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# Expression profiles of genes in wild-type DJ-1 and A39S DJ-1 mutant cells

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**ABSTRACT**

**Objective:** To elucidate the role of A39S mutation of DJ-1 in the onset of Parkinson's disease (PD) and identify genes for which expressions are abnormally regulated by A39S DJ-1 mutation.

**Methods:** We established HEK293 cell lines which stably expressed empty vector, wild-type DJ-1 and A39S mutated DJ-1 respectively. DNA microarrays were used to identify genes for which expressions change in wild-type DJ-1 cells and A39S DJ-1 mutant cells.

**Results:** Compared with the cell line expression empty vector, we identified 42 differentially regulated genes (including 14 up-regulated genes and 28 down-regulated genes) in the wild-type DJ-1 cells and 8 differentially regulated genes (including 6 up-regulated genes and 2 down-regulated genes) in the A39S DJ-1 mutant cells. Compared with the wild-type DJ-1 cells, only the expression of UGT2B7 gene was down-regulated in A39S DJ-1 mutant cells. These differentially regulated genes were mainly related to signal transduction, regulation of transcription, apoptosis and metabolism.

**Conclusion:** A39S mutated DJ-1 may disturb the transcriptional activities of DJ-l and involve in the pathogenesis of PD.

**KEY WORDS** DJ-1; A39S mutation; expression profile of gene; DNA microarray; UGT2B7 gene

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**Biography**: LIU Zhenhua, M.D., mainly engaged in the research of molecular genetics in Parkison's diseases.

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# 野生型 DJ-1 与 A39S 突变型 DJ-1 表达的单克隆细胞株基因表达谱分析

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[摘要] **目的：**探讨 DJ-1 基因 A39S 突变在帕金森病发病过程中的作用机制，以及其是否可能通过转录调控活性导致相关基因表达异常。**方法：**建立能够稳定表达空载体和野生型 DJ-1 蛋白，以及 A39S 突变型 DJ-1 蛋白的 HEK293 单克隆细胞株。利用基因芯片技术对不同组别细胞株进行差异性表达基因筛选。**结果：**与空载体组比较，野生型 DJ-1 组有 14 个基因表达上调，28 个基因表达下调；A39S 突变型 DJ-1 组有 6 个基因表达上调；2 个基因表达下调；A39S 突变型 DJ-1 组与野生型型 DJ-1 组比较发现只有 1 个基因表达下调。具有表达差异性的基因分别参与信号转导、基因转录调控、细胞周期、细胞凋亡、氧化应激等生物学过程。**结论：**A39S 突变型 DJ-1 蛋白可能通过直接或间接方式对这些差异基因进行表达调控影响这些通路的正常功能，而参与帕金森病的发病。

[关键词] DJ-1；A39S 突变；基因表达谱；DNA 基因芯片；UGT2B7 基因

Parkinson disease (PD) is the second most common neurodegenerative disorder. PD is thought to result from a complex interaction between multiple genetic and environmental factors, though rare monogenic forms of the disease do exist[1]. Mutations in certain genes are found to cause monogenic forms of the disorder, with autosomal dominant or autosomal recessive inheritance. These genes include SNCA, Parkin, PINK1, DJ-1, LRRK2, and ATP13A2[2-3]. DJ-1 deletions and point mutations have been found, and loss of functional protein was shown to cause autosomal recessive PD[4-5].

The function of DJ-1 is still unclear, however, many evidences support that DJ-1 is associated with various cellular processes, including response to oxidative stress, cellular transformation, RNA binding, androgen-receptor signaling, spermatogenesis and fertilization[6-7]. DJ-1 also involves in transcriptional regulation of genes. Researches showed that DJ-1 could regulate the androgen receptor, pyrimidine tract-binding protein-associated splicing factor (PSF), PTEN tumor suppressor and p53[7-9]. DJ-1 is also required for the activity of nuclear factor erythroid 2-related factor (Nrf2), which is the master regulator of response to oxidative stress[10]. These evidence suggested that DJ-1 may contribute to the onset of PD by affecting transcriptional regulation[11].

In the previous study, we found a new mutation of DJ-1 which we named as A39S. DJ-1 gene encodes the first frame 115 bp from the G→T, so that the DJ-1 protein in the first 39 on Alanine replaced by Serine(A39S)[12]. To elucidate the effect of the A39S mutation, we established HEK293 cell lines which can stably express wild-type and A39S DJ-1 mutant in this study. DNA microarray analyses were carried out to identify genes for which expressions are regulated by DJ-1 in three HEK293 cell lines, including empty-vector cells, wild-type DJ-1 cells and A39S DJ-1 mutant cells.

