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Original Article

Dysregulated pathways identification analysis in Parkinson disease based on attractor of within-pathway effects and crosstalk inter-pathways

Yang Xu[1*], Xinyan Yi[2*], Hongmei Yue[1]

[1]*Department of Neurology, Jining No. 1 People's Hospital, 272011, Jining, Shandong, P. R. China;* [2]*Health Management Center, Affiliated Hospital of Jining Medical University, 272100, Jining, Shandong, P. R. China.*
[*]*Equal contributors and co-first authors.*

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Abstract: The etiology of Parkinson disease (PD) is not well established. In order to identify dysregulated pathways in the pathogenesis of PD, gene expression profiling of 38 Parkinson's disease patients and 23 healthy controls were collected. The pathway crosstalk networks were constructed to assess interactions inter-pathways. A total of 18 differentially expressed genes were identified in Parkinson's disease. There were 39 attractors with $P<0.01$ and 27 pathways with $RP<0.01$. Finally, 19 significantly dysfunctional pathways with strong interactions directly related to Parkinson disease progression were found. Among them, Epstein-Barr virus infection was the most significantly different pathway. In conclusion, a novel pipeline that identified the dysregulated pathways in Parkinson's disease was constructed based on attractor of within-pathway effects and crosstalk inter-pathways.

Keywords: Parkinson disease, crosstalk, epstein-barr, dysregulated pathways

Introduction

Parkinson disease (PD) is a degenerative disorder of the central nervous system mainly affecting the motor system [1-3]. Early in the course of the disease, the most obvious symptoms are movement-related. Later, thinking and behavioral problems may arise, with dementia commonly occurring in the advanced stages of the disease, and depression being the most common psychiatric symptom [4]. The disease can be either primary or secondary. Primary Parkinson's disease has no known cause, although some atypical cases have a genetic origin. Secondary parkinsonism is due to known causes like toxins. Many risks and protective factors have been investigated: the clearest evidence is for an increased risk in people exposed to certain pesticides and a reduced risk in tobacco smokers. The motor symptoms of the disease result from the death of cells in the substantia nigra, a region of the midbrain. Parkinson's disease in most people is idiopathic (having no specific known cause). However, a small proportion of cases can be attributed to known genetic factors. Other factors have been associated with the risk of developing PD, but no causal relationships have been proven [5].

It is a significant task that identifying dysregulated pathways from high-throughput experimental data in order to infer potential molecular and functional insights [6]. The differentially expressed genes (DEG) and pathways can help to understand high-level functions between normal and disease groups. Recently, canonical reports claimed that gene expression patterns could identify biomarkers of Parkinson's disease, which highlighted the relevance of the innate immune system through signaling pathways [3, 7-17].

There are abundant pathways related to Parkinson's disease in Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database, which provides useful pathway topology information. Kauffman' attractor theory was famous for finding one or more well-defined ensembles of model networks whose statistical features matched those of real cells and organisms [4, 16, 18-22]. Mar et al. [23] reported that *attract* was a new approach that could

leverage both existing pathway databases and the DEG between cell phenotypes. We employed it to screen attractors within pathways from vast data of KEGG pathway database, in order to narrow down the number of correlated dysregulated pathways.

Screened differentially expressed pathways are efficient to identify target functions. However, they invariably focus on internal effects of single pathway and are fail to consider the inherent interdependency inter-pathways. Pathway crosstalk refers to the phenomenon of interaction or cooperation between pathways. The construction of a pathway crosstalk network (PCN) inter-pathways is conductive to understand the comprehensive interactions in Parkinson's disease [24-28]. Then a scoring scheme was utilized to comprehensively identify these pathways, taking into account both attractors of internal pathway effects and crosstalk inter-pathways.

In this study, we introduced a novel pipeline to identify dysregulated pathways associated with Parkinson's disease. Ultimately several significantly dysfunctional pathways with strong interactions which directly related to Parkinson's disease progression were found. Attractor and crosstalk were designed to complement each other in order to increase the integrity of pathways assessment. The new method was hoped to be meaningful in seeking influential pathways by reinforce of attractor and crosstalk, which served as therapy targeting markers.

