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PI3K polymorphism in patients with sporadic Parkinson's disease

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Abstract

Parkinson's disease (PD) is a common irreversible neurodegenerative disease associated with cognitive impairment. To investigate the serum level of phosphatidylinositol-3-kinase (PI3K) and the distribution of the genotypes and alleles of 3 PI3K single-nucleotide polymorphisms (RS37,30,087, RS37,30,088, and RS37,30,089) in PD patients with different clinical characteristics. A total of 54 PD patients and 50 healthy individuals were recruited. The serum PI3K level was measured using the enzyme-linked immunosorbent assay. The severity of PD was assessed using the modified Hoehn-Yahr scale. The cognitive function of PD patients was evaluated using the Mini-Mental State Examination scale and the Montreal Cognitive Assessment. The distribution of the alleles and genotypes of PI3K single-nucleotide polymorphisms (SNPs) was calculated using the Hardy-Weinberg equilibrium. PD patients showed a significantly higher serum level of PI3K compared to healthy individuals. Increased serum PI3K level was observed in PD patients with more severe disease, longer disease duration, and impaired cognitive function. Additionally, no significant differences were observed in the distributions of the genotypes and alleles of 3 PI3K SNPs between PD patients with normal cognitive function and those with cognitive impairment. PD patients with different levels of disease severity, disease duration, and cognitive function had significantly different serum levels of PI3K. However, the PI3K SNPs in patients with normal cognitive function were not significantly different from those in patients with cognitive impairment. These findings contribute to a better understanding of the roles of PI3K and SNPs of the *PI3K* gene in PD.

Abbreviations: Akt = protein kinase B, GSK3β = glycojen synthase kinase-3, MMSE = mini-mental state examination, MOCA = montreal cognitive assessment, PD = Parkinson's disease, PI3K = phosphatidylinositol-3-kinase, SNP = sinle nucleotide polymorphism.

Keywords: gene polymorphism, genotype, Hoehn-Yahr scale, mini-mental state examination, montreal cognitive assessment, Parkinson's disease, PI3K

1. Introduction

Parkinson's disease (PD) is the second most common irreversible neurodegenerative disease in middle-aged and elderly people.[1] Non-motor symptoms are also commonly observed in patients with PD, such as hyposmia, sleep disturbance, cognitive impairment, pain, salivation, and constipation.[2] The majority of PD cases are sporadic and likely have a multifactorial etiology.[3] Epidemiological studies have shown that the average age-of-onset of PD is around 60 years, and the prognosis of most patients is poor.[4,5] Neurodegeneration, evidenced by both motor and non-motor symptoms, may occur 10 years before the diagnosis of PD, which significantly affects the quality of life of patients and places huge physical and emotional burdens on patients and their families.[6] Therefore, early diagnosis and timely treatment are of great significance for patients with PD.

The main pathological features of PD are the progressive loss of dopaminergic neurons and the accumulation of misfolded proteins in the substantia nigra pars compact.[7] Both genetic and environmental factors contribute to the dysregulation of dopaminergic neurons and eventually the progression of PD.[8] Genetic polymorphisms are associated with an increased risk of PD. Gorecki et al reported that single-nucleotide polymorphisms

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of the Hainan Provincial People's Hospital. All subjects voluntarily participated in this study and provided written informed consent.

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(SNPs) in genes responsible for intestinal homeostasis modulate the risk and age-of-onset in PD.[9] Taximaimaiti et al showed that SNPs of the gene encoding mitochondrial ubiquitin ligase 1 were significantly associated with the risk of PD in a Chinese cohort.[10] Inflammation-related gene polymorphisms are also associated with susceptibility to PD.[11] Therefore, investigations of SNPs may further elucidate the pathogenic mechanisms of PD and help identify people at a high risk of developing this disease.

