Genome-Scale Expression Pattern of Long Non-Coding RNAs in Chinese Uyghur Patients with Parkinson’s Disease

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Background: Long non-coding RNAs (lncRNAs) are transcripts thought to regulate gene expression at the post-transcriptional level. Some lncRNAs are associated with Parkinson’s disease (PD) and participate in pathological processes of PD. The incidence of PD is relatively high in members of the Uyghur minority living in Xingjiang province of China. This study measured the expression of lncRNAs in the peripheral blood cells of Chinese Uyghur individuals with and without PD and analyzed the possible function of these lncRNAs in the development of PD.

Material/Methods: Peripheral blood samples were collected from 55 Uyghur patients with PD and 55 healthy volunteers. Total RNA was extracted, and the levels of expression of whole-genome lncRNAs and mRNAs in 10 samples (5 PD and 5 controls) were determined by microarray method. The expression levels of lncRNAs in all 100 subjects were determined by qRT-PCR. The lncRNA expression profiles of PD patients were determined based on lncRNA microarray chip analysis, and differentially expressed lncRNAs were identified. The results of chip analysis were confirmed in a large clinical cohort.

Results: Comparison of subjects with and without PD identified 32 significantly up-regulated and 18 significantly down-regulated lncRNAs in the PD group. GO analysis showed that mRNAs encoding proteins involved in the regulation of biological processes were differentially expressed, with the inflammatory immune response being the most significantly related pathway.

Conclusions: The expression of lncRNAs in peripheral blood differed significantly in PD patients and controls. These differentially expressed lncRNAs may play a role in the development of PD.

MeSH Keywords: Microarray Analysis • Parkinson Disease • RNA, Long Noncoding

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Background

Parkinson’s disease (PD) is a common neurodegenerative disease, characterized by resting tremors, stiffness, bradykinesia and postural instability, as well as non-motor symptoms such as psychosis, sensory symptoms, autonomic dysfunction, and sleep disturbances. The main pathological changes of PD are the degeneration of dopamine neurons in the dense substantia nigra of the midbrain and the subsequent depletion of striatal dopamine [1,2]. Various epidemiological and experimental investigations have shown that aging, genetic factors and environmental toxins synergistically participate in degenerative damage to dopaminergic neurons [3–5]. The slow progression of PD and the continuous deterioration of clinical characteristics lead to disability and related complications. Identifying new biological information or biomarkers can better explore the pathogenesis of PD, improve its early diagnosis and identify potential therapeutic targets.

Long non-coding RNAs (lncRNAs) are a recently discovered group of RNA molecules, ranging in length from 200 bp to 10 kbp, which are thought to regulate gene expression at the post-transcriptional level, including in PD [6,7]. Although lncRNAs lack the ability to encode any proteins, they have crucial regulatory potential in processing proteins during many biological processes [8–10]. LncRNAs may play important roles in the pathological changes of PD, including in gene transcription, DNA methylation, post-transcriptional processes, epigenetic modification, direct protein binding and regulation of protein functions [11–13].

The Uyghur constitute an ethnic minority within China. Most Uyghur people live in Xinjiang Province, on the northwestern border of China. These people have a lifestyle and dietary habits different from those of Han Chinese, as well as a relatively high incidence of PD [14,15]. Few epidemiological studies have assessed PD in the Uyghur population. The present study assessed the expression of lncRNAs in Uyghur individuals with and without PD and analyzed the possible biological functions of these lncRNAs in the development of PD.

Material and Methods

The study protocol was approved by the ethics committee of Second Affiliated Hospital of Xinjiang Medical University. All participants were recruited between December 2017 and September 2018 from the Department of Neurology and pro- Affiliated Hospital of Xinjiang Medical University. All blood samples were obtained by venipuncture after an overnight fast and preserved at –80°C until analysis. Five age-matched Uyghur individuals with and without PD were randomly selected for microarray analysis.

RNA extraction

Total RNA was extracted from peripheral blood cells using mir-Vana extraction kits (Ambion, Austin, TX, USA), and purified by Qiagen RNeasy® kits [17–19]. RNA 6000 Nanochip Lab-on-a-Chip kits and the Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA, USA) were used to detect RNA integrity by capillary electrophoresis. Only RNA samples with RNA integrity values ≥6 were further analyzed. For chip preparation, total RNA samples were amplified in vitro and fluorescently labeled, with the labeling, hybridization, and scanning of the chip completed by Beijing Boao Biological Co. Ltd.

