Letter to the Editor

Bioinformatics Analysis Raises Candidate Genes in Blood for Early Screening of Parkinson's Disease[*]

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Parkinson's disease (PD) is a typical degenerative disease, which is characterized by the most obvious symptoms of movement dysfunction, including shaking, rigidity, slowness of movement and difficulty in walking and gait. This disease can not be clearly identified through laboratory tests at present, thus application of high-throughput technique in studying the expression profiles of PD helps to find the genetic markers for its early diagnosis. Studies on expression profiles of neurodegenerative diseases have revealed the novel genes and pathways involved in the progress of illness. In this study, the expression profiles of PD in blood were compared, showing that 181 differentially expressed genes (DEG) exhibit a similar expression trend both in patients and in normal controls. These genes are enriched significantly in some biological processes, including development, response to drugs, and DNA-dependent regulation of transcription, etc, highlighting that the genetic markers can be used in early diagnosis of PD.

Parkinson's disease (PD) is a degenerative disorder, which mainly affects motor neurons[1]. The most obvious symptoms in its early stage are shaking, rigidity, slowness of movement and difficulty in walking and gait. Behavioral and thinking problems may occur with development of dementia in its advanced stage[1]. PD usually disturbs people over 50 years of age. The lifetime risk of PD is 1.5% and 1.5-fold higher in men than in women[2]. The pathology of PD is characterized by the accumulation of alpha-synuclein into inclusions called Lewy bodies in neurons, and from insufficient formation and activity of dopamine produced in certain neurons within parts of the midbrain. The cause of PD is complex[3]. PD can be diagnosed according to the medical history and neurological examinations. PD can not be clearly identified through laboratory tests at present, although brain scanning can sometimes exclude disorders that give rise to similar symptoms. Usually, the diagnosis of PD can be established when Lewy bodies are found in the midbrain. As a matter of fact, some authorities recommend that periodic diagnosis should be conducted, as the progress of the illness over time may reveal that it is actually not PD[4].

A common strategy for studying neurodegenerative diseases is to the high-throughput technique for screening the gene expression profiles in diseased and neurologically healthy control brain samples. Our recent studies on prion disease showed that genes are differentially expressed in disease samples. Moreover, s Alzheimer's disease and oxidative phosphorylation, etc, may play an essential role in the pathogenesis of PD[5-6].

However, it is hardly to obtain brain tissue samples from healthy people for early diagnosis of neurodegenerative diseases. Therefore, finding markers in blood will greatly contribute to the early diagnosis of neurodegenerative diseases. Scherzer et al.[7] showed that 8 genes display a significant difference in 66 patients. In the present study, both cortex and blood expression profiles of PD in blood were analyzed in order to find more candidate genes in blood for its early diagnosis. Particularly, we are looking for those genes with similar expression trends in patients versus normal controls in both brain and blood.

Expression profiles of both cortex and blood samples of PD patients were obtained from the ExpressArray database. Twenty-seven microarray

data from PD patients' cortex and 26 controls (E-GEOD-20168)[8], and 50 microarray data from PD patients' blood and 23 controls (E-GEOD-6613)[7] were used in the analysis of expression profiles. The microarrays from different platforms were normalized using the software dChip, and the normalized signal values were to represent the expression levels of individual genes in blood. The normalization was performed using an 'invariant set' automatically selected by dChip and then followed by a 'Running median' method. The normalization processes made each microarray's scatterplot comparable. After normalization, 8 475 differentially expressed genes (DEG) shared by all microarrays were used in further analysis and the DEG with a ratio greater than 1.2 were filtered. A total of 1 280 or 2 101 DEG were detected in brain cortex or blood in PD patients and filtered, showing 96 genes were up-regulated and 85 genes were down-regulated in both samples.

The ontology (GO) of 181 genes with a similar expression trend in both cortex and blood were analyzed, showing that the up-regulated genes affect 322 terms of biological processes (BP) while the down-regulated genes affect 161 terms of BP. The top three-affected BP were the development, response to drugs, and DNA-dependent regulation of

transcription (Table 1) with 11, 4, and 9 genes involved. The P- and Q-values were very low, implying a significant significance in BP. It should note that the 'response to drug', which was significantly affected, was possibly the result of the use of drug in patients. In addition to the three BP, the processes of signal transduction, cell differentiation, nervous system development, and immune response affected more than 5 genes. The down-regulated genes were enriched within synaptic transmission, DNA-dependent regulation of transcription, and vesicle docking during exocytosis, etc (Table 2). It was interesting that both up-regulated and down-regulated genes were enriched within the following biological processes: DNA-dependent regulation of transcription, development, and signal transduction, suggesting that the three BP are significantly affected in the course of PD.

The genes with a same expression trend in cortex and blood, and the genes with 1.4-fold higher expression level are listed in Table 3. The GFAP gene was most significantly up-regulated and its level was 1.7-fold higher in cortex and 1.6-fold higher in blood in PD patients than in normal controls. The GFAP was a marker that can distinguish astrocytes from other glial cells during development, indicating that the astrocytes are affected in the early stage of PD. The

Table 1. Biological Processes of Up-regulated DEG in both Cortex and Blood

Biological Process	Count	*P*-Value	*Q*-Value	Protein
GO:0007275 development	11	1.33E-10	1.64E-10	ANGPT1; CSRP2; FGF2; FZD9; MTL5; CDX4; MAB21L1; SEMA3A; HEYL; TNFRSF12A; APOLD1
GO:0042493 response to drug	4	8.58E-09	8.58E-09	BCAR3; RAD54L; SLC1A3; SEMA3C
GO:0006355 regulation of transcription, DNA-dependent	9	2.88E-08	2.70E-08	AEBP1; SALL1; TAF4; LHX2; BCL3; CDX4; CEBPD; BAZ1A; HEYL
GO:0007165 signal transduction	9	1.05E-06	7.32E-07	BDKRB1; ANGPT1; CD33; FGF2; LALBA; ROS1; BCAR3; IL18R1; RIN3
GO:0030206 chondroitin sulfate biosynthesis	2	2.23E-06	1.43E-06	CHST3; CHST11
GO:0030154 cell differentiation	6	2.48E-06	1.53E-06	ANGPT1; CSRP2; MTL5; SEMA3A; TNFRSF12A; APOLD1
GO:0042742 defense response to bacterium	3	3.74E-06	2.22E-06	LALBA; BCL3; GNLY
GO:0007399 nervous system development	5	4.36E-06	2.49E-06	FGF2; FZD9; LHX2; SEMA3A; HEYL
GO:0042088 T-helper 1 type immune response	2	5.26E-06	2.63E-06	BCL3; EBI3
GO:0006955 immune response	5	6.04E-06	2.93E-06	IL1R2; IGSF6; SEMA3C; CCL27; LILRB1