Phosphatidylinositol-3-kinase (PI3K), a key component of the PI3K/protein kinase B (Akt) signaling pathway, is implicated in the differentiation, survival, and apoptosis of glial cells and neuronal cells.[12,13] Aberrant expression of PI3K has been shown to promote inflammatory cytokine infiltration, increase the deposition of β-amyloid proteins in neuronal cells, induce neuronal apoptosis, and cause degenerative changes in neurons.[14] The dysregulation of the PI3K/Akt signaling pathway has been observed in both PD patients and animal models, suggesting that PI3K plays a key role in the pathogenesis of PD.[15,16] Zheng et al showed that the genotypes and alleles of 3 PI3K SNPs (RS37,30,087, RS37,30,088, and RS37,30,089) were significantly different between patients with Alzheimer's and healthy subjects.[17] As Alzheimer's disease and Parkinson's disease are both neurodegenerative diseases and have common pathological manifestations (i.e., mutated aggregation-prone proteins), we speculated that *PI3K* gene polymorphisms might also be associated with the characteristics of PD.

In this study, we aimed to investigate the serum PI3K level and the distribution of the genotypes and alleles of 3 PI3K SNPs (RS37,30,087, RS37,30,088, and RS37,30,089) in PD patients with different clinical characteristics.

2. Materials and Methods

2.1. Participants

A total of 54 patients who were diagnosed with PD and admitted to our hospital from January 2019 to December 2019 were enrolled (the PD group). The diagnosis of PD was in accordance with the Chinese Parkinson's Disease Diagnostic Standards (version 2016).[18] A control group consisting of 50 healthy individuals who underwent physical examination at our hospital was also recruited. They were matched with the PD group in gender, age, education level, and ethnicity. The exclusion criteria for both groups were as follows: Diagnosed with immune-related diseases, malignant tumors, or other diseases with severe organ dysfunction; Diagnosed with Parkinson's superimposed syndrome or other secondary Parkinson's syndrome diseases; Had a history of mental illnesses, vascular dementia, Alzheimer's disease, frontotemporal dementia, and other types of cognitive dysfunction diseases. This study was approved by the Ethics Committee of the Hainan Provincial People's Hospital. All subjects voluntarily participated in this study and provided written informed consent.

2.2. Demographic and clinical data collection

The demographic information of all participants was collected, including gender, age, education level, and ethnicity. The medical records of PD patients, including the clinical manifestations of PD and the duration of the disease (<5 years, 5–10 years, or > 10 years), were also obtained.

2.3. Assessment of disease severity and cognitive function

The severity of PD was assessed using the modified Hoehn-Yahr (H-Y) scale (stage 0–1.5: mild; stage 2–3: moderate, stage: 4–5: severe).[19] The cognitive function of PD patients was evaluated using the Mini-Mental State Examination (MMSE; score 27–30: normal cognitive function; score < 27: cognitive dysfunction) and the montreal cognitive assessment (MoCA) (score ≥ 26: normal cognitive function; score < 26: cognitive dysfunction).[20,21]

2.4. Blood sample collection

A volume of 10 mL fasting peripheral blood was collected from each participant and transferred to an EDTA anticoagulation tube (5 mL) and a vacuum blood collection tube containing separating gel and coagulant (5 mL). The blood samples in the EDTA tube were stored at–20°C. The samples in the vacuum blood collection tube were kept at room temperature for 2 hours and then centrifuged at 2000 to 3000 rpm for 20 minutes at 4°C (Thermo Fisher Scientific, USA). The upper layer of the serum was collected and stored at–80°C.

2.5. Enzyme-linked immunosorbent assay (ELISA)

The level of PI3K in the serum of each participant was measured using the PI3K ELISA Kit (Shanghai Enzyme-linked Biotechnology Co., Ltd., China) following the manufacturer's instructions. The absorbance value was measured at 450 nm using a microplate reader (RT-6100, Rayto)

