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Original Article

Comprehensive analysis of core genes and key pathways in Parkinson's disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative disease that occurs mostly in middle-aged and older adults. Its main pathological feature is the progressive death of substantia nigra dopaminergic neurons. As the world's population ages, the number of PD patients is increasing. In this study, we explored the relationship between PD and the cell cycle. In this study, we collected two independent PD transcriptomic datasets, GSE54536 and GSE6613, from the Gene Expression Omnibus (GEO) database. Gene set enrichment analysis (GSEA) was used to identify dysregulated pathways in PD samples. Gene expression was verified by qPCR in PD patients. Nineteen pathways were negatively enriched in both the GSE54536 and GSE6613 datasets. Seven of these 19 pathways were cell cycle-related pathways, including the M/G1 transition, S phase, G1/S transition, mitotic G1-G1/S phases, CDT1 association with the CDC6 ORC origin complex, cell cycle checkpoints and synthesis of DNA. Next, we found that eight genes (PSMA4, PSMB1, PSMC5, PSMD11, MCM4, RPA1, POLE, and PSME4) were mainly enriched in the GSE54536 and GSE6613 datasets. In GSE54536, PSMA4, PSMB1, PSMC5, and PSME4 could significantly predict the occurrence of PD, whereas, in GSE6613, RPA1 and PSME4 could significantly predict the occurrence of PD. Only PSME4 showed significant results in both datasets. Finally, we assessed blood samples from PD patients and controls. Compared with the control samples, the PD samples had lower mRNA levels of PSME4. In summary,these findings can significantly enhance our understanding of the causes and potential molecular mechanisms of PD; the cell cycle signaling pathways and PSME4 may be therapeutic targets for PD.

Keywords: Parkinson's disease, bioinformatics, signaling pathway, cell cycle, PSME4

Introduction

Parkinson's disease (PD) is a neurodegenerative disease that occurs mostly in middle-aged and older adults [1, 2]. Its main pathological feature is the progressive death of substantia nigra dopaminergic neurons. The onset of PD is insidious, and its progression is slow. The first symptom is usually a tremor or awkward movement of one limb, which in turn affects the contralateral limb [3]. The main clinical manifestations of PD are resting tremors, bradykinesia, myotonia, and posture gait disorder [4]. In recent years, an increasing number of people have noticed that nonmotor symptoms such as depression, constipation, and sleep disorders are also common complaints of patients with PD, and their effects on the quality of life of patients even exceed the benefits of exercise. In people over the age of 65, the incidence of PD is approximately 2% [5]. As the world's population ages, the number of PD patients is increasing [6].

The main pathological features of patients with PD are the damage of dopaminergic neurons in the dense substantia nigra and the reduction in striatal dopamine content [7]; the latter in turn

causes a decrease in the dopaminergic innervation function of the nigrostriatal pathway. Alkaline nerve function is relatively enhanced, and patients have symptoms such as motor dysfunction. The incidence of PD is currently thought to be primarily related to age, environment, and genetic factors [8]. It is presently believed that the pathogenic factors of PD mainly affect the degradation of protein, mitochondrial function, and oxidative stress, which leads to the death of dopamine neurons. Although the mechanism of action of PD has been extensively studied and its pathogenic factors are relatively clear, its pathogenesis remains to be further elucidated [9]. Fortunately, there are many studies focused on PD's pathogenesis, neurorestorative mechanisms and therapeutic explorations [10-13]. The occurrence and development of PD areassociated with a variety of factors, such as genetic aberrations and cellular and environmental factors. Due to the high morbidity and mortality of PD, elucidating the etiology and underlying molecular mechanisms and discovering molecular biomarkers for early diagnosis, prevention, and personalized therapy are critically important and in high demand.

Gene chips can be used to quickly detect the expression information of all genes in the same sample at a specific time point. Gene chips are particularly suitable for screening differentially expressed genes [14]. RNA-Seq is the basis and starting point for gene function and structure research [10]. With the widespread use of gene chips, a large amount of core slice data has been generated, and most of the data are stored in public databases [15]. Integrating and reanalyzing these data can provide valuable clues for new research [16, 17]. Also, recent advances in genome-wide sequencing and bioinformatics technology have provided a new perspective for studying PD. This study was the first to use systematic bioinformatics analysis to report critical genes and signaling pathways in PD and to validate the results in blood samples from patients with PD.

Materials and methods

Transcriptomic data

Two independent PD transcriptomic datasets, GSE54536 and GSE6613, were collected from the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) database. GSE54536 used the GPL10558 platform and contained four PD blood samples and four control blood samples [18]. GSE6613 used the GPL96 platform and included 50 PD blood samples and 22 control blood samples [19, 20].