Materials and methods

Gene expression datasets

The transcription profile was obtained from EMBIE-BI ArrayExpress [29]. Gene expression profiling of 38 Parkinson's disease patients and 23 healthy controls were collected from E-GEOD-16561 [30]. The platform was A-MEXP-1172-Illumina HumanRef-8 v 3.0 Expression Bead Chip. Data of the gene chip was read in the affy [31]. The Linear Models for Microarray Data (LIMMA) was then used to preprocess data. Background adjustment and quantile data normalization were performed by robust multi-array average (RMA) [32]. To protect against outlier probes we used a robust procedure, median polish [33], to estimate model parameters. The average value of a gene symbol with multiple probes was calculated. To scree differentially expressed genes (DEG), $P \leq 0.01$ and |log fold change (FC) I≥2 were set as the threshold levels.

Pathway data

Information from gene sets representing biological pathways of human was obtained from Kyoto encyclopedia of Genes and Genomes (KEGG) database [34] which provides copious pathway information [35, 36]. A set of pathways of which gene set size is >100 or <5 were filtered. After these size cutoffs were set up, 294 pathways were obtained for downstream analysis.

Protein interaction data

The human protein-protein interaction (PPI) sets representing biological genes were obtained from the Retrieval of Interacting Genes (STRING; v 9.0) [37]. After removing self interactions, we ended up with 787896 PPI sets.

Attractor analysis within pathways

Based on attractor theory [38], *attract* was used to screen differentially expressed pathways related to Parkinson's disease from 294 KEGG pathways. To test data of 294 KEGG pathways, GSEA-ANOVA was employed as a gene set enrichment algorithm, which was different from other methods in multiple classes [23]. Obtained differences among the expression profile of samples were identified as attractors. From the ANOVA model, we compute the *F*-statistic for gene *i*:

$$F^{(i)} = \frac{MSS_i}{RSS_i} \tag{1}$$

where MSS_i represents the mean treatment sum of squares, and captures the amount of variation due to group-specific effects:

$$MSS_i = \frac{1}{K-1}\sum_{k=1}^{k} r_k \left[y_k^{(i)} - y^{(i)} \right]^2 \tag{2}$$

and RSS_i represents the residual sum of squares:

$$RSS_i = \frac{1}{N-K}\sum_{K=1}^{K}\sum_{j=1}^{r_j} \left[y_{jk}^{(i)} - y^{(i)} \right]^2 \tag{3}$$

where N is the total number of samples, and the overall mean is given by:

$$Y^{(i)} = \frac{1}{K}\sum_{K=1}^{K}\left[\frac{1}{r_k}\sum_{j=1}^{r_k} y_{jk}^{(i)} \right] \tag{4}$$

The *F*-statistic captures the strength of different expression observed in genes of Parkinson's

disease. Large values of the *F*-statistic mean a strong association with Parkinson's disease-specific expression changes.

For pathway *P* consisting of g_p genes, the *T*-statistic takes the following form:

$$T_P = \frac{\left[\frac{1}{g_p}\sum_{i=1}^{g_p} F^{(i)}\right] - \left[\frac{1}{G}\sum_{j=1}^{G} F^{(j)}\right]}{\sqrt{\left[\frac{s_p^2}{g_p}\right] + \left[\frac{S_G^2}{G}\right]}} \quad (5)$$

where *G* represents the total number of genes with a pathway annotation and the sample variances s_p^2 and s_G^2 are defined as:

$$S_p^2 = \frac{1}{g_p - 1}\sum_{j=1}^{g_p}\left[F^{(j)} - \frac{1}{g_p}\sum_{i=1}^{g_p} F^{(i)}\right]^2 \quad (6)$$

$$S_G^2 = \frac{1}{G - 1}\sum_{j=1}^{G}\left[F^{(j)} - \frac{1}{G}\sum_{i=1}^{G} F^{(i)}\right]^2 \quad (7)$$

and the degrees of freedom are specified by the Welch-Satterwhaite equation:

$$V = \frac{\left[\frac{s_p^2}{g_p} + \frac{s_G^2}{G}\right]^2}{\frac{s_p^4}{g_p^2(g_p - 1)} + \frac{s_G^4}{G^2(G - 1)}} \quad (8)$$

Attractors were ranked according to the significance of difference.

Crosstalk analysis of inter-pathways

The pathway crosstalk network (PCN) of control group was constructed in Li et al. [24] method. The value of weight of the background PCN was defined as the number of PPI sets.

(1) Fish Exact test was performed to evaluate gene overlap between any pair of 294 pathways [39]. Raw *P*-values were adjusted by false discovery rate (FDR) [40]. Pathway pairs with adjusted P<0.05 were removed.

(2) The number of PPI sets was counted between any pair of pathways. For each pathway pair, count all interactions after removing genes shared in both pathways.