## 1 Materials and methods

### 1.1 Materials

#### 1.1.1 Plasmids source

The eukaryotic expression plasmid of Wild-type and A39S DJ-1 mutant (pCMV-Tag 2A-Flag-DJ-1, pCMV-Tag 2A-Flag-DJ-1-A39S) were constructed by State Key Laboratory of Medical Genetics.

#### 1.1.2 Cells source

Human embryonic kidney (HEK293) cells, which were used to establish empty vector, wild-type DJ-1 and A39S DJ-1 mutant monoclonal cell lines, were offered by the Shanghai Institute of Cell Research Center and had passaged to the 35th in vitro.

#### 1.1.3 Grouping

The experiment were divided into three groups, empty vector group, wild type DJ-1 group and A39S DJ-1 mutant

group. In order to enhance the accuracy of the cDNA microarray analysis, each test was carried twice, so that each experimental group was divided into two groups, namely the empty vector group 1 and group 2, the wild-type group 1 and group 2 and A39S mutation group 1 and group 2.

### 1.2 Construction and identification of monoclonal cell lines

In order to study DJ-1 gene function, we has successfully constructed the wild-type and A39S DJ-1 mutant eukaryotic expression plasmid (pCMV-Tag 2A-Flag-DJ-1, pCMV-Tag 2A-Flag-DJ-1-A39S). Following with the transfection procedures of the liposome Lipofectamine 2000 kit instructions, pCMV-Tag 2A-Flag, pCMV-Tag 2A-Flag-DJ-1 and pCMV-Tag 2A-Flag-DJ-1-A39S were transfected to HEK293 cells respectively. After cell selecting, monoclonal picking and culturing, we verified the monoclonal cell line at the DNA, RNA and protein levels in order to make sure whether there were constructed successfully..

### 1.3 Extraction of RNA

According to the procedure of Trizol Reagent kit, Total RNA from each HEK293 cell lines was extracted in 1.0 mL of TRIzol reagent. We used the automatic spectrophotometer UV to measure the optical density (OD) of the total RNA at 260 and 280 nm , then used 1% agarose gel electrophoresis to test the quality of total RNA.

### 1.4 cDNA synthesize and hybridization

For Illumina microarray analysis, biotinylated cRNA was prepared by using Illumina TotalPrepTM RNA Amplification Kit (Ambion, Inc., USA) according to the manufacturer's directions. Double-stranded cDNA was synthesized from the total RNA using a Superscript choice kit (Illumina) with T7 RNA polymerase promoter. cRNA was prepared and biotin labeled by in vitro transcription (Illumina). The labeled cRNA produced with the kit was developed for hybridization with Illumina arrays.

### 1.5 Data extraction and normalization

After genetic hybrid chip scan using the Illumina BeadChip Reader, images were converted to a digital signal based on the fluorescence intensity. The automatic and manual positioning were arranged to determine the scope of the crossover point, filter the background noise, extracte the fluorescence signal intensity of genes expression, and finally output in a list form. Thereby the scanning image were transformed into numeric value. Cubic spline function method was used for data correction and Illumina developed algorithms was used for identifying the differentially expressed genes. The diff score of a certain gene was obtained through averaging the corresponding score of all probes.

### 1.6 Data processing

The chip hybridization were performed twice, and gene wes considered to differentially expressed gene when its diff score was < –20 or > 20.

## 2 Results

### 2.1 Establishment of stably transfected HEK293 cell lines

After transfected by Lipofectamine 2000 and screened with G418, we established stably transfected empty vector, wild type DJ-1 and A39S DJ-1 mutant HEK293 cell lines. DNA sequence analysis was used to test the expression of transfected genes (Figure 1). In the empty vector group, there is no DJ-1 expression, but DJ-1 expression is obvious in the wild type DJ-1 group and A39S DJ-1 mutant group(Figure 2).

### 2.2 Measurement of total RNA

An effective measure of RNA purity was the ratio of the readings at 260 and 280 nm. The ratio of A260 to A280 values should be in the range of 1.7–2.1. Electropherogram of RNA in agarose gel electrophoresis showed three clear bands of 28 S, 18 S and 5 S rRNA. Those bands did not degrade obviously at 70°C for 1 h in thermal stability test indicated the quality of total RNA was reliable.