Gene set enrichment analysis

Gene set enrichment analysis (GSEA) was used to identify the dysregulated pathways in the PD samples [21]. Reactome gene sets were downloaded from the Molecular Signatures Database (MSigDB, http://software.broadinstitute.org/gsea/downloads.jsp). The samples were classified into two groups (PD and control). As a metric for ranking genes in GSEA, signal-to-noise ratios between the PD and control sample expression means were used, and all other parameters were set to default values.

qPCR

Blood samples were collected from 32 PD patients at the Department of Neurology, The 960th Hospital of Chinese PLA, China. Thirty healthy people were used as a control group. The mRNA expression of PSME4 was examined using qPCR. Blood RNA extraction was carried out using Trizol (Invitrogen, United States). RNA was converted into cDNA using the FastKing gDNA Dispelling RT SuperMixKit (KR118, TIANGEN, China). qPCR was performed using the Talent qPCR PreMix (SYBR Green) Kit (FP209, TIANGEN, China). PSMA4 was amplified using forward primer 5'-AGTGTGGCAGGCATAACTTCT-3' and reverse primer 5'-TCACAAGGTATTGGCTCCTGA-3'. PSMB1 was amplified using forward primer 5'-CCTCTACAGCCATGTATTCGGC-3' and reverse primer 5'-CGTTGAAAACGTAGGGCGAAAAT-3'. PSMC5 was amplified using forward primer 5'-AGAATGGTGAGGGAGCTGTT-3' and reverse primer 5'-GTTGAGCAACTCCAGCATCG-3'. PSME4 was amplified using forward primer 5'-ATTTGGAGTTACCCTGGAGACC-3' and reverse primer 5'-GCAGCTTTTCACGAGTGTTTTG-3'. The qPCR system used was the RocheLightCycler480. All experimental procedures were approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University.

Statistical analysis

Receiver operating characteristic (ROC) curves were generated with GraphPad Prism 8. An