2.6. Genetic analysis

The genomic DNA was extracted from blood samples using the DNA Extraction Kit (TIANGEN Biotech [Beijing] Co., Ltd., China) according to the manufacturer's protocol. The quality of the DNA was examined using the 1-Drop quantometer (OD-1000, Nanjing Wuyi Technology Company, China). Polymerase chain reaction (PCR) was performed using the KAPA2G Fast Multiplex PCR Kit (KAPA Biosystems, Boston) and the LongGene A200 PCR System (LongGene, China). The reaction condition was as follows: initial denaturation at 96℃ for 5 minutes, then at 96℃ for 30 seconds, annealing at 58℃ for 30 seconds, extension at 72℃ for 30 seconds (10 cycles), and final extension at 72 ℃ for 5 minutes. The products were then electrophoresed on 3% agarose gel, followed by targeted sequencing using an ABI 3730xl DNA Analyzer (Applied Biosystems, California). The results were then analyzed by the Qubit 3.0 Fluorometer (Invitrogen, USA). The sequencing results were viewed using the CodonCodeAligner software and compared to the reference genome sequences. The primers of PI3K RS37,30,087, PI3K RS37,30,088, and PI3K RS37,30,089 were designed by Shanghai WeHealth Biotech Co., Ltd. (China) using the Primer3Plus software (http://www.primer3plus.com/cgibin/dev/primer3plus.cgi): rs3730087 forward: 5'-GCATGGAATTGTGAACTAATGC-3', RS37,30,087 reverse: 5'-CGCAATCCCAACTACATTAGAAC-3'; RS37,30,088 forward: 5'-GCATGGAATTGTGAACTAATGC-3'; RS37,30,088 reverse: 5'- CGCAATCCCAACTACATTAGAAC-3'; RS37,30,089 forward: 5'-CCTCCTAAACCACCAAAACCT-3'; RS37,30,089 reverse: 5'- TGGATGATATCCTAAAAATGGAAC-3'.

2.7. Statistical analysis

Data were analyzed using SPSS (version 23.0). Quantitative data were expressed as mean ± standard deviation and compared using the Student's *t*-test (between 2 groups) or the analysis of variance (among multiple groups). The least significant difference method was used for pairwise comparison. Qualitative data were expressed as percentage (%). The Chi-square test was used for comparisons between 2 groups. The distribution of the alleles and genotypes of PI3K SNPs was calculated using the Hardy-Weinberg equilibrium. A *P*-value of less than 0.05 indicated statistical significance. Graphs were plotted using GraphPad 7.0.

3. Results

3.1. Demographic and clinical characteristics of PD patients and healthy controls

A total of 54 patients with PD and 50 healthy individuals were recruited in this study. In the PD group, there were 34 men (63%) and 20 women (37%), with an average age of 61.24 ± 10.37 years (range: 37–84 years). In the control group, there were 33 men (66%) and 17 women (34%), with an average age of 60.24 ± 11.56 years (range: 35–88 years). There was no significant difference in age and gender between the 2 groups. The education level and ethnicity of the 2 groups were matched.

We compared the serum levels of PI3K between the PD patients and control group. The results showed that the PI3K level of PD patients was significantly higher than that of healthy controls (188.68 ± 20.94 vs 111.50 ± 21.88 mU/L, $P < .001$; Fig. 1).

3.2. The serum PI3K levels in PD patients according to gender, age, disease severity, and cognitive function

We further compared the serum PI3K level in PD patients with different demographic and clinical characteristics, including gender, age, disease severity, duration of disease, and cognitive function. There was no significant difference in the PI3K level between male and female patients (185.73 ± 20.88 vs 185.60 ± 21.58 mU/L, $P > .05$). Additionally, no significant difference was observed between patients younger than 60 years and those 60 years of age or older (184.84 ± 20.02 vs 186.19 ± 21.75 mU/L, $P > .05$)

PD patients were classified into "mild," "moderate," and "severe" subgroups according to the severity of the disease measured with the modified H-Y scale. The differences in the serum PI3K levels of patients with mild, moderate, and severe PD were statistically significant (177.75 ± 20.37, 190.15 ± 19.56, and 207.35 ± 7.04 mU/L, respectively; $P < .05$). A pairwise comparison using the least significant difference method showed that the PI3K level of patients with mild PD was significantly lower than that of the "moderate" subgroup ($P < .05$). The PI3K concentration of patients with moderate PD was also significantly lower than that of the "severe" subgroup ($P < .05$), indicating that the more severe the disease is, the higher the PI3K level will be in the serum (Fig. 2a).