(3) Background distribution of PPI sets counted in each pair of pathways was estimated. Every pathway was randomized repeating 1000 times. When a gene in the pathway has interactions, it is considered that there is crosstalk between pathways. First count the number of genes it interacts with, and randomly draw a gene from the PPI data base which interacts with similar number of genes. Then the original gene was replaced with this newly selected gene. Once both pathways were randomized, Step 2 was performed to count the number of interactions between them.

Table 1. 18 DEG identified in the Parkinson's disease

DEG	Log FC	*P*-value
Up-regulated		
RGS2	1.0107	3.24E-14
PDK4	2.0079	7.54E-11
ARG1	2.6940	1.70E-09
IQGAP1	2.0330	9.65E-09
CRISPLD2	2.0690	5.39E-08
PADI4	2.0232	6.95E-08
MMP9	2.4304	1.36E-07
CSPG2	2.0757	4.93E-07
CA4	2.0994	3.35E-06
S100A12	2.2762	5.03E-06
ACSL1	2.0946	8.29E-06
FOLR3	2.0949	1.87E-05
AKAP7	2.1421	2.27E-05
LY96	2.1194	2.86E-05
ORM1	1.1837	0.00014
FCGR3B	1.1743	0.00066
APOBEC3A	2.1644	0.00092
Down-regulated		
CCR7	-1.0838	5.70E-07

(4) The one-sided Fisher Exact test on all pathway pairs was performed using the 2 × 2 contingency table. *P*-values of Fisher exact test were adjusted using FDR BH procedure [40] and empirical *P*-value was calculated by counting the number of permutations in which the count of random interactions is higher than or equal to that of true interactions.

(5) All pathway pairs with adjusted Fisher P<0.05 were used to construct the PCN, where a node represents a pathway and an edge is crosstalk between two pathways. To clean up the network, two types of 'redundant' edges were removed: (a) Edges with significant gene overlap identified in Step 1 were removed from the network. (b) The two edges between two overlapping pathways were considered redundant.

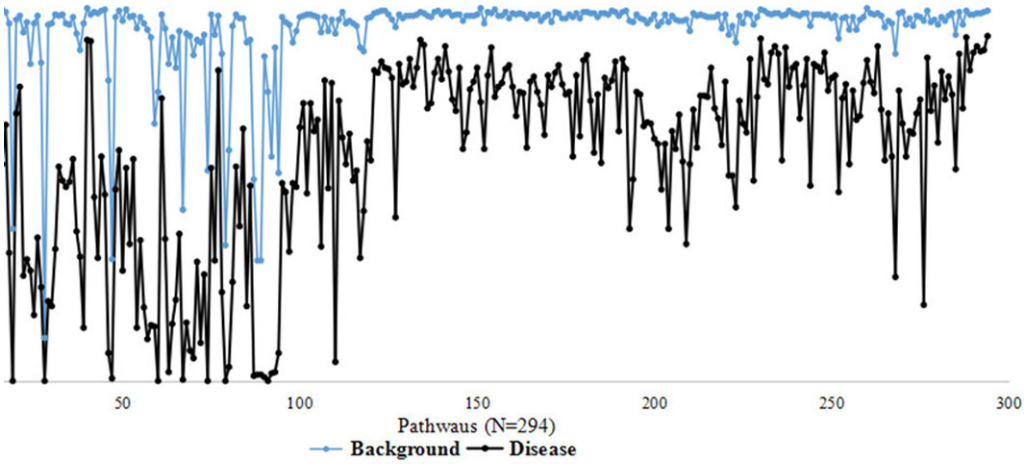

Figure 1. The crosstalk difference of background and Parkinson's disease.

Network of Parkinson's disease

Base on the original method of crosstalk [24], the network of Parkinson's disease can be constructed. In Step 3, we modified it to narrow down the number of edges in the network.

A gene in the pathway has interactions when it met one of the two conditions: (1) Spearman correlation coefficients of every PPI set were calculated in control and normal group. When the absolute value of different value between them >0.7, the edge was remained. Geometric mean of the absolute value was defined as the value of weight between the two pathways. (2). The two genes in an interaction were differentially expressed genes (DEG). P<0.01 and |log fold change (FC)|>1 were set as the threshold levels for the identification of DEG.

Important crosstalk pathways

The PCN was performed in topology analysis. Pathways were ordered by the degree of nodes. The scores of pathways were calculated.