LncRNA and mRNA analysis

Human LncRNA Array V4. 4×180k Agilent IncRNA was used for analysis, based on the latest information on lncRNAs in the GENCODE/ENSEMBL database, LNCipedia, the human LncRNA Catalog [20], the ncRNA expression database (NRED), and the RefSeq and UCSC databases. This array allowed lncRNAs and mRNAs to be analyzed simultaneously, and their correlations determined. LncRNA expression profiling analyses were completed by Beijing Boao Biotechnology Co., Ltd.

GeneSpring software V13.0 (Agilent) was used for data aggregation, standardization and quality control analysis of lncRNA and mRNA array data.

LncRNA related functional analyses

The potential functions of lncRNAs were predicted based on related cis- and trans-mRNAs. The regulated target gene was selected and sequences located 10 kb upstream and downstream of the coding gene position were subjected to Gene Ontology (GO) analysis to predict the biological significance of the target genes. Target genes were mapped to the Kyoto Encyclopedia of Genes and Genomes (KEGG) advanced database resource, and the main pathways of differentially expressed genes were identified based on KEGG results [21]. The lncRNA/mRNA co-expression networks were constructed based on Pearson correlation coefficients not less than 0.99 [22].

qRT-PCR

Total RNA was extracted and reverse transcribed to cDNA using RNeasy Mini kits (Fermentas, K1622). The cDNA was analyzed by quantitative real-time polymerase chain reaction
(qRT-PCR) using Power SYBR Green PCR Master (Applied Biosystems, Foster City, CA USA) and the primer sequences shown in Table 1. The expression of each was normalized to that of GAPDH mRNA in the same sample, and fold change (FC) of target gene expression in the experimental group relative to the control group calculated using the 2\(^{-\Delta\Delta CT}\) method.

### Statistical analysis

All statistical data were analyzed with SPSS Statistics 18.0 software. Qualitative variables were compared by Pearson’s Chi-squared test. The normality of quantitative variables was determined. Normally distributed variables were expressed as mean±standard deviations (SD) and compared by Student’s t-tests, whereas non-normally distributed variables were reported as median (interquartile range [IQR]) and compared by Mann-Whitney U tests.

### Table 1. PCR primers used in the amplification of lncRNAs.

| Gene name     | Forward primer       | Reverse primer       |
|---------------|----------------------|----------------------|
| uc.175+       | ACCATACTTAATGGACGACCC| CATTAGAACAGACGGCATCTCA|
| TCONS_00023421| GCTGGATCTCCTGGCCCTTCT| ACCTCTGAAAAGCCCATCTCC|
| ENST00000435434.1 | CGTTCTCCTGGCCCTTCTCT | GATTGATGCCAGCCTTCTCA |

### Table 2. Clinical characteristics of the included participants.

|                      | PD (n=55) | Control (n=55) | t/\chi^2   | P   |
|----------------------|-----------|----------------|------------|-----|
| Age, yr, mean (SD)   | 61.91 (6.09) | 63.93 (5.68) | 1.798     | 0.075 |
| Sex                  |           |                |           |     |
| Male                 | 21 (38.2%) | 22 (40%)       | 0.038     | 0.845 |
| Female               | 34 (61.8%) | 33 (60%)       |           |     |
| Hypertension         |           |                |           |     |
| Yes                  | 21 (38.2%) | 18 (32.7%)     | 0.358     | 0.55 |
| No                   | 34 (61.8%) | 37 (67.3%)     |           |     |
| Diabetes             |           |                |           |     |
| Yes                  | 9 (16.4%)  | 11 (20.0%)     | 0.244     | 0.621 |
| No                   | 46 (83.6%) | 44 (80.0%)     |           |     |
| CHD                  |           |                |           |     |
| Yes                  | 10 (18.2%) | 12 (21.8%)     | 0.227     | 0.634 |
| No                   | 45 (81.8%) | 43 (78.2%)     |           |     |
| Smoking              |           |                |           |     |
| Yes                  | 10 (18.2%) | 10 (18.2%)     | <0.001    | >0.999 |
| No                   | 45 (81.8%) | 45 (81.8%)     |           |     |
| Alcohol              |           |                |           |     |
| Yes                  | 13 (23.6%) | 12 (21.8%)     | 0.052     | 0.82 |
| No                   | 42 (76.4%) | 43 (78.2%)     |           |     |
| UPDRS, median (IQR)  |           |                |           |     |
| Part I               | 18.00 (11.00) |                   |           |     |
| Part II              | 27.84 (9.50) |                   |           |     |
| HY                   | 3.00 (1.00) |                   |           |     |