We divided all PD patients into "< 5 years," "5 to 10 years," and "> 10 years" subgroups according to the duration of the disease. The serum PI3K levels of PD patients with different disease durations were significantly different ($P < .05$). The PI3K level of patients with a disease duration of < 5 years (176.39 ± 19.32 mU/L) was significantly lower than that of patients in the "5 to 10 years" (193.83 ± 16.76 mU/L) and "> 10 years" (193.54 ± 22.07 mU/L) subgroups ($P < .05$). However, no significant differences were found in the PI3K levels between patients with a disease duration of 5 to 10 years and > 10 years (Fig. 2b).

The P13K levels in PD patients with or without cognitive impairment were also compared. The cognitive function of PD patients was evaluated with the MMSE scale and the MoCA. Patients were then categorized into normal cognitive function and cognitive impairment subgroups. There were 23 patients diagnosed with cognitive impairment based on the MMSE scale, while 25 patients were diagnosed based on the MoCA. The PI3K level of patients with cognitive impairment measured with the MMSE scale was significantly higher than that of the subgroup with normal cognitive function (193.34 ± 20.99 vs 180.00 ± 19.33 mU/L, $P < .05$; Fig. 3a). Consistently, the PI3K concentration in patients with cognitive impairment evaluated with the MoCA was also significantly higher compared to the concentration in those with normal cognitive function (194.71 ± 20.41 vs 181.17 ± 19.97 mU/L, $P < .05$; Fig. 3b).

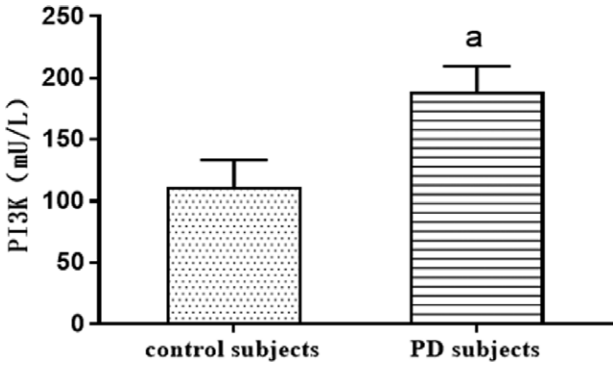

Figure 1. The serum PI3K level of PD patients and healthy controls. The level of PI3K (mU/L) in the serum samples of PD patients and healthy controls was measured with ELISA. [a] $P < .05$ compared to the control group. PD = Parkinson's disease, PI3K = phosphatidylinositol-3-kinase.

