Research Article

Potential Therapeutic Drugs for Parkinson’s Disease Based on Data Mining and Bioinformatics Analysis

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The objective is to search potential therapeutic drugs for Parkinson’s disease based on data mining and bioinformatics analysis and providing new ideas for research studies on “new application of conventional drugs.” Method differential gene candidates were obtained based on data mining of genes of PD brain tissue, original gene data analysis, differential gene crossover, pathway enrichment analysis, and protein interaction, and potential therapeutic drugs for Parkinson’s disease were obtained through drug-gene relationship. Result. 250 common differential genes were obtained from 3 research studies, and 31 differential gene candidates were obtained through gene enrichment analysis and protein interaction. 10 drugs such as metformin hydrochloride were directly or indirectly correlated to differential gene candidates. Conclusion. Potential therapeutic drugs that may be used for prevention and treatment of Parkinson’s disease were discovered through data mining and bioinformatics analysis, which provided new ideas for research and development of drugs. Results showed that metformin hydrochloride and other drugs had certain therapeutic effect on Parkinson’s disease, and melbaine (DMBG) can be used for treatment of Parkinson’s disease and type 2 diabetes patients.

1. Introduction

With a high morbidity and a high disability rate, Parkinson’s disease is the second degenerative disease of nervous system. Presently, treatment Parkinson’s disease focuses on symptomatic treatment, which can just relief the symptoms and can neither effectively inhibit the progression of the disease nor cure it [1, 2]. Research studies on “new application of conventional drugs” based on differential genes of the brain tissue may enable to cure Parkinson’s disease (PD). Aspirin is a famous drug with “new application of conventional drugs.” Aspirin was first applied to antipyretic-analgesic and anti-inflammatory treatment as a nonsteroidal anti-inflammatory drug. Then, it was found to be able to inhibit antiplatelet aggregation of TXA2, and thus it has been extensively applied to treatment of cardiovascular and cerebrovascular diseases [3, 4]. However, the mining model of indications for drug therapy was different from traditional drug R&D modes. The latter depended on physical tests, such as cell test, animal test, and clinical test, which were made to determine chemical components of relevant substances, and synthesis of drug compounds and featured high investment, high risk, and long R&D cycle [5, 6]. It was an alternative solution for drug R&D to readjust existing drugs for treatment of other diseases, guarantee of drug safety, lower cost, and higher R&D efficiency [7].

This paper was aimed at providing new drug candidates for PD treatment and providing new methods and ideas for drug screening through data mining and bioinformatics analysis of PD brain tissue.

2. Method

(i) As shown in Figure 1, “PD (Parkinson’s disease)” and “gene expression profiling” were retrieved in GEO dataset (gene expression omnibus dataset), and references were screened. Selection criteria for retrieved references: the approval of Ethics Committee was
indicated in the research; diagnosis of PD was demonstrated by clinic and neuropathology; the brain tissue of normal people and PD patients was the research object; original gene data can be obtained; original gene chip had high quality. Exclusion criteria: the approval of Ethics Committee was not indicated in the research; diagnosis of PD was not demonstrated by clinic and neuropathology; the research object was not the brain tissue of normal people and PD patients; original gene data cannot be obtained; original gene chip had poor quality. Screened original gene data was obtained and downloaded.

(ii) The quality of original gene data was evaluated using R language and RStudio software, and $\log_{10}(FC) > 1$ or $\log_{10}(FC) < (-1)$ was set to obtain differential genes.

(iii) Venn diagram of differential genes obtained in the research studies using bioinformatics and evolutionary genomics (http://bioinformatics.psb.ugent.be/webtools/venn/), and common differential genes were obtained.

(iv) KEGG pathway analysis of common differential genes was made using DAVID (https://david.ncifcrf.gov/) and differential genes closely related to PD were screened [8].

(v) Protein-protein interaction of genes closely related to PD was figured out using STRING (https://string-db.org/), so as to make the protein-protein interaction closer and reduce the range of differential gene candidates. Confidence level $\geq 0.90$ was set using STRING and protein-protein interactions, and differential gene candidates were obtained [9].