Score = degree of Parkinson's disease/degree of background (9)

Comprehensive analysis

Impact factor was used to assess the interactions between a pathway with other pathways.

Impact factor = outer × (1-p) (10)

Outer means the degree of interactions from crosstalk analysis and p represents the *P*-value of the attractor.

R*P*-value was used to evaluate the comprehensive identified ability within pathways and between pathways [41].

R*P*-value = (rank inter/total) × (rank outer/total) (11)

Rank inter represents the ranking of attractor's *P*-value and rank outer means the ranking of interactions. Total means the sum of inter and outer.

Results

DEG in the Parkinson's disease

According to the criteria outlined (|log FC|≥2; P≤0.01), a total of 18 DEG were identified in Parkinson's disease, of which 17 were up-regulated and 1 was down-regulated (**Table 1**). These DEG might identify molecular alterations and provided diagnostic biomarkers to the Parkinson's disease.

Crosstalk of the Parkinson's disease related pathways

The PCNs of background and Parkinson's disease were generated with gene expression profiling of 39 Parkinson's disease patients and 24 controls, respectively. The detail of PCNs was showed in the supplement material. The crosstalk difference of background and Parkinson's disease was shown in **Figure 1**. In control group, a majority of degrees in 294 pathways were between 255 and 300. The Parkinson's disease group was significantly different with

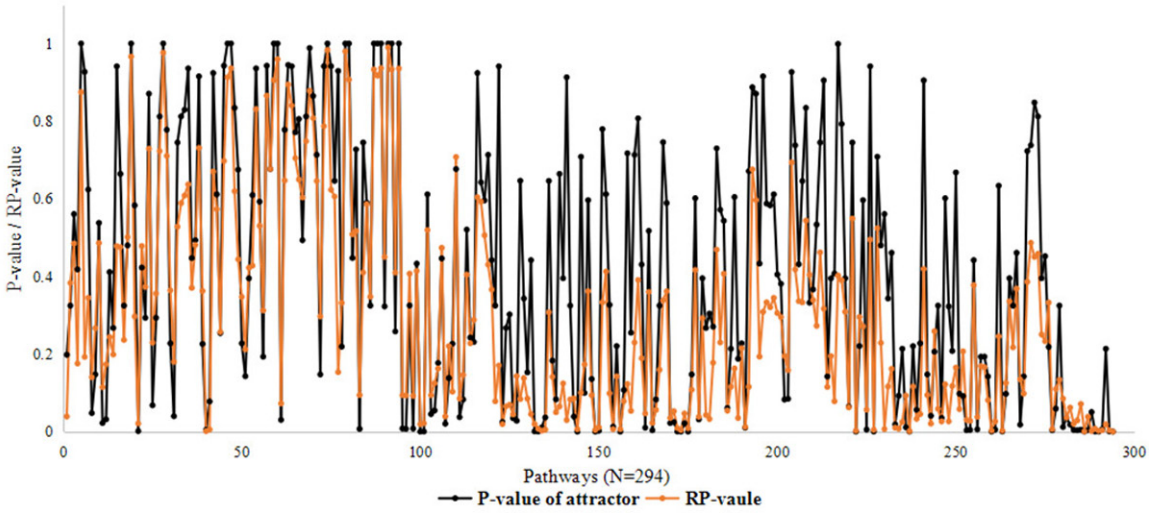

Figure 2. Differentially expressed pathways in Parkinson's disease patients.