Unless indicated, all results are reported as number (%).
Table 3. LncRNAs differentially expressed in PD patients and controls.

| Probe name | p (Corr) | p | FC (abs) | Regulation | lncRNA ID | Class | Database |
|------------|----------|---|----------|------------|-----------|-------|----------|
| p6243      | 0.241805 | 0.023952 | 10.02382 | Up         | ENST0000562027.1 | Antisense | ENSEMBL |
| p2252      | 0.143293 | 0.003567 | 3.768559 | Up         | ENST0000531966.1 | Antisense | ENSEMBL |
| p35771_v4  | 0.231806 | 0.020754 | 3.710862 | Down       | TCONS_00023420 | Intergenic | Human LincRNA Catalog |
| p43010_v4  | 0.279495 | 0.03715 | 3.594939 | Up         | XR_429535.1 | Antisense | Ensembl |
| p317       | 0.116851 | 0.001489 | 3.454431 | Up         | ENST0000043543.1 | Antisense | ENSEMBL |
| p1724      | 0.242774 | 0.024334 | 3.468111 | Up         | ENST0000043543.1 | Antisense | ENSEMBL |
| p35771_v4  | 0.231806 | 0.020754 | 3.710862 | Down       | TCONS_00023420 | Intergenic | Human LincRNA Catalog |
| p19760     | 0.179978 | 0.00873 | 3.113262 | Down       | TCONS_00023420 | Intergenic | Human LincRNA Catalog |
| p18732     | 0.205126 | 0.013639 | 2.797274 | Up         | TCONS_00020975 | Intergenic | Human LincRNA Catalog |
| p27596     | 0.297495 | 0.044486 | 2.616316 | Down       | uc.175- | Intronic | UCR |
| p27309     | 0.116851 | 0.001363 | 2.528911 | Down       | uc.436- | Intronic | UCR |
| p37172_v4  | 0.286468 | 0.040126 | 2.511514 | Down       | ENST00000605437.1 | Antisense | ENSEMBL |
| p20336     | 0.207196 | 0.014158 | 2.469166 | Up         | TCONS_00025471 | Intergenic | Human LincRNA Catalog |
| p778       | 0.19561 | 0.011811 | 2.440392 | Down       | ENST00000448179.1 | Antisense | ENSEMBL |
| p39783_v4  | 0.116851 | 0.001438 | 2.351895 | Up         | XR_245040.2 | RefSeq |
| p9380      | 0.149003 | 0.004317 | 2.351043 | Up         | ENST00000447019.1 | Intergenic | ENSEMBL |
| p18579     | 0.232472 | 0.020902 | 2.317187 | Up         | TCONS_00020677 | Intergenic | Human LincRNA Catalog |
| p18734     | 0.141803 | 0.003493 | 2.296254 | Up         | TCONS_00020978 | Intergenic | Human LincRNA Catalog |
| p37810_v4  | 0.135067 | 0.003000 | 2.276699 | Up         | ENST0000060385.1 | Intergenic | ENSEMBL |
| p34569_v4  | 0.266353 | 0.032203 | 2.269158 | Up         | ENST00000582564.1 | Antisense | ENSEMBL |
| p12485     | 0.162983 | 0.006192 | 2.267334 | Down       | ENST00000513542.1 | Antisense | ENSEMBL |
| p35646_v4  | 0.190787 | 0.010549 | 2.266483 | Up         | TCONS_00021439 | Intergenic | Human LincRNA Catalog |
| p14290     | 0.128822 | 0.002286 | 2.252301 | Up         | ENST0000041895.1 | Sense | ENSEMBL |
| p27540     | 0.144871 | 0.00369 | 2.251183 | Up         | uc.129- | Intronic | UCR |
| p20968     | 0.147824 | 0.003998 | 2.2487 | Up         | TCONS_0004538 | Intergenic | Human LincRNA Catalog |
| p15970     | 0.278082 | 0.036622 | 2.234251 | Up         | TCONS_0002190 | Intergenic | Human LincRNA Catalog |
| p37247_v4  | 0.194763 | 0.011625 | 2.207759 | Up         | ENST00000603052.1 | Intergenic | ENSEMBL |
Table 3 continued. LncRNAs differentially expressed in PD patients and controls.

