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

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INTRODUCTION

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.

ANALYTICAL PROCEDURES

In the current work, we adopt the following analytical procedure (see figure 1):

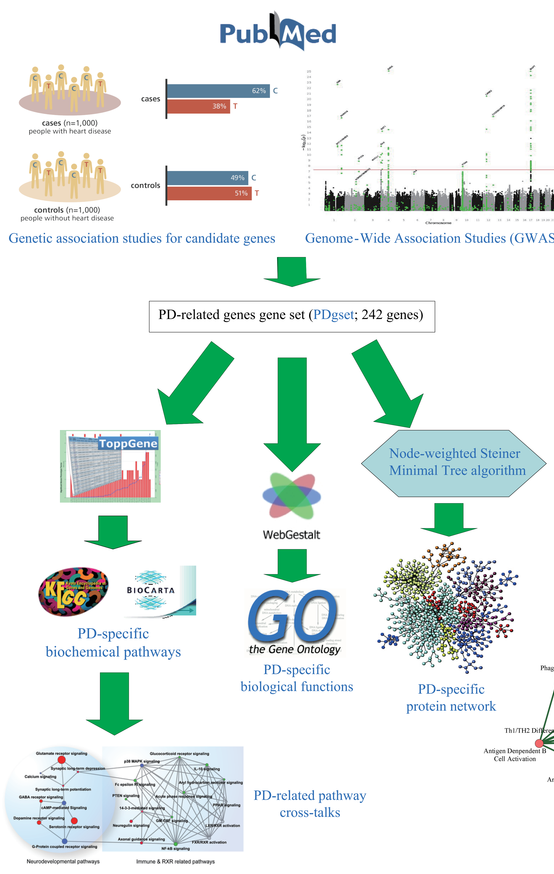

Figure 1 Workflow of the current study.

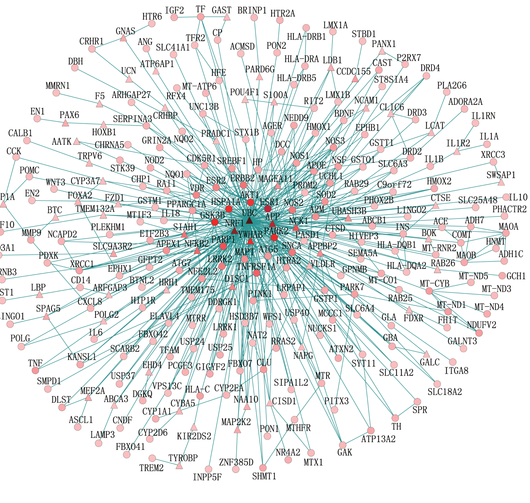

Figure 4 Parkinson's disease-specific network.

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.

RESULTS

A) Biological Functions Enriched in PDgset

Among the GO terms significantly enriched in the candidate genes, include those associated with drug response, neurodevelopment, or synaptic transmission. Also, GO terms related to immune function were also enriched in these genes (details are not shown here).

B) Pathway Enrichment Analysis in PDgset

We identified 44 significant enrichment pathways for PD (see Figure 2). Pathways related to metabolism, neurotransmitter-related, and immune-associated biological processes, were found. Furthermore, pathways related to estrogen signaling and adipocytokine signaling were also enriched in the candidate genes, which deserve further investigations.

C) In-depth dissection of molecular mechanisms of PD

Pathway crosstalk analysis was used to study interrelationship among PD-specific pathways (see Figure 3). Figure 4 shows the PD-distinctive protein network via node-weighted Steiner Minimal Tree algorithm. Finally, we summarized main pathway network of PD based on the above results (see Figure 5).

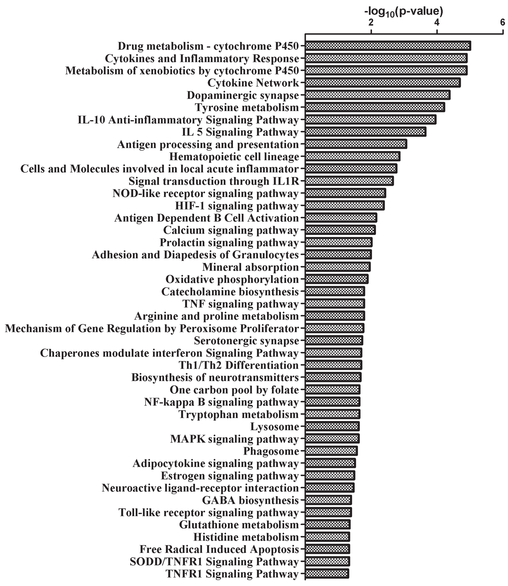

Figure 2 Significantly enriched pathways for PD.

Pathways from KEGG and BioCarta databases are enriched among PDgset, with corrected p-value no more than 0.05. Y-axis designates names of 44 pathways and x-axis corresponds to –log10 transformation of p-values. Larger transformed p-values suggest more significantly enriched pathways.

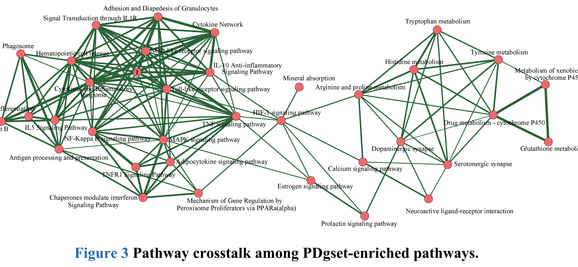

Figure 3 Pathway crosstalk among PDgset-enriched pathways.

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".

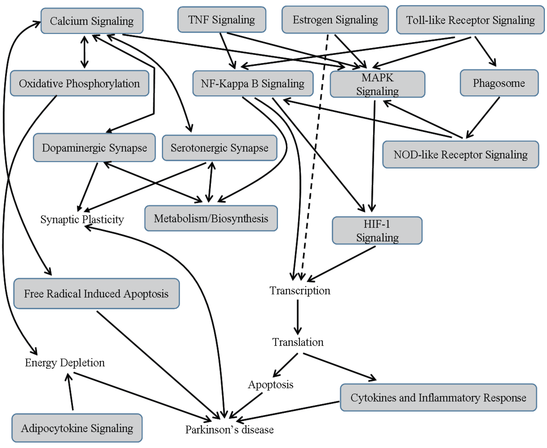

Figure 5 Schematic representation of the major pathways involved in Parkinson's disease.

Genetic studies have indicated that Parkinson's disease is a complex disorder. These main pathways were connected on the basis of their biological relations.