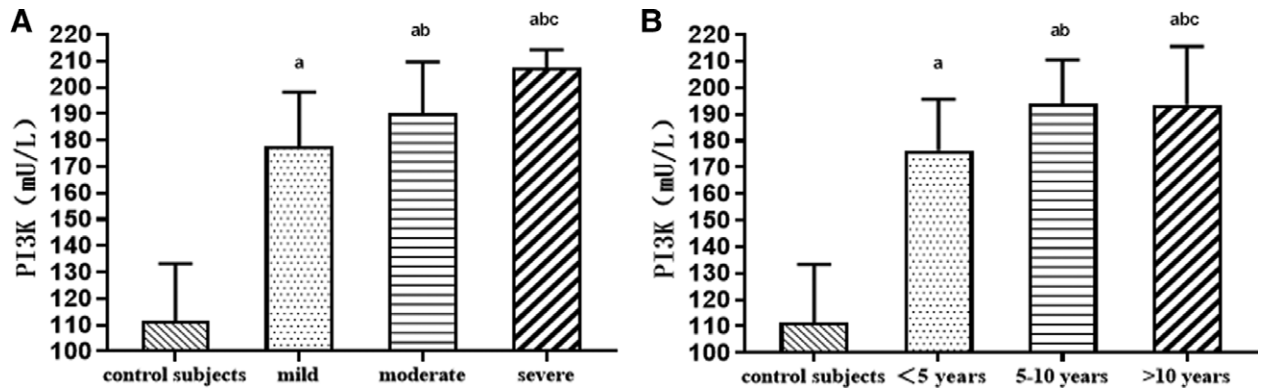

Figure 2. The serum PI3K level of PD patients with different levels of severity and duration of the disease. (a) PD patients were classified into "mild," "moderate," and "severe" subgroups according to the severity of the disease measured with the modified H-Y scale. The level of PI3K (mU/L) in their serum samples was measured with ELISA and compared. [a] $P < .05$ compared to the control group. [b] $P < .05$ compared to the "mild" group. [c] $P < .05$ compared to the "moderate" group. (b) PD patients were divided into "< 5 years," "5–10 years," and "> 10 years" subgroups according to the duration of the disease. The level of PI3K (mU/L) in their serum samples was measured with ELISA and compared. [a] $P < .05$ compared to the control group. [b] $P < .05$ compared to the "< 5 years" group. [c] $P < .05$ compared to the "5–10 years" group. PD = Parkinson's disease, PI3K = phosphatidylinositol-3-kinase.

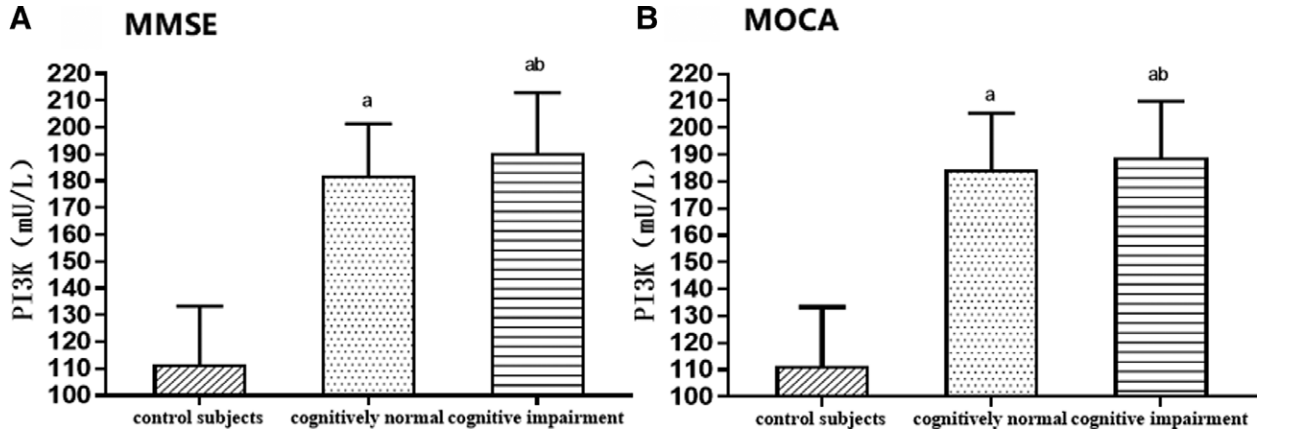

Figure 3. The serum PI3K level of PD patients with or without cognitive impairment. The cognitive function of PD patients was evaluated with (a) the MMSE scale and (b) the MoCA. Patients were then divided into the normal cognitive function and cognitive impairment subgroups. The P13K level (mU/L) in their serum samples was compared. [a] $P < .05$ compared to the control group. [b] $P < .05$ compared to the "cognitively normal" group. MMSE = mini-mental state examination, MOCA = montreal cognitive assessment, PD = Parkinson's disease, PI3K = phosphatidylinositol-3-kinase.

3.3. The serum PI3K levels of PD patients with different genotypes of PI3K polymorphism

To compare the serum PI3K levels of PD patients with different genotypes of PI3K SNPs, we first calculated the distribution of the genotypes of PI3K RS37,30,087, RS37,30,088, and RS37,30,089 SNPs in the PD and control groups. The distribution conformed with the Hardy-Weinberg equilibrium, suggesting that the collected samples were broadly representative of the actual population.