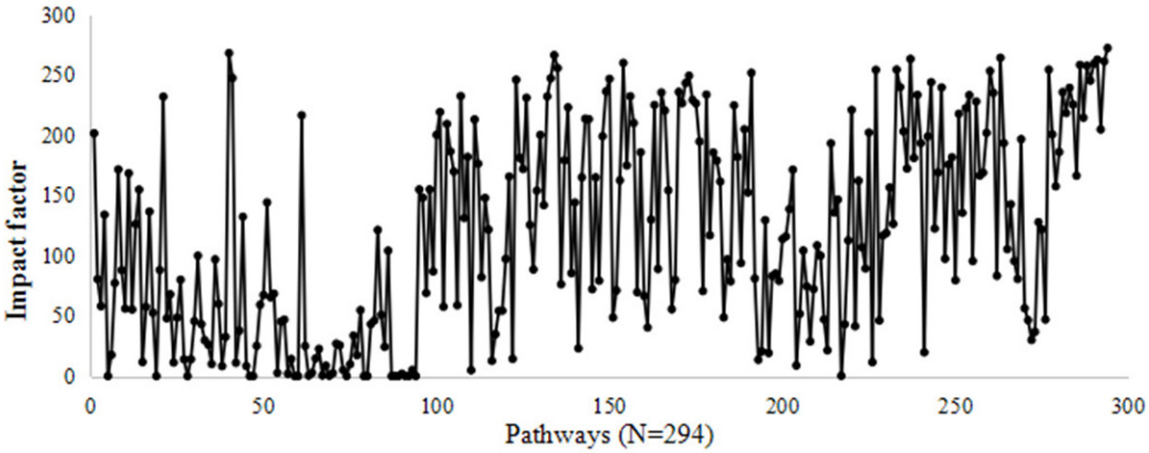

Figure 3. Interactions inter-pathways were assessed by Impact factor.

the background. This result gives evidence for the strong relationship between these pathways with the Parkinson's disease.

Bigger value of scores indicated more important crosstalk pathways. The top 3 important pathways were Pyrimidine metabolism (KEGG ID: 00240), HTLV-I infection (KEGG ID: 05166) and Epstein-Barr virus infection (KEGG ID: 05169). They provided valuable information for the mechanism of the Parkinson's disease.

Identification of KEGG pathways

A total of 294 KEGG pathways were evaluated comprehensively by Kauffman' attractor, impact factor and R*P*-value. There were 68 attractors with P<0.05 and 39 attractors with P<0.01 (**Figure 2**), which indicated these 68 attractors were significantly different in the Parkinson's disease. There were some molecular alterations existed in pathways themselves related to the Parkinson's disease, which sh-owed they were differentially expressed pathways.

In terms of interactions inter-pathways, impact factor was used to assess their contact. There were different values varied 0 to 272 showed in **Figure 3**, which indicated that there were different degree of interactions inter-pathways.

R*P*-value was used to comprehensively assess 294 pathways, including within pathways and inter-pathways. There were 64 pathways with RP<0.05 and 27 pathways with RP<0.01 (**Figure 2**). Finally screened from 39 attractors, 19

Table 2. Top 9 of significant pathways identified by Kauffman' attractor, Impact factor and R*P*-value

KEGG ID	KEGG Pathway	Attractor *P*-value	Impact factor	R*P*-value
05169	Epstein-Barr virus infection	1.12E-11	272	2.31E-05
05152	Tuberculosis	2.83E-06	257.9992701	0.000659447
05203	Viral carcinogenesis	5.18E-05	262.9863678	0.001353603
00230	Purine metabolism	0.004527077	267.7822164	0.00138831
05164	Influenza A	0.000100413	258.9739931	0.002221297
05016	Huntington's disease	0.000282903	263.9253137	0.002290712
05168	Herpes simplex infection	0.000412243	260.8924045	0.003077421
04380	Osteoclast differentiation	0.000282903	253.9281427	0.004720255
04932	Non-alcoholic fatty liver disease (NAFLD)	0.003514779	254.1037314	0.006363089

pathways matched with attractor P<0.01, big value of impact factor and R*P*-value <0.01. They were considered to be significantly dysfunctional pathways with strong interactions which directly related to Parkinson's disease progression. Top 9 of significant pathways were shown in **Table 2**. These pathways might play more important roles in the development of Parkinson's disease due to their dysfunctional expression and strong interactions. Among them, Epstein-Barr virus infection (KEGG ID: 05169) was the most significantly different pathway.

Discussion

Attractor theory was famous as a knowledge-driven analytical way to distinguish and annotate the gene-sets [38]. It was used to elevate expression across pathways in embryonic stem cells [23]. The results with pathways will be more complete instead of traditional DEG analysis due to narrowing down the number of correlated dysregulated pathways.

In this study, 68 attractors (P<0.05) with statistically significant alteration were screened from 294 KEGG pathways in response to molecular mechanism and pathology process of Parkinson's disease. We found that most of them were related to diseases, such as Tuberculosis (KEGG ID: 05152), Alzheimer's disease (KEGG ID: 05010), Measles (KEGG ID: 05162) and Huntington's disease (KEGG ID: 05016). They were differentially expressed pathways in Parkinson's disease patients, however, the integral influence to the system was absent. From **Figure 2**, we can see that the variation trend of attractor were not absolutely consistent with that of R*P*-value. Therefore, crosstalk was employed to assess the interactions inter-pathways. Pathways with big value of impact factor were considered to have strong contact with other pathways. Interestingly, most of 68 attractors were with big values of impact factor, but 13 pathways were not (impact factor <190). Meanwhile, the R*P*-values of most of the 14 pathways were >0.05. It claimed that pathways screened by attractor were not exactly dysregulated and influential ones. Those pathways with attractor P<0.05 and small values of impact factor were considered to have small effect and should be filtered.