| Probe name | p (Corr) | p | FC (abs) | Regulation | IncRNA ID | Class | Database |
|------------|----------|---|---------|------------|-----------|-------|----------|
| p1265      | 0.11382  | 0.001073 | 2.19148 | Up | ENST00000440321.1 | Antisense | ENSEMBL |
| p18739      | 0.272422 | 0.033959 | 2.19138 | Up | TCONS_00020982 | Intergenic | ENSEMBL |
| p36897_v4 | 0.240995 | 0.023739 | 2.182665 | Up | ENST00000607528.1 | Intergenic | ENSEMBL |
| p21174      | 0.241976 | 0.024 | 2.173662 | Up | TCONS_0003759 | Divergent | ENSEMBL |
| p8580      | 0.19327 | 0.011292 | 2.150622 | Down | ENST000005598450.1 | Antisense | ENSEMBL |
| p3014      | 0.191399 | 0.010655 | 2.147698 | Down | ENST00000527712.1 | Intergenic | ENSEMBL |
| p27630      | 0.229008 | 0.01996 | 2.142132 | Down | uc.175+ | Intronic | UCSC |
| p21491      | 0.208024 | 0.014417 | 2.132571 | Up | TCONS_00028488 | Intergenic | ENSEMBL |
| p29550      | 0.180019 | 0.00884 | 2.110589 | Down | TCONS_00000075 | Intergenic | ENSEMBL |
| p3447      | 0.276483 | 0.035979 | 2.091668 | Up | ENST00000536517.1 | Intergenic | ENSEMBL |
| p7319      | 0.114947 | 0.001141 | 2.054854 | Down | TCONS_00022624 | Intergenic | ENSEMBL |
| p4387      | 0.190608 | 0.010404 | 2.008121 | Down | ENST00000425554.1 | Intergenic | ENSEMBL |

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Results

Clinical characteristics

This study included a total of 55 patients with PD and 55 age-matched healthy controls. Assessments of their clinical characteristics showed no significant differences (Table 2).

Differentially expressed lncRNAs in PD patients and healthy controls

Analysis of lncRNAs in samples from 5 Uyghur PD patients and 5 age-matched Uyghur healthy controls identified 50 differentially expressed lncRNAs with FC $\geq 2.0$ and $P < 0.05$. Of these 50 lncRNAs, 32 were up-regulated and 18 were down-regulated in PD patients relative to healthy controls (Table 3).

The relationships of lncRNAs between Uyghur PD and healthy controls were analyzed by hierarchical clustering [23,24]. The 2 groups of hierarchical clusters showed different expression profiles of lncRNAs (Figure 1A). The clustering of the same group of samples indicated consistent gene expression trends. The scatter plots and volcano plots provide a visual representation of the differences in lncRNA expression between the 2 groups (Figure 1B–1C).

Functional annotation of lncRNAs in PD

The potential function of lncRNAs was evaluated by annotation of co-expressed mRNAs. Ninety-seven differentially expressed mRNAs, with FC $\geq 2.0$ and $P < 0.05$ were identified, with 65 up-regulated and 32 down-regulated in PD patients relative to healthy controls (Figure 2A). The top 25 differentially expressed mRNAs are listed in Table 4. The scatter plots and
volcano plots showed clear differences in expression of mRNAs between the 2 groups (Figure 2B–2C).