### 2.3 Microarray gene expression pattern

Gene expression profiles of the cell lines were obtained by scanning hybridization chip. We obtained the value of the original signal genes and control genes by chip image analysi software, normalized these data, and descripted the scatter plots of gene expression in all groups. The scatter plots of gene expression pattern could show the different expression of genes (Figure 3).

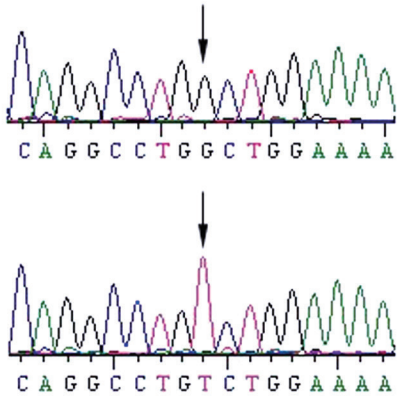


**Figure 1 Monoclonal cell line gDNA PCR sequencing graph**

A: Transfection of wild-type DJ-1 sequence map of selected monoclonal cell lines; B: Transfection of A39S mutant DJ-1 selected sequence map of monoclonal cell lines

## 2.4 Temporal profile of gene expression

Compared with empty-vector cells, 42 genes were altered in wild-type cells including 14 up-regulated genes and 28 down-regulated genes (Table 1), and eight genes were altered in A39S DJ-1 mutant cells including six up-regulated genes and two down-regulated genes (Table 2). Compared with wild-type cells, only one gene (UGT2B7) was down-regulated in A39S DJ-1 mutant cells. According to the functional analysis, these differentially regulated genes were mainly related to signal transduction, cell adhesion, regulation of transcription, G-protein coupled receptor protein signaling pathway, regulation of cell cycle, transport, protein modification, immune response development, apoptosis and metabolism (Table 1, 2).

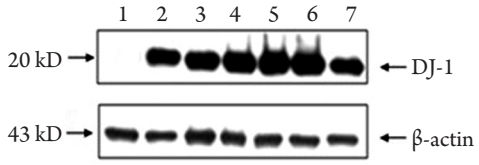


**Figure 2 Monoclonal cell line Western blot results**

1: Cells transfected with empty vector group; 2–4: Transfection of wild-type DJ-1 group; 5–7: Transfection of A39S mutant DJ-1

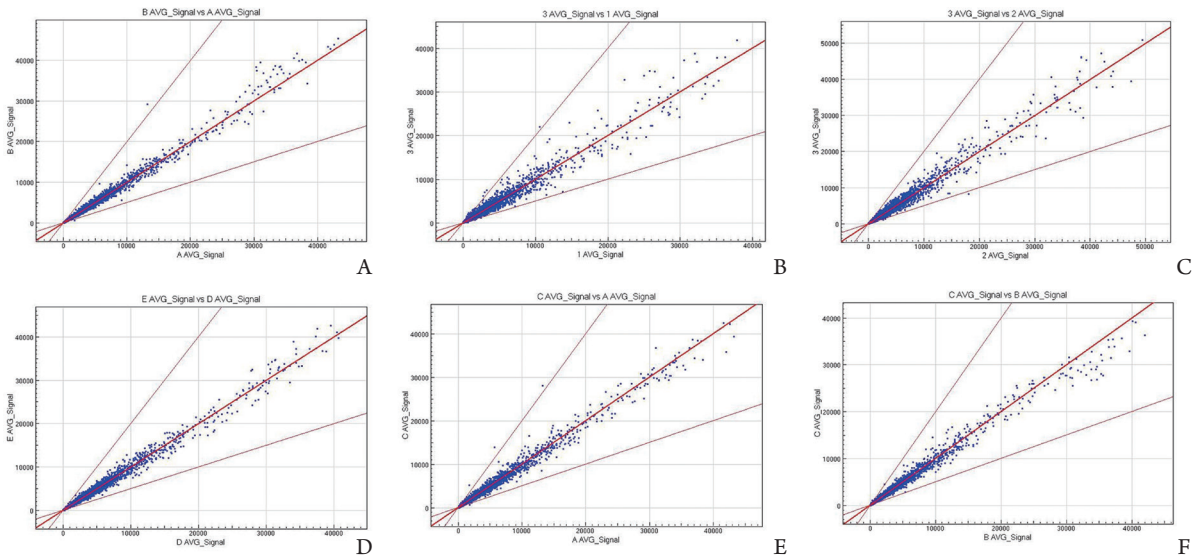


**Figure 3 Scatter plots of gene expression pattern**

A: Wt group 1 and BK group 1 scatter plot; B: A39S group 1 and BK group 1 scatter plot; C: A39S group 1 and Wt group 1 scatter plot; D: Wt group 2 and BK group 2 scatter plot; E: A39S group 2 and BK group 2 scatter plot; F: A39S group 2 and Wt group 2 scatter plot; BK: Empty vector; Wt: Wild type DJ-1; A39S: A39S mutant DJ-1