The results suggested attractor might fail to identify pathways effectively because of incomplete information on inherent interdependency inter-pathways pathway. This is similar to the challenge faced by other pathway-identification methods that apply topological pathway information [36]. After assessing the interactions inter-pathways by crosstalk, the novel approach enhanced attractor to identify dysregulated pathways. Recently, ways to comprehensively identify dysregulated pathways have become a major focus [6]. The novel method combined attractor and crosstalk is hoped to be further applied to other diseases.

We applied R*P*-value to evaluate the comprehensive identified ability both within pathways and inter-pathways. What we want is influential dysregulated pathways which with attractor P<0.05, big value of impact factor and R*P*-value <0.05. Screened from 68 attractors, 46 pathways matched the condition. Screened from 39 attractors, 19 pathways matched with attractor *P*<0.01 and R*P*-value <0.01. We found that most of them were pathways related to diseases, such as Influenza A (KEGG ID: 05164), Huntington's disease (KEGG ID: 05016), Hepatitis B (KEGG ID: 05161) and Non-alcoholic

fatty liver disease (NAFLD) (KEGG ID: 04932). The pathway Epstein-Barr virus infection (KEGG ID: 05169) owned minimum R*P*-value and maximal impact factor among them. Meanwhile it was one of the most important crosstalk pathways. It is well known that distinct forms of Epstein-Barr virus can cantribute to the different infectious diseases and tumors [42]. Therefore, the pathway Epstein-Barr virus infection was considered to be important in the molecular mechanism of Parkinson's disease.

Conclusion

Based on our results, we conclude that a novel pipeline that identified the dysregulated pathways in Parkinson's disease. It is based on attractor of within-pathway effects and crosstalk inter-pathways. We hope the constructed process can be efficient in the upcoming era of medicine.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hongmei Yue, Department of Neurology, Jining No. 1 People's Hospital, 272011, Jining, Shandong, P. R. China. Tel: +86-13963750808; E-mail: yhmthsd@163.com

References

[1] Mandel S, Grunblatt E, Riederer P, Amariglio N, Jacob-Hirsch J, Rechavi G and Youdim MB. Gene expression profiling of sporadic Parkinson's disease substantia nigra pars compacta reveals impairment of ubiquitin-proteasome subunits, SKP1A, aldehyde dehydrogenase, and chaperone HSC-70. Ann N Y Acad Sci 2005; 1053: 356-375.

[2] Lu L, Neff F, Alvarez Fischer D, Henze C, Xie Y, Oertel WH, Schlegel J and Hartmann A. Gene expression profiling of lewy body-bearing neurons in Parkinson's disease. Exp Neurol 2005; 195: 27-39.

[3] Pierson J, Norris JL, Aerni HR, Svenningsson P, Caprioli RM and Andren PE. Molecular profiling of experimental Parkinson's disease: direct analysis of peptides and proteins on brain tissue sections by MALDI mass spectrometry. J Proteome Res 2004; 3: 289-295.

[4] Luan H, Liu LF, Tang Z, Zhang M, Chua KK, Song JX, Mok VC, Li M and Cai Z. Comprehensive urinary metabolomic profiling and identification of potential noninvasive marker for idiopathic Parkinson's disease. Sci Rep 2015; 5: 13888.

[5] Martins M, Rosa A, Guedes LC, Fonseca BV, Gotovac K, Violante S, Mestre T, Coelho M, Rosa MM, Martin ER, Vance JM, Outeiro TF, Wang L, Borovecki F, Ferreira JJ and Oliveira SA. Convergence of miRNA expression profiling, alpha-synuclein interacton and GWAS in Parkinson's disease. PLoS One 2011; 6: e25443.

[6] Han J, Li C, Yang H, Xu Y, Zhang C, Ma J, Shi X, Liu W, Shang D, Yao Q, Zhang Y, Su F, Feng L and Li X. A novel dysregulated pathway-identification analysis based on global influence of within-pathway effects and crosstalk between pathways. J R Soc Interface 2015; 12: 20140937.