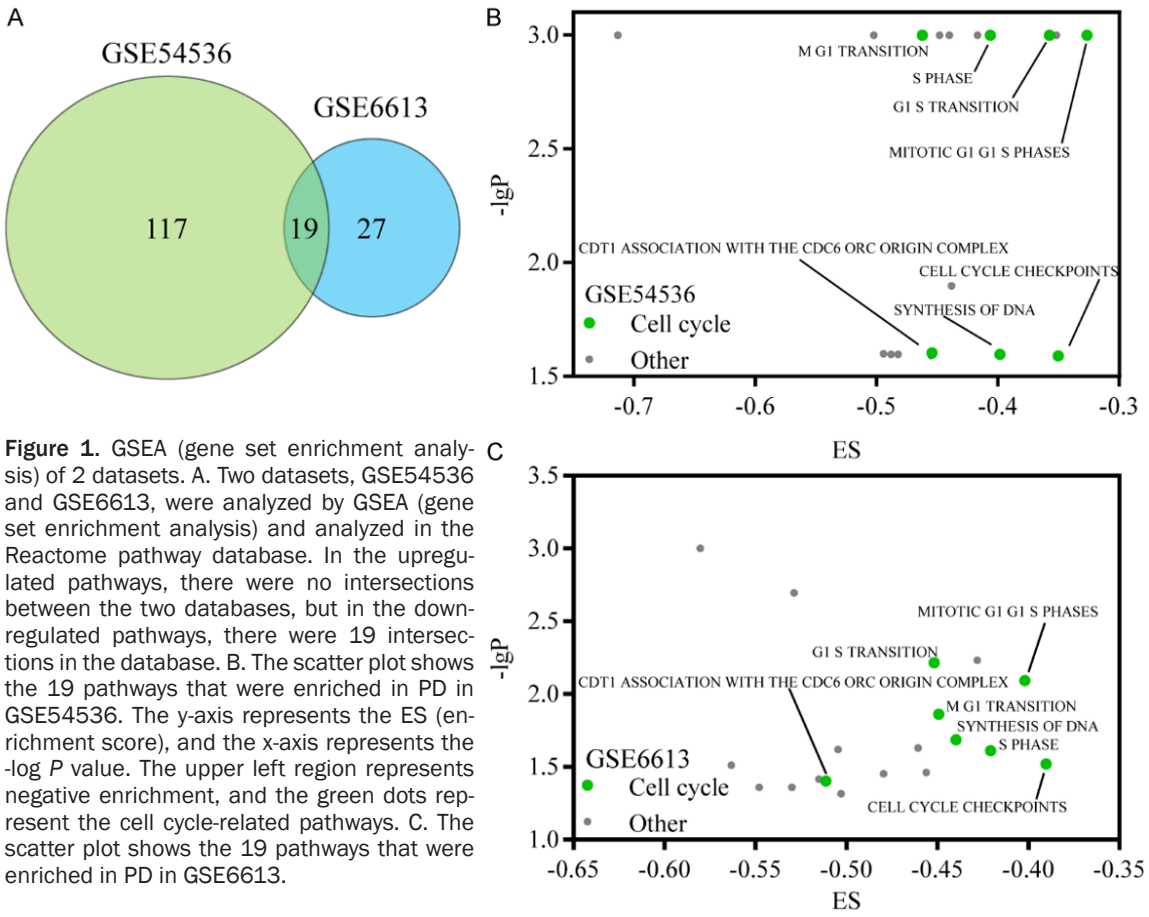


Figure 1. GSEA (gene set enrichment analysis) of 2 datasets. A. Two datasets, GSE54536 and GSE6613, were analyzed by GSEA (gene set enrichment analysis) and analyzed in the Reactome pathway database. In the upregulated pathways, there were no intersections between the two databases, but in the downregulated pathways, there were 19 intersections in the database. B. The scatter plot shows the 19 pathways that were enriched in PD in GSE54536. The y-axis represents the ES (enrichment score), and the x-axis represents the -log *P* value. The upper left region represents negative enrichment, and the green dots represent the cell cycle-related pathways. C. The scatter plot shows the 19 pathways that were enriched in PD in GSE6613.

area under the curve (AUC) of > 0.6 and $P < 0.05$ wasregarded as significant results. A Venn diagram was constructed with Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/index.html). Other plots were generated with GraphPad Prism 8.

Results

Cell cycle-related pathways were negatively enriched in PD samples

To identify dysregulated pathways in PD, GSEA was used to analyze Reactome gene sets in PD samples versus control samples. We found seven pathways positively enriched in GSE5-4536 PD samples and 22 pathways positively enriched in GSE6613 PD samples, but there was no intersection between the two datasets. A total of 136 pathways were positively enriched in GSE54536 PD samples, and 46 pathways were negatively enriched in GSE6613 PD samples. Interestingly, 19 pathways were negatively enriched in both the GSE54536 and GSE6613 datasets (**Figure 1A**). Seven of these 19 pathways were cell cycle-related pathways, including the M/G1 transition, S phase, G1/S transition, mitotic G1-G1/S phases, CDT1 association with the CDC6 ORC origin complex, cell cycle checkpoints and synthesis of DNA. These cell cycle-related pathways showed negative enrichment scores and significant *P* values ($P < 0.05$) in GSE54536 (**Figure 1B**) and GSE6613 (**Figure 1C**) PD samples. **Figures 2** and **3** demonstrate GSEA plots of these 7 cell cycle-related pathways in GSE54536 (**Figure 2**) and GSE6613 (**Figure 3**). These findings suggested that the activity of cell cycle-related pathways was decreased in PD progression.

Identification of core enrichment genes in the cell cycle-related pathways in PD

To investigate the mechanisms of how cell cycle-related pathways are negatively enriched in PD, we identified the core enrichment genes of these pathways. We statistically analyzed the core enrichment genes of each cell cycle-