**Table 1 Abnormal gene expression of wild-type DJ-1 compared with empty-vector**

| Gene | Accession | Empty-vector AVG signal | A39S mutation AVG signal | Diff score | Ratio | Ontology process |
|---|---|---|---|---|---|---|
| PARK7 | NM_007262.3 | 13235.84 | 29254.91 | 61.91 | 2.21 | protein folding; Ras protein signal transduction |
| MXRA5 | NM_015419.1 | 87.33 | 229.86 | 41.15 | 2.63 | protein amino acid phosphorylation |
| EPHA4 | NM_004438.3 | 241.85 | 421.24 | 25.34 | 1.74 | signal transduction; transmembrane receptor protein tyrosine kinase signaling pathway; protein amino acid phosphorylation |
| FSTL1 | NM_007085.3 | 5681.42 | 9611.20 | 25.13 | 1.69 | protein binding |
| SAMD11 | NM_152486.2 | 587.36 | 935.88 | 24.69 | 1.59 | regulation of transcription |
| COL5A1 | NM_000093.2 | 1970.75 | 3235.44 | 23.76 | 1.64 | cell adhesion; phosphate transport |
| JOSD3 | NM_024116.1 | 435.09 | 685.42 | 22.94 | 1.58 | protein binding |
| TM7SF2 | NM_003273.1 | 1302.85 | 1970.53 | 21.95 | 1.51 | cholesterol biosynthesis |
| HOXB5 | NM_002147.2 | 489.47 | 768.45 | 21.11 | 1.57 | regulation of transcription, DNA-dependent; morphogenesis |
| SLIT2 | NM_004787.1 | 2413.55 | 3481.19 | 21.06 | 1.44 | G-protein coupled receptor protein signaling pathway; sensory perception; mesoderm migration; cell differentiation; positive regulation of axonogenesis; sensory perception of smell; chemotaxis; induction of negative chemotaxis; motor axon guidance; glial cell migration; ureteric bud development; neurogenesis; neuron recognition |
| JAK1 | NM_002227.1 | 369.61 | 571.62 | 21.00 | 1.55 | intracellular signaling cascade; protein amino acid phosphorylation |
| NPNT | NM_001033047.1 | 295.96 | 488.44 | 20.96 | 1.65 | cell adhesion; regulation of transcriotion |
| TCTEX1D1 | NM_152665.1 | 6.45 | 65.73 | 20.30 | 10.19 | protein binding |
| RRM2 | NM_001034.1 | 1708.52 | 2498.90 | 20.24 | 1.46 | deoxyribonucleoside diphosphate metabolism; DNA replication |
| RASD1 | NM_016084.3 | 242.00 | 139.70 | –20.23 | 0.58 | intracellular protein transport; signal transduction; G-protein coupled receptor protein signaling pathway; small GTPase mediated signal transduction |
| FADS3 | NM_021727.3 | 1169.93 | 736.30 | –20.40 | 0.63 | fatty acid desaturation |
| TRIB1 | NM_025195.2 | 1333.96 | 918.02 | –20.46 | 0.69 | protein amino acid phosphorylation |
| FLNC | NM_001458.2 | 1552.48 | 1034.51 | –20.66 | 0.67 | cell junction assembly |
| COL7A1 | NM_000094.2 | 281.80 | 164.70 | –20.67 | 0.58 | epidermis development; cell adhesion; phosphate transport |
| FRG1 | NM_004477.2 | 383.67 | 237.60 | –21.36 | 0.62 | rRNA processing |
| AXL | NM_001699.3 | 199.41 | 97.61 | –22.94 | 0.49 | signal transduction; regulation of cell cycle; protein amino acid phosphorylation |
| PHLDA2 | NM_003311.3 | 345.40 | 199.05 | –22.97 | 0.58 | apoptosis; imprinting |
| C5orf16 | NM_173828.3 | 129.40 | 49.25 | –24.43 | 0.38 | regulation of cell adhesion |
| DUSP5 | NM_004419.3 | 736.17 | 452.27 | –24.47 | 0.61 | protein amino acid dephosphorylation |
| SLC25A13 | NM_014251.1 | 313.75 | 190.87 | –25.29 | 0.61 | transport |
| SLC1A5 | NM_005628.1 | 1541.30 | 975.89 | –25.49 | 0.63 | transport; neutral amino acid transport; dicarboxylic acid transport |
| PLEK2 | NM_016445.1 | 390.12 | 237.12 | –26.33 | 0.61 | intracellular signaling cascade; actin cytoskeleton organization and biogenesis |
| HPCAL4 | NM_016257.2 | 157.93 | 68.86 | –27.05 | 0.44 | central nervous system development |
| PERP | NM_022121.2 | 546.83 | 317.11 | –27.12 | 0.58 | cell adhesion |
| KIAA1914 | NM_001001936.1 | 316.83 | 171.20 | –27.16 | 0.54 | regulation of transcription |