[7] Moran LB, Duke DC, Deprez M, Dexter DT, Pearce RK and Graeber MB. Whole genome expression profiling of the medial and lateral substantia nigra in Parkinson's disease. Neurogenetics 2006; 7: 1-11.

[8] Na SJ, DiLella AG, Lis EV, Jones K, Levine DM, Stone DJ and Hess JF. Molecular profiling of a 6-hydroxydopamine model of Parkinson's disease. Neurochem Res 2010; 35: 761-772.

[9] Ohnuki T, Nakamura A, Okuyama S and Nakamura S. Gene expression profiling in progressively MPTP-lesioned macaques reveals molecular pathways associated with sporadic Parkinson's disease. Brain Res 2010; 1346: 26-42.

[10] Papapetropoulos S, Ffrench-Mullen J, McCorquodale D, Qin Y, Pablo J and Mash DC. Multiregional gene expression profiling identifies MRPS6 as a possible candidate gene for Parkinson's disease. Gene Expr 2006; 13: 205-215.

[11] Papapetropoulos S, Shehadeh L and McCorquodale D. Optimizing human post-mortem brain tissue gene expression profiling in Parkinson's disease and other neurodegenerative disorders: from target "fishing" to translational breakthroughs. J Neurosci Res 2007; 85: 3013-3024.

[12] Reynolds AD, Glanzer JG, Kadiu I, Ricardo-Dukelow M, Chaudhuri A, Ciborowski P, Cerny R, Gelman B, Thomas MP, Mosley RL and Gendelman HE. Nitrated alpha-synuclein-activated microglial profiling for Parkinson's disease. J Neurochem 2008; 104: 1504-1525.

[13] Simunovic F, Yi M, Wang Y, Macey L, Brown LT, Krichevsky AM, Andersen SL, Stephens RM, Benes FM and Sonntag KC. Gene expression profiling of substantia nigra dopamine neurons: further insights into Parkinson's disease pathology. Brain 2009; 132: 1795-1809.

[14] Sinha A, Patel S, Singh MP and Shukla R. Blood proteome profiling in case controls and