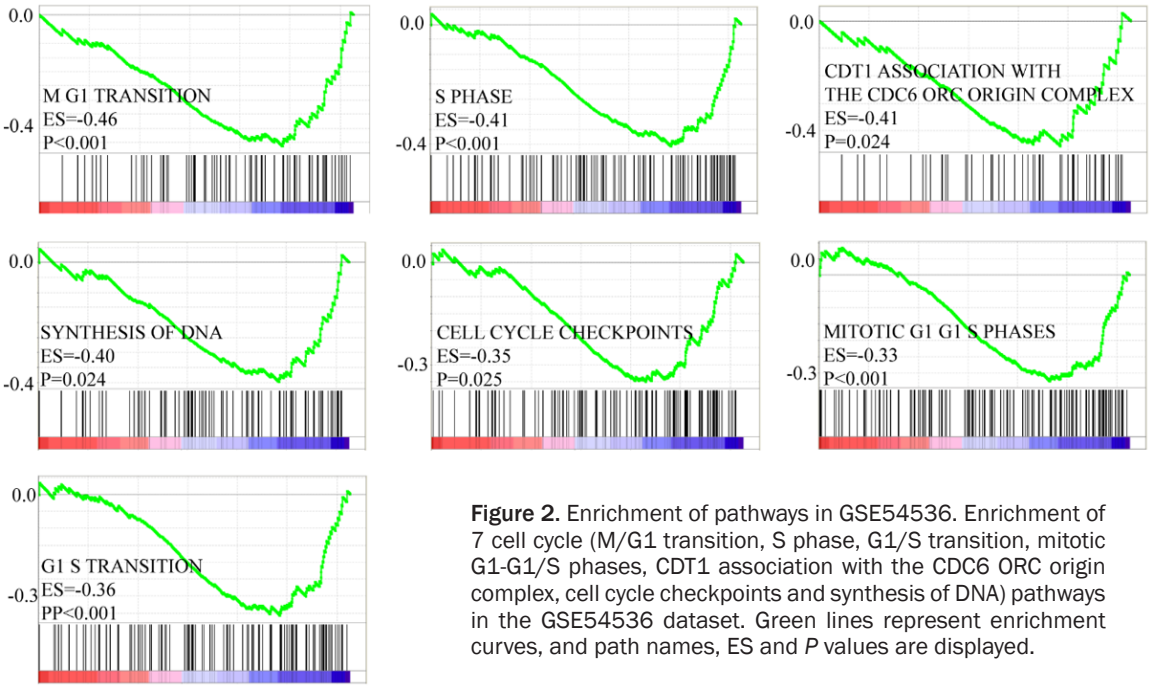


Figure 2. Enrichment of pathways in GSE54536. Enrichment of 7 cell cycle (M/G1 transition, S phase, G1/S transition, mitotic G1-G1/S phases, CDT1 association with the CDC6 ORC origin complex, cell cycle checkpoints and synthesis of DNA) pathways in the GSE54536 dataset. Green lines represent enrichment curves, and path names, ES and *P* values are displayed.

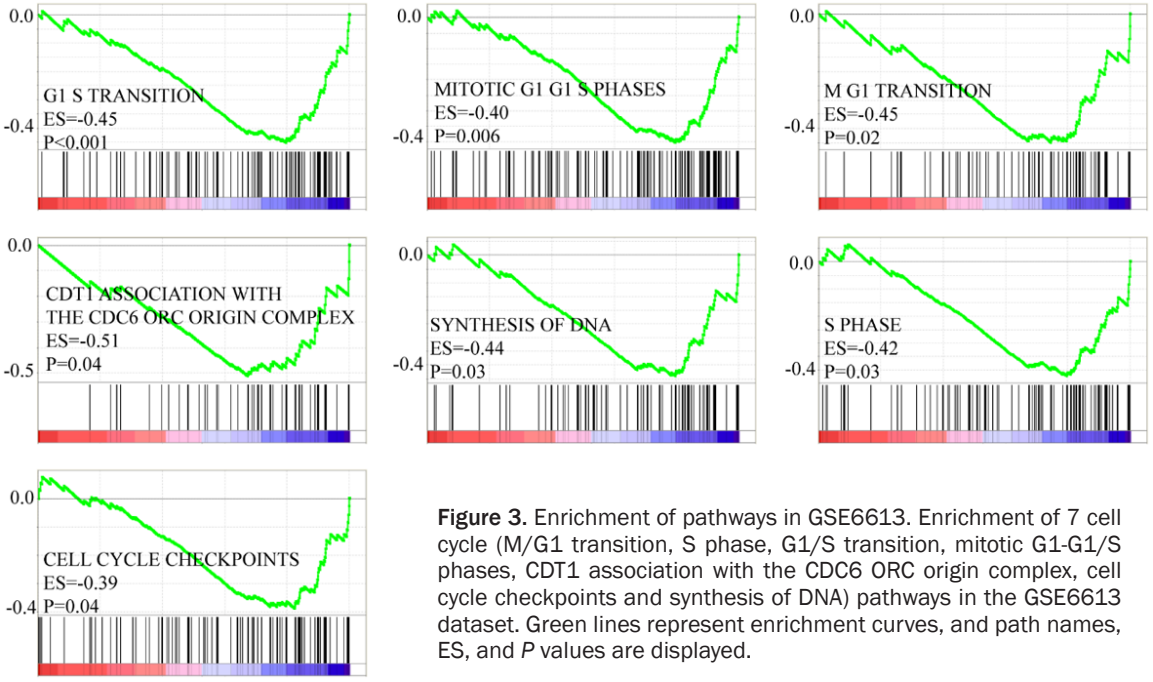


Figure 3. Enrichment of pathways in GSE6613. Enrichment of 7 cell cycle (M/G1 transition, S phase, G1/S transition, mitotic G1-G1/S phases, CDT1 association with the CDC6 ORC origin complex, cell cycle checkpoints and synthesis of DNA) pathways in the GSE6613 dataset. Green lines represent enrichment curves, and path names, ES, and *P* values are displayed.