Continued

| Gene | Accession | Empty-vector AVG signal | A39S mutation AVG signal | Diff score | Ratio | Ontology process |
|---|---|---|---|---|---|---|
| DNAH17 | NM_003727.1 | 416.89 | 214.69 | −28.00 | 0.51 | microtubule-based movement |
| ITGB1BP3 | NM_014446.1 | 215.98 | 90.96 | −28.45 | 0.42 | pyridine nucleotide biosynthesis |
| MYC | NM_002467.3 | 531.09 | 301.10 | −30.58 | 0.57 | iron ion homeostasis; cell proliferation; positive regulation of cell proliferation; cell cycle arrest; regulation of transcription from RNA polymerase II promoter |
| HCP5 | NM_006674.2 | 548.48 | 318.57 | −30.96 | 0.58 | defense response |
| CALCB | NM_000728.3 | 617.53 | 359.13 | −31.82 | 0.58 | signal transduction; calcium ion homeostasis |
| NIF3L1 | NM_021824.2 | 9214.72 | 5595.37 | −31.93 | 0.61 | regulation of transcription |
| ETV5 | NM_004454.1 | 241.48 | 94.97 | −32.17 | 0.39 | regulation of transcription, DNA-dependent |
| HIST1H1C | NM_005319.3 | 616.20 | 336.85 | −33.25 | 0.55 | nucleosome assembly; chromosome organization and biogenesis (sensu Eukaryota) |
| ARC | NM_015193.3 | 223.90 | 86.25 | −39.21 | 0.39 | regulation of cell proliferation; cell migration |
| SPINK1 | NM_003122.2 | 123.14 | 15.77 | −41.52 | 0.13 | regulation of signal transduction |
| IL8 | NM_000584.2 | 188.52 | 32.40 | −62.49 | 0.17 | G-protein coupled receptor protein signaling pathway; neutrophil chemotaxis; sensory perception; induction of positive chemotaxis; negative regulation of cell proliferation; intracellular signaling cascade; regulation of retroviral genome replication; chemotaxis; cell-cell signaling; cell cycle arrest; neutrophil activation; calcium-mediated signaling; angiogenesis; regulation of cell adhesion; cell motility |
| EGR1 | NM_001964.2 | 1802.87 | 659.42 | −78.95 | 0.37 | regulation of transcription, DNA-dependent; transcription |

**Table 2 Abnormal gene expression of A39S mutation compared with empty-vector**

| Gene | Accession | Empty-vector AVG signal | A39S mutation AVG signal | Diff score | Ratio | Ontology process |
|---|---|---|---|---|---|---|
| MXRA5 | NM_015419.1 | NIPSNAP1NIF3L1 | 413.72 | 117.36 | 4.74 | protein amino acid phosphorylation |
| HOXB5 | NM_002147.2 | 489.47 | 926.22 | 47.93 | 1.90 | regulation of transcription, DNA-dependent; morphogenesis |
| NIPSNAP1 | NM_003634.1 | 958.65 | 1491.74 | 27.09 | 1.56 | sensory perception of pain |
| P8 | NM_012385.1 | 168.50 | 338.93 | 24.84 | 2.01 | induction of apoptosis; cell growth |
| HOXB9 | NM_024017.3 | 2081.84 | 3066.75 | 24.67 | 1.47 | regulation of transcription, DNA-dependent; development |
| CPS1 | NM_001875.2 | 364.45 | 571.49 | 21.54 | 1.57 | nitrogen compound metabolism; glutamine metabolism; pyrimidine base biosynthesis; arginine biosynthesis; urea cycle |
| NIF3L1 | NM_021824.2 | 9214.72 | 6069.91 | −25.84 | 0.66 | regulation of transcription, DNA−dependent |
| MYC | NM_002467.3 | 531.09 | 283.68 | −38.96 | 0.53 | iron ion homeostasis; cell proliferation; positive regulation of cell proliferation; cell cycle arrest |