Parkinson's disease patients in Indian population. Clin Chim Acta 2007; 380: 232-234.
[15] Wang YH, Samoylenko V, Tekwani BL, Khan IA, Miller LS, Chaurasiya ND, Rahman MM, Tripathi LM, Khan SI, Joshi VC, Wigger FT and Muhammad I. Composition, standardization and chemical profiling of banisteriopsis caapi, a plant for the treatment of neurodegenerative disorders relevant to Parkinson's disease. J Ethnopharmacol 2010; 128: 662-671.
[16] West RJ, Elliott CJ and Wade AR. Classification of Parkinson's disease genotypes in drosophila using spatiotemporal profiling of vision. Sci Rep 2015; 5: 16933.
[17] Xun Z, Sowell RA, Kaufman TC and Clemmer DE. Lifetime proteomic profiling of an A30P alpha-synuclein drosophila model of Parkinson's disease. J Proteome Res 2007; 6: 3729-3738.
[18] Liu S, Zhang Y, Bian H and Li X. Gene expression profiling predicts pathways and genes associated with Parkinson's disease. Neurol Sci 2016; 37: 73-79.
[19] Hossein-Nezhad A, Fatemi RP, Ahmad R, Peskind ER, Zabetian CP, Hu SC, Shi M, Wahlestedt C, Zhang J and Faghihi MA. Transcriptomic profiling of extracellular RNAs present in cerebrospinal fluid identifies differentially expressed transcripts in Parkinson's disease. J Parkinsons Dis 2016; 6: 109-117.
[20] Li L, Zhang CW, Ge J, Qian L, Chai BH, Zhu Q, Lee JS, Lim KL and Yao SQ. A small-molecule probe for selective profiling and imaging of monoamine oxidase b activities in models of Parkinson's disease. Angew Chem Int Ed Engl 2015; 54: 10821-10825.
[21] Cui S, Sun H, Gu X, Lv E, Zhang Y, Dong P, Fu C and Zhu C. Gene expression profiling analysis of locus coeruleus in idiopathic Parkinson's disease by bioinformatics. Neurol Sci 2015; 36: 97-102.
[22] Chen X, Xie C, Sun L, Ding J and Cai H. Longitudinal metabolomics profiling of Parkinson's disease-related alpha-synuclein A53T transgenic mice. PLoS One 2015; 10: e0136612.
[23] Mar JC, Matigian NA, Quackenbush J and Wells CA. Attract: a method for identifying core pathways that define cellular phenotypes. PLoS One 2011; 6: e25445.
[24] Li Y, Agarwal P and Rajagopalan D. A global pathway crosstalk network. Bioinformatics 2008; 24: 1442-1447.
[25] Zhang AM, Ma K, Song Y, Wang B, Feng Y, Liu L and Xia X. Genetic polymorphisms of the IFNlambda genes are associated with biochemical features in Han Chinese with HCV infection from Yunnan province, China. Infect Genet Evol 2014; 21: 161-165.
[26] Zhang AM, Ma K, Song Y, Feng Y, Duan H, Zhao P, Wang B, Xu G, Li Z and Xia X. Mitochondrial DNAs decreased and correlated with clinical features in HCV patients from Yunnan, China. Mitochondrial DNA 2015; 27: 2516-9.
[27] Ma K, Guo L, Xu A, Cui S and Wang JH. Molecular mechanism for stress-induced depression assessed by sequencing miRNA and mRNA in medial prefrontal cortex. PLoS One 2016; 11: e0159093.
[28] Ma K, Zhang H and Baloch Z. Pathogenetic and therapeutic applications of tumor necrosis factor-alpha (TNF-alpha) in major depressive disorder: a systematic review. Int J Mol Sci 2016; 17: E733.
[29] Parkinson H, Kapushesky M, Shojatalab M, Abeygunawardena N, Coulson R, Farne A, Holloway E, Kolesnykov N, Lilja P, Lukk M, Mani R, Rayner T, Sharma A, William E, Sarkans U and Brazma A. Arrayexpress--a public database of microarray experiments and gene expression profiles. Nucleic Acids Res 2007; 35: D747-750.
[30] Barr TL, Conley Y, Ding J, Dillman A, Warach S, Singleton A and Matarin M. Genomic biomarkers and cellular pathways of ischemic stroke by RNA gene expression profiling. Neurology 2010; 75: 1009-1014.
[31] Gautier L, Cope L, Bolstad BM and Irizarry RA. Affy--analysis of affymetrix genechip data at the probe level. Bioinformatics 2004; 20: 307-315.
[32] Irizarry RA, Hobbs B, Collin F, Beazer-Barclay YD, Antonellis KJ, Scherf U and Speed TP. Exploration, normalization, and summaries of high density oligonucleotide array probe level data. Biostatistics 2003; 4: 249-264.
[33] Sasik R, Calvo E and Corbeil J. Statistical analysis of high-density oligonucleotide arrays: a multiplicative noise model. Bioinformatics 2002; 18: 1633-1640.
[34] Kanehisa M and Goto S. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res 2000; 28: 27-30.
[35] Rahnenfuhrer J, Domingues FS, Maydt J and Lengauer T. Calculating the statistical significance of changes in pathway activity from gene expression data. Stat Appl Genet Mol Biol 2004; 3: article16.
[36] Hung JH, Whitfield TW, Yang TH, Hu Z, Weng Z and DeLisi C. Identification of functional modules that correlate with phenotypic difference: the influence of network topology. Genome Biol 2010; 11: R23.
[37] Franceschini A, Szklarczyk D, Frankild S, Kuhn M, Simonovic M, Roth A, Lin J, Minguez P, Bork P, von Mering C and Jensen LJ. String v9.1: protein-protein interaction networks, with increased coverage and integration. Nucleic Acids Res 2013; 41: D808-815.
[38] Kauffman S. A proposal for using the ensemble approach to understand genetic regulatory networks. J Theor Biol 2004; 230: 581-590.

[39] Al-Shahrour F, Diaz-Uriarte R and Dopazo J. FatiGO: a web tool for finding significant associations of gene ontology terms with groups of genes. Bioinformatics 2004; 20: 578-580.
[40] Benjamini Y, Drai D, Elmer G, Kafkafi N and Golani I. Controlling the false discovery rate in behavior genetics research. Behav Brain Res 2001; 125: 279-284.
[41] Hong F, Breitling R, McEntee CW, Wittner BS, Nemhauser JL and Chory J. RankProd: a bioconductor package for detecting differentially expressed genes in meta-analysis. Bioinformatics 2006; 22: 2825-2827.
[42] Young KA, Herbert AP, Barlow PN, Holers VM and Hannan JP. Molecular basis of the interaction between complement receptor type 2 (CR2/CD21) and Epstein-Barr virus glycoprotein gp350. J Virol 2008; 82: 11217-11227.