(vi) Differential gene candidates were inputted into DGIdb dataset (http://dgidb.genome.wustl.edu/) so as to obtain the interaction between drug and gene and drug candidates for treatment of PD. Relevant information of drug was obtained using PubChem dataset, the approval for clinic or clinical test was searched in ClinicalTrials dataset, and drug candidates were analyzed [10, 11].

3. Result

One hundred sixty-three retrieved results were obtained from the retrieval of “PD (Parkinson’s disease)” and “gene expression profiling” in GEO dataset, and based on strict screening, 3 of them conformed the screening requirements and can be applied to our research studies (Moran et al. [12] (chip number: GSE8397); Lewandowski et al. [13] (chip number: GSE19587); Edna et al. [14] (chip number: GSE20333)). 3 searches were analyzed using RStudio software, and 1191, 4484, and 2173 differential genes were obtained, respectively. The Venn diagram of 3 groups of differential genes was drawn using “bioinformatics and evolutionary genomics,” as shown in Figure 2, and 250 common differential genes were obtained.

KEGG pathway analysis was made for 250 differential genes using DAVID, and pathways whose $P$ value was less than 0.05 were screened. Figure 3 showed KEGG pathway analysis of 250 differential genes whose $P$ value was less than 0.05. Metabolic pathways, carbon metabolisms, cysteine and methionine metabolism, and Parkinson’s disease were 4 KEGG pathways with a smaller $P$ value, and they contained 51, 12, 7, and 12 differential genes, respectively, as shown in Table 1. 82 differential genes of the aforesaid 4 pathways were further analyzed.

Protein-protein interaction of 82 differential genes of the aforesaid 4 pathways was obtained using STRING, and confidence level $\geq 0.90$ was set in STRING so as to ensure proteins were closely related. As shown in Figure 4, 31 proteins were closely connected. It indicated that the drug had direct or indirect effect on 31 proteins when it acted on one or more proteins.

31 differential gene candidates were inputted into DGIdb dataset so as to obtain the drug interacting with the aforesaid genes, and 10 drug candidates were obtained through
screening their biological characteristics and clinical application. As shown in Table 2, 10 drugs, such as metformin hydrochloride, were directly or indirectly correlated to differential gene candidates.

**4. Conclusions**

Drugs that may be used for prevention and treatment of PD were discovered through data mining and pathway analysis, which provided new ideas for drug R&D.

Based on the research result and information retrieval relating to drug candidates, 10 drugs such as metformin hydrochloride had certain therapeutical effect on PD, and melbine (DMBG) can be used for treatment of PD and type 2 diabetes patients.

**5. Discussion**

PD had a high morbidity, and drug therapy represented by dopaminergic drugs was a main treatment method for PD
Nevertheless, anti-Parkinson’s disease drugs mainly acted on dopamine metabolism and cholinergic metabolic pathways instead of the apoptosis mechanism of dopaminergic neuron, so it can neither inhibit the progress of the disease effectively nor cure the disease. Whereas traditional drugs synthesized based on physical tests and drug compounds featured long R&D cycle, high investment, high risk, and poor curative effect of clinical test, anti-Parkinson’s disease drugs fell behind in drug R&D and could not accommodate to the rapid growth of PDs [16].

Data mining was an emerging research area in recent years that aimed to excavate potential and possible data pattern, internal relation, rule and development trend, etc. from unorganized data information, extract effective, novel, useful, understandable, and scattered valuable knowledge from text files and to make use of such knowledge for better information organization. Data mining of biomedical literature was construed as effective formation of research hypothesis, since it can reveal a new relationship between gene and pathogenesis. New evidences of adjustment of existing indications for drug therapy can be obtained through data mining combined with other bioinformatics tools [17–19] and reliable conclusions were drawn from drug R&D based on data mining.

In this research, macromining and microanalysis were combined innovatively, the direction of drug screening was
determined, and targeting and high efficiency of drug mining were guaranteed based on big data analysis, bioinformatics analysis, and molecular pathology. 3 research studies were included in this research based on data mining of PD in GEO dataset. 250 differential genes were obtained from 3 groups of differential genes after gene crossover based on data mining of original gene and underwent KEGG analysis. KEGG pathway included Parkinson’s disease and other pathways. 82 differential genes selected from 4 KEGG pathways with a smaller $P$ value were further analyzed in order to ensure the reliability of differential gene candidates, drug-gene correlation of 31 differential gene candidates was analyzed, and finally 10 drug candidates were screened out.