## 3 Discussion

In recent years, DNA microarray technology is widely applied in the study of gene expression profile and exploring potentially causative genes[13]. Gene expression profile chip was used to study neural drug toxicity, nervous protection agents and oxidative stress in nervous system diseases such as Alzheimer's disease, multiple sclerosis and PD[14-16]. The samples that can be used to analyze the gene expression patterns are various in PD from cells to brain tissues. The gene expression profiles in PD gene model have also been reported[17-18]. Miller analyzed three gene expression patterns including wild- type, the A53T mutated and double (A53T and A30P) mutated α-synuclein, and found that α-synuclein regulated several genes which mainly participated in the regulation of synapse transport and necrosis of neurons[18].

Our study showed that 14 genes were up-regulated and 28 genes were down-regulated in wild-type DJ-1 cells, and 6 genes were up-regulated and 2 genes were down-regulated in A39S DJ-1 mutant cells compared with the empty vector cells. Compared with wild-type DJ-1 cells, we found UGT2B7 gene was down-regulated in A39S DJ-1 mutant cells. These differentially regulated genes play a role mainly in regulation of transcription, signal transduction, cell adhesion, cell cycle, apoptosis and metabolism. It indicated that wild-type DJ-1 and A39S DJ-1 mutant may participate in the regulation of these differential genes, modulate the corresponding biological pathways and finally involve in the pathogenesis of PD. Compared with the empty vector cells, expression of some genes were regulated in both wild-type DJ-1 cells and A39S DJ-1 mutant cells, for instance, MXRA5 gene and HOXB5 gene were up-regulated and NIF3L1 gene and MYC gene were down-regulated in both groups. It suggested that the function of A39S DJ-1 keep accordance with wild-type DJ-1 in some extent and A39S DJ-1 did not completely lose the transcription activity. However, the transcription activity of wild type DJ-1 and A39S mutant DJ-1 were not exactly the same. UGT2B7 gene was down-regulated in A39S mutated DJ-1 protein cells compared with wild-type DJ-1 protein cells, which implied that the A39S mutant may regulate UGT2B7 gene and involve in the pathogenesis of PD.

UGT2B7 is located on chromosome 4q13 and encode 529-amino-acid protein. UGT2B7 mainly functions as metabolic enzymes and belongs to UDP-glucuronosyltransferase (UGT) protein super-family[19]. Several transcription factors participate in the regulation of UGT2B7, including hepatocyte nuclear factor-1 octamer transcription factor-1 caudal-related homeodomain protein-2 and farnesoid X receptor[20]. Recently, Nakamura found that the nuclear factor erythroid 2-related factor (Nrf2) gene could regulate the transcription of UGT2B7. Clements discovered that DJ-1 could adjust Nrf2 expression through inhibiting Keap1 (the inhibitor of Nrf2) and ubiquitinoylation of Nrf2, and then regulate the expression of anti-oxidation genes[21]. Deficiency in the function of DJ-1 protein may reduce the stability and transcription activity of Nrf2 protein, which resulted in the down-regulation of anti-oxidation genes expression[10]. The down-regulation of anti-oxidation genes expression would participate in the pathogenesis of PD because of excessive oxidative stress.

A39S mutation of DJ-1 was firstly reported by our work group, and related function of it is still unknown. This is the first functional research of A39S mutation. The microarray results showed that there are many differences in gene expression of wild-type DJ-1 cells and A39S DJ-1 mutant cells compared with the empty vector cells. Some of differentially expressed genes were found in the wild-type DJ-1 group and A39S mutant DJ-1 group, but UGT2B7 gene was down-regulated in A39S DJ-1 mutantcells compared with wild-type DJ-1 cells. Whether A39S mutation of DJ-1 may disturb the transcriptional activities of DJ-l and involve in the pathogenesis of PD through regulating UGT2B7 and other genes requires further exploration.

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