There were no significant differences in the serum PI3K levels of PD patients with different genotypes of PI3K RS37,30,087 (CC, CT, and TT), RS37,30,088 (AA, AG, and GG), or RS37,30,089 (GG, GA, and AA) SNPs. Additionally, no significant differences were found in the PI3K concentration of healthy individuals with different genotypes of PI3K SNPs (Table S1–3, Supplemental Digital Content , http://links.lww.com/MD/I168).

3.4. The distribution frequency of the genotypes and alleles of PI3K SNPs between PD patients and healthy controls

By comparing the distribution of the genotypes and alleles of 3 PI3K SNPs between PD patients and healthy controls, we found that there were no significant differences in either the genotype or allele distribution of PI3K SNPs between the 2 groups (Table S4–6, Supplemental Digital Content, http://links.lww.com/MD/I169).

3.5. The distribution frequency of the genotypes and alleles of PI3K SNPs in PD patients with normal or impaired cognitive function

Lastly, we investigated the distributions of the genotypes and alleles of 3 PI3K SNPs in PD patients with normal or impaired cognitive function. The results of both the MMSE scale (Table 1) and the MoCA (Table 2) showed that the distributions of the genotypes and alleles of PI3K RS37,30,087, RS37,30,088, and RS37,30,089 in PD patients with normal cognitive function and those with cognitive impairment were not significantly different.

4. Discussion

In the current study, we observed increased serum PI3K levels in PD patients with more severe disease, longer disease duration, and impaired cognitive function. However, no significant differences were observed in the serum PI3K levels of PD patients with different genotypes of PI3K RS37,30,087, RS37,30,088, or RS37,30,089. Further, there were no significant differences in the distributions of the genotypes and alleles of 3 PI3K SNPs between PD patients with normal cognitive function and those with cognitive impairment. These findings contribute to a better understanding of the roles of PI3K and SNPs of the *PI3K* gene in PD.

The common pathological feature of neurodegenerative diseases, including PD, is the abnormal accumulation of proteins in neurons, which eventually leads to neuronal death.[22] Previous studies have confirmed that the aggregated proteins are mainly eliminated by autophagy, a highly conserved cellular process that maintains the stability of the intracellular environment by degrading, recycling, and removing damaged or excessive proteins and organelles in cells.[23,24] PI3K has been identified as a negative regulator of autophagy and inhibits this process by binding to Akt after phosphorylation.[25] High PI3K expression has been shown to promote mitochondrial oxidation and neuronal autophagy, hinder the clearance of damaged organelles, induce the accumulation of misfolded proteins, and therefore increase neuronal apoptosis.[26] Recent studies have also reported that the activation of the PI3K/Akt signaling pathway aggravated neuro-inflammatory response in PD patients and promoted disease progression via inducing the release of inflammatory factors.[27] Recent evidence has shown that glycogen synthase kinase 3 beta (GSK3β), a downstream substrate of the PI3K/Akt pathway, activates glial cells, increases the expression of pro-inflammatory factors, and suppresses the production of anti-inflammatory factors, thereby contributing to the development of PD.[28] Consistent with the above findings, we discovered that the serum PI3K level of PD patients was significantly higher than that of healthy controls. Furthermore, in this cohort, patients with moderate or severe PD and a disease duration of ≥ 5 years had a significantly higher serum PI3K level than those with mild PD and a disease duration of < 5 years, which was in line with the data published by Armentero et al[29]

Cognitive impairment, ranging from mild cognitive impairment to dementia, is one of the most common and significant aspects of PD.[30] Clinical data showed that the progression of cognitive impairment was comparatively quick in PD patients.[31] Cognitive deficits such as predominant executive deficits and visuospatial disturbances seriously prolong the duration of hospitalization, affect the quality of life, and reduce the life expectancy of PD patients.[32] Tau protein, a microtubule-associated protein predominantly expressed in the neurons, has been shown to interact with α-synuclein, an abundant neuronal protein associated with cognitive function, during the progression

Table 1

The distributions of the genotypes and alleles of PI3K SNPs in PD patients with normal or impaired cognitive function (MMSE scale).

