's disease. Neuropsychology 17(2):230
60. Postuma RB, Gagnon JF et al (2009) Idiopathic REM sleep behavior disorder in the transition to degenerative disease. Mov Disord 24(15):2225–2232
61. Saur R, Maier C et al (2012) Clock test deficits related to the global cognitive state in Alzheimer's and Parkinson's disease. Dement Geriatr Cogn Disord 33(1):59–72
62. Rosenkranz D, Weyer S et al (2007) Higher frequency of regulatory T cells in the elderly and increased suppressive activity in neurodegeneration. J Neuroimmunol 188(1):117–127
63. Wang Y, Hancock AM et al (2011) Complement 3 and factor h in human cerebrospinal fluid in Parkinson's disease, Alzheimer's disease, and multiple-system atrophy. Am J Pathol 178(4):1509–1516
64. Alam Q, Alam MZ et al (2016) Inflammatory process in Alzheimer's and Parkinson's diseases: central role of cytokines. Curr Pharm Des 22(5):541–548
65. Shen J (2010) Impaired neurotransmitter release in Alzheimer's and Parkinson's diseases. Neurodegener Dis 7(1-3):80–83
66. Xu Y, Yan J et al (2012) Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease. Prog Neurobiol 97(1):1–13
67. Battaglia F, Ghilardi MF et al (2006) Impaired long-term potentiation-like plasticity of the trigeminal blink reflex circuit in Parkinson's disease. Mov Disord 21(12):2230–2233
68. Cooke SF, Bliss TV (2006) Plasticity in the human central nervous system. Brain 129(Pt 7):1659–1673
69. Costa C, Sgobio C et al (2012) Mechanisms underlying the impairment of hippocampal long-term potentiation and memory in experimental Parkinson's disease. Brain 135(Pt 6):1884–1899
70. Weng Z, Signore AP et al (2007) Leptin protects against 6-hydroxydopamine-induced dopaminergic cell death via mitogen-activated protein kinase signaling. J Biol Chem 282(47):34479–34491
71. Cali T, Ottolini D et al (2014) Calcium signaling in Parkinson's disease. Cell Tissue Res 357(2):439–454
72. Haleem DJ (2015) 5-HT1A receptor-dependent control of nigrostriatal dopamine neurotransmission in the pharmacotherapy of Parkinson's disease and schizophrenia. Behav Pharmacol 26(1-2):45–58
73. Politis M, Niccolini F (2015) Serotonin in Parkinson's disease. Behav Brain Res 277:136–145
74. Thacker EL, O'Reilly EJ et al (2007) Temporal relationship between cigarette smoking and risk of Parkinson disease. Neurology 68(10):764–768
75. Roumier A, Béchade C et al (2004) Impaired synaptic function in the microglial KARAP/DAP12-deficient mouse. J Neurosci 24(50):11421–11428
76. Kittappa R, Chang WW et al (2007) The foxa2 gene controls the birth and spontaneous degeneration of dopamine neurons in old age. PLoS Biol 5(12):e325
77. Cao JP, Wang HJ et al (2008) The involvement of NF-kB p65/p52 in the effects of GDNF on DA neurons in early PD rats. Brain Res Bull 76(5):505–511
78. Tang S, Zhang Z et al (2009) MDPD: an integrated genetic information resource for Parkinson's disease. Nucleic Acids Res 37(Database issue):D858–862
79. Yang JO, Kim WY et al (2009) PDbase: a database of Parkinson's disease-related genes and genetic variation using substantia nigra ESTs. BMC Genomics 10(3):S32
80. Lill CM, Roehr JT et al (2012) Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database. PLoS Genet 8(3):e1002548
81. Ideker T, Sharan R (2008) Protein networks in disease. Genome Res 18(4):644–652
82. Koh GC, Porras P et al (2012) Analyzing protein-protein interaction networks. J Proteome Res 11(4):2014–2031