related pathway according to the GSEA results in the GSE54536 (**Figure 4A**) and GSE6613 (**Figure 4B**) datasets. We found that proteasome subunit family genes, such as PSMA4, PSMB1, and PSMC5, occurred more frequently and had a number > 4. Interestingly, eight of these genes were mainly enriched in both the GSE54536 and GSE6613 datasets (**Figure 4C**): PSMA4, PSMB1, PSMC5, PSMD11, MCM4, RPA1, POLE, and PSME4.

PSME4 displayed considerable predictive significance in PD

ROC curves were calculated to evaluate the sensitivity and specificity of PSMA4, PSMB1,

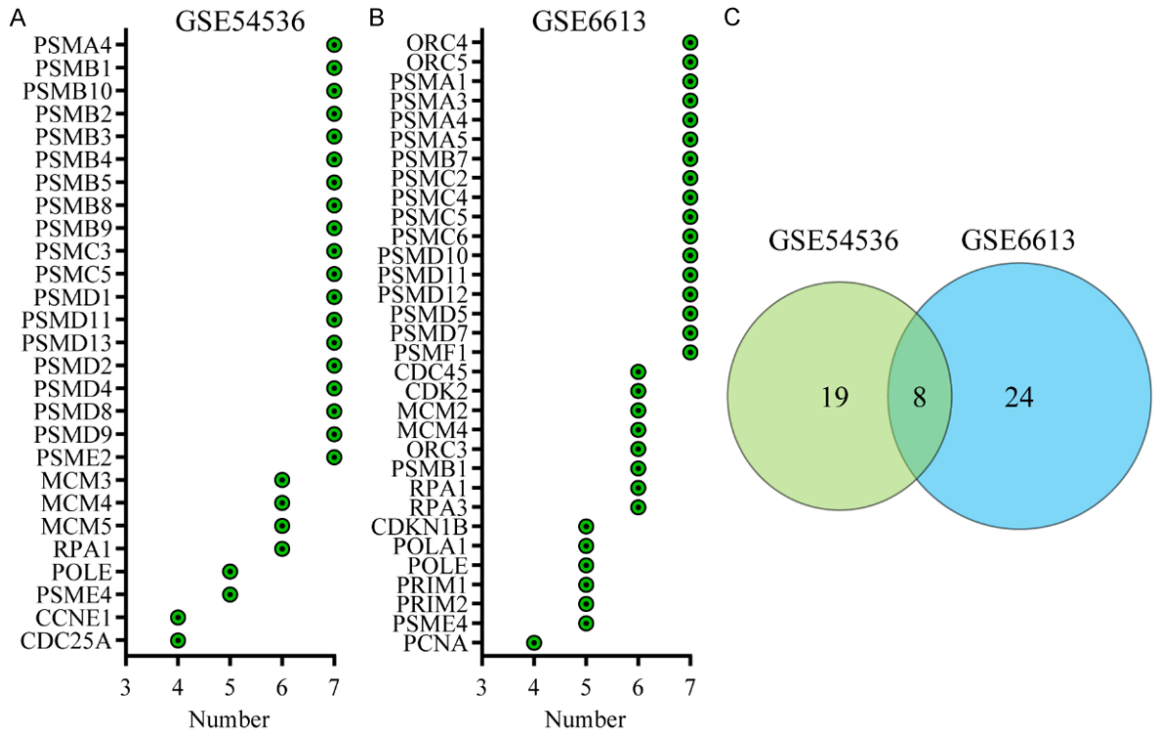


Figure 4. Screening for core enriched genes. A, B. The scatter plot shows the number of occurrences of core enriched genes in the seven cell cycle pathways of GSE54536 and GSE6613, respectively. The core enrichment genes are displayed here four or more times. C. The intersection of the results of the above two datasets shows eightcore enriched genes.

PSMC5, PSMD11, MCM4, RPA1, POLE, and PSME4 expression in predicting PD samples from normal tissue samples. In the GSE54536 dataset, PSMA4, PSMB1, PSMC5, and PSME4 displayed considerable predictive significance, with AUCs of 1.000, 0.9375, 1.000, and 1.000, respectively (**Figure 5A**). RPA1 and PSME4 showed considerable predictive significance in the GSE6613 dataset (**Figure 5B**). These results may be due to the difference in the PD samples. Notably, PSME4 could significantly predict PD in both the GSE54536 and GSE6613 datasets.