GO annotation showed that the top 5 terms related to biological processes in PD patients included: (1) cellular processes, (2) single-organism processes, (3) biological regulation, (4) regulation of biological processes, and (5) responses to stimuli. The GO terms most significantly associated with cellular components in PD patients included: (1) cells, (2) parts of cells, (3) organelles, (4) membranes, and (5) parts of membranes.

The GO terms most significantly associated with molecular function in PD patients included: (1) binding, (2) catalytic activity, (3) molecular transduction, (4) regulation of molecular function, and (5) nucleic acid binding transcription factor (Figure 3).

KEGG pathway analysis showed that the most enriched pathways corresponding to PD-related LncRNA disorders included:

Cytokine-cytokine receptor interactions, chemokine receptors binding to chemokines, natural killer cell-mediated cytotoxicity, immunoregulatory interactions between lymphoid and non-lymphoid cells, and the NF-kappa B signaling pathway (Figure 4).

The most significantly enriched disease terms included: (1) immune system diseases, (2) allergies and autoimmune diseases, (3) gastric cancer, somatic, (4) common variable immunodeficiency, and (5) primary immunodeficiency (Figure 5).

**LncRNA-mRNA network analysis**

Based on Pearson correlation coefficients not less than 0.99, a co-expression network of differentially expressed LncRNAs and mRNAs was constructed (Figure 6).
Validation of lncRNA by qRT-PCR

To verify the results of microarray analysis of lncRNA expression, the levels of expression of 3 randomly selected lncRNAs of 50 Uyghur PD patients and 50 healthy controls were evaluated by qRT-PCR (Table 5). These results were consistent with those from microarray analysis.

Discussion

PD is a typical progressive neurodegenerative disease with a high prevalence worldwide. Although the pathogenesis of PD remains unclear, genetic factors are involved [25]. LncRNAs were shown to be involved in various neurodegenerative diseases, such as PD, Huntington's disease, Alzheimer's disease (AD), and spinocerebellar ataxia [26–28].

Table 4. The top 25 differentially expressed mRNAs in the PD and control groups.

| ProbeName    | p         | FC (abs) | Regulation | Gene symbol | Ensembl ID |
|--------------|-----------|----------|------------|-------------|------------|
| A_23_P149613 | 0.003126  | 10.4693  | Down       | FMO1        | ENST00000469711 |
| A_23_P214080 | 0.0046    | 6.526025 | Up         | EGR1        | ENST00000239938 |
| A_23_P77502  | 0.009533  | 5.032134 | Down       | PKD1        | ENST00000262304 |
| A_23_P412321 | 0.008783  | 4.032254 | Up         | CCR5        | ENST00000292303 |
| A_23_P55961  | 0.001511  | 3.870449 | Up         | TULP2       | ENST00000221399 |
| A_33_P3363355| 0.016505  | 3.637605 | Up         | ICAM4       | ENST00000393717 |

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LncRNAs have been linked to the occurrence and development of PD. An analysis of the levels of expression of lncRNAs in 30 brain specimens from 20 PD patients and 10 controls found that 5 lncRNAs were significantly differentially expressed in these samples. Interestingly, analysis of the levels of expression of lncRNAs and disease stages showed that changes in lncRNA expression can be detected in patients with early PD, suggesting that lncRNA dysregulation may have occurred before PD [29]. Analysis of brain nigra tissue samples from 11 PD patients and 14 normal controls showed obvious changes.
Figure 3. GO enrichment terms of differentially expressed lncRNAs in PD patients.

Figure 4. Pathway analysis of differentially expressed lncRNAs. Different colors represent different databases.
in 87 lncRNAs. Among them, lncRNA AL049437 may trigger the development of PD, whereas lncRNA AK021630 may inhibit its occurrence [30]. Whole-transcriptome RNA sequencing technology has been used to determine all transcripts encoding proteins and lncRNAs in peripheral blood leukocytes of PD patients before and after deep brain stimulation (DBS). A comparison with healthy controls identified associations between expression of lncRNAs and selective PD-induced changes. Of the more than 6000 lncRNAs detected, 13 showed PD-induced changes, with 4 experiencing reverse changes after DBS [12]. Previous experimental results showed that a large number of lncRNAs were differentially expressed in both animal [31] and cell [32,33] models of PD.