Some potential therapeutic drugs for PD were discovered in our research studies, among which melbine (DMBG) was worth noting. Current research studies showed that mitochondrial function disorder, abnormal protein aggregation, neuroinflammation increase, and impaired cerebral glucose metabolism were common processes of insulin resistance, diabetes, and nervous system degeneration and have been identified as the key mechanism for the progress of PD and cognitive disorder [20]. Besides, it has been considered that melbine (DMBG) cannot be applied to treatment of type 2 diabetes through adjustment of glucose metabolism disorder, but it had obvious protective effect on the nerve cells of PD and other nervous system degenerations [21]. This research showed that metformin hydrochloride can be combined with NDUFA10, NDUFA7, NDUFA9, NDUFB5, NDUFS1, NDUFS2, and other acceptors and thus affect the mitochondrial respiratory chain. Information retrieval indicated that melbine (DMBG) had therapeutic effect on the animal model of PD, and epidemiological survey also indicated that it had effect on prevention and treatment of PD. Mark et al. carried out epidemiological survey on type 2 diabetes patients with PD and found that the probability of type 2 diabetes patients suffering PD was 2.2 times higher than normal people. However, melbine (DMBG) could control blood glucose so as to reduce the probability of type 2

### Table 2: Thirty-one drug candidates for differential gene prediction (drug-gene connection table).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Interaction types</th>
<th>Approved?</th>
<th>Administration</th>
<th>Approved use</th>
<th>PubMed ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>MDH2</td>
<td>N/A</td>
<td>Yes</td>
<td>Oral administration</td>
<td>Anticoagulation</td>
<td>10592235</td>
</tr>
<tr>
<td>Folic acid</td>
<td>MTR</td>
<td>N/A</td>
<td>Yes</td>
<td>Oral administration</td>
<td>Trophic nerve</td>
<td>18565, 1744096, 7599160, 3812589, 9587031, 17139284, 17016423, 8288265, 17139284, 17016423, 17444813</td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>MTR</td>
<td>Cofactor</td>
<td>Yes</td>
<td>Oral administration</td>
<td>Neuroprotection</td>
<td></td>
</tr>
<tr>
<td>L-glutamate</td>
<td>ASNS, GLUD1,</td>
<td>N/A</td>
<td>Phase 3</td>
<td>Oral administration</td>
<td>Neuroprotection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GOT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin hydrochloride</td>
<td>NDUFA10,</td>
<td>Inhibitor</td>
<td>Yes</td>
<td>Oral administration</td>
<td>Hypoglycemic effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDUFA7,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDUFA9,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDUFB5,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDUFS1,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDUFS2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>MTR</td>
<td>Product</td>
<td>Yes</td>
<td>Oral administration</td>
<td>Liver protection</td>
<td></td>
</tr>
<tr>
<td>Niacinamide</td>
<td>LDHA</td>
<td>N/A</td>
<td>Yes</td>
<td>Oral administration</td>
<td>Cardiac disease, cognitive disorder</td>
<td></td>
</tr>
<tr>
<td>Pyridoxal phosphate</td>
<td>GOT1, SDS</td>
<td>Activator</td>
<td>Phase 2</td>
<td>Oral administration</td>
<td>Dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td>ATP5B</td>
<td>N/A</td>
<td>Phase 1</td>
<td>Oral administration</td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Serine</td>
<td>SDS</td>
<td>N/A</td>
<td>Phase 2</td>
<td>Oral administration</td>
<td>Cognitive improvement</td>
<td></td>
</tr>
</tbody>
</table>

Mark et al. carried out epidemiological survey on type 2 diabetes patients with PD and found that the probability of type 2 diabetes patients suffering PD was 2.2 times higher than normal people. However, melbine (DMBG) could control blood glucose so as to reduce the probability of type 2
Paying attention to the side effects. Therefore, metformin hydrochloride may have great clinical effect on treatment of PD, but we suggested using melbin (DMBG) for treatment of PD with type 2 diabetes and loss of substantia nigra dopaminergic neurons [45]. The authors declare that they have no conflicts of interest.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


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