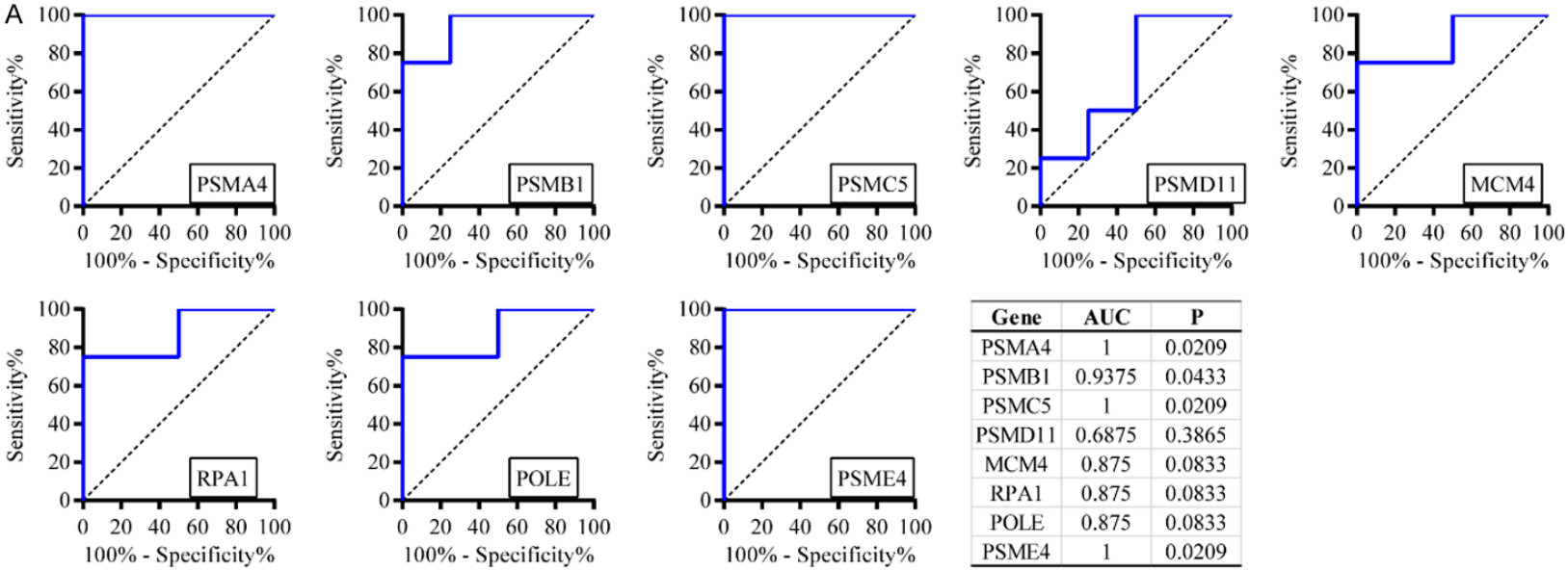
Determination of PSME4 expression in the blood of patients with PD by qPCR

We determined the PSMA4, PSMB1, PSMC5, and PSME4 mRNA expression in PD blood samples and paired control samples by qPCR (**Figure 6**). Compared with the control samples, the PD samples had lower PSME4 mRNA levels (P=0.002). There were no significant differences in PSMA4, PSMB1, and PSMC5 between the two groups (P=0.058, P=0.086, P=0.102).