This study also used microarray technology to assess whole-genome expression profiles of lncRNAs in Uyghur individuals with and without PD. Fifty differentially expressed lncRNAs were identified in these 2 groups, as were 97 mRNAs.

The relationship between lncRNA and PD is still unclear. Studies have found abnormal expression of lncRNAs in early PD [34,35], and antisense lncRNAs have been shown to regulate PD characteristics [36]. For example, NEAT1 lncRNA was found to inhibit the degradation of PINK1 protein, and interference with NEAT1 has been found to ameliorate damage to dopaminergic neurons [37]. Moreover, lncRNAs extracted from plasma exosomes were found to be differentially expressed. The results of bioinformatics analysis suggest that lnc-MKRN2-42 may be related to the occurrence and development of PD [13]. These studies also suggest that lncRNAs may be biomarkers for PD and may play important roles in the pathogenesis of PD. Further studies are needed to determine the role of lncRNAs in personalized neurology.

GO, KEGG enrichment, and pathway analyses are all important components of bioinformatics analysis. GO analysis of differentially expressed mRNAs of Uyghur PD patients and healthy controls identified GO terms close to biological processes, including cellular processes, single-organism processes, biological regulation, regulation of biological processes, and metabolic processes. In addition, the first few terms were closely related to the degree of cellular components included cells, parts of cells, organelles, and membranes. The first few terms more closely related to molecular

**Figure 5.** Disease analysis of differentially expressed lncRNAs.
Figure 6. LncRNA-mRNA-network. Yellow dots indicate lncRNAs, and green nodes indicate target mRNAs.

Table 5. Randomly selected lncRNAs.

| lncRNA ID | p    | FC (abs) | Regulation | Probe | Start | End   | class   | Database             |
|-----------|------|----------|------------|-------|-------|-------|---------|----------------------|
| uc.175+   | 0.01996 | 2.142132 | Down       | p27630 | 1.58E+08 | 1.58E+08 | Intronic | UCR                  |
| TCONS_00023421 | 0.00873 | 3.113262 | Down       | p19760 | 57592197 | 5.8E+07 | Intergenic | Human LincRNA Catalog |
| ENST00000435434.1 | 0.024334 | 3.446811 | Up         | p1724 | 1.06E+08 | 1.06E+08 | Antisense | ENSEMBL              |

functions included binding, catalytic activity, molecular transduction activity, and regulation of molecular function regulator. GO analysis initially addressed the biological information of genes with significantly different levels of expression in the PD and control groups at these 3 levels, providing direction for basic research on the pathogenesis of PD.

In this study, differentially expressed lncRNAs and mRNAs were selected by comparing their levels of expression in the Uyghur PD and healthy control groups. Pathway analysis revealed that the most enriched pathways corresponding to the dysregulation of lncRNAs related to PD were the inflammatory signaling pathway and its corresponding NF-kappa B signaling pathway. Inflammation plays an important role in the pathophysiology and etiology of neurodegenerative diseases [38,39]. Studies have suggested a possible connection between the loss of dopaminergic neurons and autoimmunity in PD [40,41]. Persistent inflammatory response is a major factor in the degeneration of dopaminergic neurons in PD [42,43]. Specific autoantibodies (AAbs) in PD may react with certain neuronal components involved in PD. Immunoregulatory therapy may have therapeutic significance for PD treatment in the future. Other dysregulated lncRNAs were related to the binding of chemokines to
chemokine receptors and cytokine-cytokine receptor interactions, as well as their subsequent signaling pathways.

This study had several limitations, including its recruitment of participants from a single ethnic group in a single center in China. Therefore, it is unclear whether these differences in expression also occur in other sets of PD patients. Another limitation was the small sample size, indicating the need to validate these results in larger populations.

Conclusions

In conclusion, a microarray method was used to detect the expression of IncRNAs in the peripheral blood of Uyghur PD patients and healthy controls. The results provided biological information on IncRNA expression and the expression of corresponding mRNAs expression throughout the entire genome. The potential functional linkage of PD revealed that IncRNA expression was dysregulated and involved several biological and pathological processes. The abnormally expressed IncRNAs were associated with the regulation of inflammation and autoimmune diseases. The biological information and functional links provided by this study may provide clues to the pathogenesis and development of PD.

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