Discussion

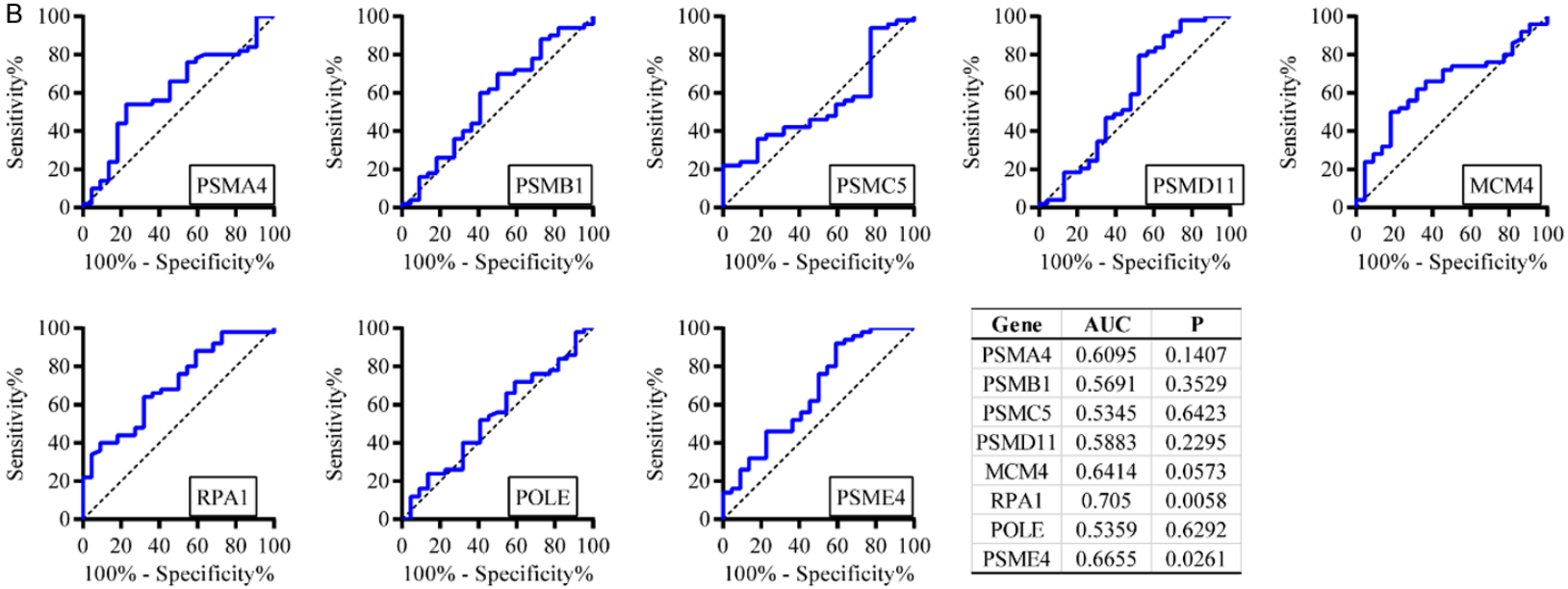
In recent years, research on the formation and development of PD has been increasing [4]. However, the occurrence and development of PD is a comprehensive disease process with multifactor, multistage, and multigene variations [22, 23]. It is difficult to understand the genetic factors in the development of PD fully. The role of these factors requires in-depth, large-scale research. Most current studies focus on the results of a single genetic event or a single cohort study [24-26]. This study integrated two cohort datasets and analyzed them using bioinformatics methods. First, we obtained data from 80 blood samples from two datasets (including 54 PD blood samples and 26 controls). The intersection of the two datasets revealed 19 intersecting signaling pathways that were downregulated, among which seven were related to the cell cycle. Enrichment analysis in these seven cell cycle pathways revealed eight core genes, including PSMA4. Finally, we verified the relationship between PSME4 expression and PD in the blood of PD patients.

A



Gene	AUC	P
PSMA4	1	0.0209
PSMB1	0.9375	0.0433
PSMC5	1	0.0209
PSMD11	0.6875	0.3865
MCM4	0.875	0.0833
RPA1	0.875	0.0833
POLE	0.875	0.0833
PSME4	1	0.0209

B



Gene	AUC	P
PSMA4	0.6095	0.1407
PSMB1	0.5691	0.3529
PSMC5	0.5345	0.6423
PSMD11	0.5883	0.2295
MCM4	0.6414	0.0573
RPA1	0.705	0.0058
POLE	0.5359	0.6292
PSME4	0.6655	0.0261

Figure 5. Core-enriched genes for ROC analysis. A. ROC analysis of the core enriched genes PSMA4, PSMB1, PSMC5, PSMD11, MCM4, RPA1, POLE, and PSME4 in the GSE54536 dataset. B. ROC analysis of the core enriched genes PSMA4, PSMB1, PSMC5, PSMD11, MCM4, RPA1, POLE, and PSME4 in the GSE6613 dataset.

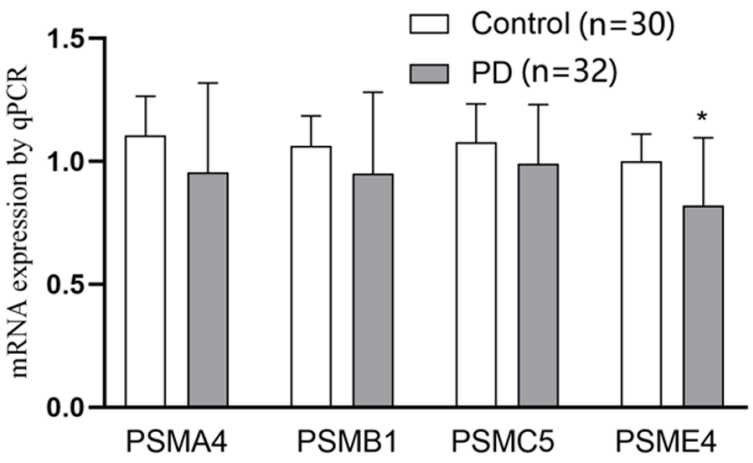


Figure 6. mRNA expression in PD. qPCR of PSMA4, PSMB1, PSMC5, and PSME4 in PD and control group patients' blood. A paired t-test was used to compare differences, $*P < 0.05$.

We found seven cell cycle pathways closely related to PD through enrichment analysis, including M/G1 transition, S phase, G1/S transition, mitotic G1-G1/S phases, CDT1 association with the CDC6 ORC origin complex, cell cycle checkpoints and synthesis of DNA. The cell cycle is divided into four stages: the G1 phase (pre-DNA synthesis phase), the S phase (DNA synthesis phase), the G2 phase (late DNA synthesis phase), and the M phase (mitotic phase) [27, 28]. To ensure the accurate transmission of genetic information, cells have gradually formed a complete set of cell cycle monitoring mechanisms in the long-term evolution process, called "cell cycle checkpoints" [29]. The cellular response triggered by some emergencies can affect the factors that drive the progression of the cell cycle, thereby arresting the cell cycle at the regulatory point to eliminate adverse effects. This process is called cell cycle arrest [30, 31]. The cell cycle "regulatory point", which is the criticaldetection stagefor the in vivo cellular stress response, is also known as the "checkpoint" of the cell cycle [32]. It is the rate-limiting step that controls the cell proliferation cycle, and its function is to determine the integrity of DNA synthesis before DNA replication and mitosis. Sexuality ensures the initiation, completion, and faithful sequence of individual cell cycle events. The response of cells to DNA damage is the activation of cell cycle regulatory points. At least two regulatory points monitor cellular DNA damage: the G1/S regulatory point (determining the transition from the G1 phase to the S phase) and the G2/M regulatory point (determining the transition from the G2 phase to the M phase), with the G1/S regulatory point being the most critical [31, 33, 34]. When the cell is damaged, the cell is blocked by the G1/S phase regulatory point in the G1 phase. After the genome is repaired, it returns to the S phase. If it cannot be repaired, the cell is triggered to enter programmed death.

The "neurodegeneration-cell cycle hypothesis" describes that cell cycle regulation abnormalities in brain neurons occur at a critical cell cycle regulatory point, the G1/S regulatory point [35, 36]. There are few reports on the role of the cell cycle in PD. Studies have found that abnormal cell cycle regulation of Alzheimer disease (AD) brain neurons occurs at the G1/S regulatory point [37-39]. Therefore, we speculate that in PD, after the damage of nerve cell DNA, the function of the G1/S regulatory point cannot be activated, losing its inherent function, so that damaged cells cannot be arrested in G1 for DNA repair. Instead, damaged cells enter the G2/M phase, but the cells cannot undergo normal division, so they eventually die. The results show that PSMA4, PSMB1, PSMC5, and PSME4 in the GSE54536 dataset can significantly predict the occurrence of PD, whereas in the GSE6613 dataset, RPA1 and PSME4 can significantly predict the occurrence of PD, and only PSME4 shows significant results in both datasets. However, this result may be related to the sample size and data variability.Proteasome activator subunit 4 (PSME4) is a broadly expressed nuclear protein that is expressed in various tissues, such as the testis, endometrium and peripheral blood [40-42]. It has been reported in the literature that PSME4 enhances proteasome-mediated cleavage after acidic residues in vitro and plays an essential role in

genomic stability [40]. Proteasome activator PA200 is required for normal spermatogenesis and is involved in the repair of DNA double-strand breaks (DSBs) [43]. This study reports for the first time that PSME4 is underexpressed in PD and is associated with the cell cycle. Further research will be conducted in animal models and in vitro cell experiments in future studies.

In summary, using multiple cohort analysis datasets and comprehensive bioinformatics analysis, combined with validation in clinical samples, we identified key candidate genes that are closely related to PD. These findings can significantly enhance our understanding of the causes and potential molecular mechanisms of PD, and these candidate genes and signaling pathways may be therapeutic targets for PD.

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Disclosure of conflict of interest

None.

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