Genotype		Normal cognitive function	Cognitive impairment	χ^2	*P*-value
RS37,30,087	CC	7 (22.58%)	3 (13.04%)	3.190	.203
	CT	14 (45.16%)	16 (69.56%)		
	TT	10 (32.26%)	4 (17.39%)		
	C	28 (45.16%)	22 (47.83%)	0.006	.937
	T	34 (54.84%)	24 (52.17%)		
RS37,30,088	AA	16 (51.61%)	13 (56.62%)	0.217	.897
	AG	14 (45.16%)	9 (39.13%)		
	GG	1 (3.22%)	1 (4.35%)		
	A	46 (74.19%)	35 (76.09%)	0	1
	G	16 (25.81%)	11 (23.91%)		
RS37,30,089	GG	1 (70.97%)	0 (0%)	0.927	.629
	GA	8 (25.81%)	5 (21.74%)		
	AA	22 (3.23%)	18 (78.26%)		
	G	10 (16.13%)	5 (10.87%)	0.250	.617
	A	52 (83.87%)	41 (89.13%)		

Table 2

The distributions of the genotypes and alleles of PI3K SNPs in PD patients with normal or impaired cognitive function (MoCA).

Genotype		Normal cognitive function	Cognitive impairment	χ^2	*P*-value
RS37,30,087	CC	5 (23.81%)	5 (16.67%)	1.002	.606
	CT	10 (47.62%)	20 (66.67%)		
	TT	6 (28.57%)	8 (26.67%)		
	C	20 (47.62%)	30 (45.45%)	0.000	.983
	T	22 (52.38%)	36 (54.54%)		
RS37,30,088	AA	12 (57.14%)	17 (56.67%)	0.343	.842
	AG	8 (38.10%)	15 (50.00%)		
	GG	1 (4.76%)	1 (3.33%)		
	A	32 (76.19%)	49 (74.24%)	0	1
	G	10 (23.81%)	17 (25.76%)		
RS37,30,089	GG	16 (76.19%)	24 (80.00%)	0.658	.720
	GA	5 (23.81%)	8 (26.67%)		
	AA	0	1 (3.33%)		
	G	37 (88.10%)	56 (84.85%)	0.036	.849
	A	5 (11.90%)	10 (15.15%)		

MOCA = montreal cognitive assessment, PD = Parkinson's disease, PI3K = phosphatidylinositol-3-kinase, SNP = sinle nucleotide polymorphism.

MMSE = mini-mental state examination, PD = Parkinson's disease, PI3K = phosphatidylinositol-3-kinase, SNP = sinle nucleotide polymorphism.

of PD.[33,34] Shekhar et al found that the level of Tau protein in PD patients with cognitive impairment was significantly higher compared with the level in healthy controls, indicating that Tau protein is related to the cognitive function of PD patients.[35] Wang et al showed that excessive activation of PI3K/Akt/GSK3β signaling induced the accumulation of Tau protein and β-amyloid, leading to neuronal degeneration.[36] The administration of GSK3β inhibitors significantly suppressed the phosphorylation of Tau protein and improved cognitive function in rats.[37] Taken together, these studies implied that aberrant activation of the PI3K/AKT pathway is related to the occurrence of cognitive impairment in PD patients. In the current study, both the MMSE scale and the MoCA were used to assess the cognitive function of PD patients. Analysis of the serum PI3K level revealed that the PI3K concentration in patients with cognitive impairment was significantly higher than the level in those with normal cognitive function.

SNPs of the *PI3K* gene have been widely reported as a risk factor for human cancers, such as breast cancer, prostate cancer, and bladder cancer.[38–40] A recent study by Zheng et al investigated the distribution of the genotypes and alleles of 3 PI3K SNPs (RS37,30,087, RS37,30,088, and RS37,30,089) in 231 patients with Alzheimer's disease and 231 healthy individuals and observed significant differences in the genotypes and alleles of PI3K RS37,30,087 between the 2 groups, suggesting that PI3K RS37,30,087 polymorphism might be related to the development of Alzheimer's disease.[17] They In our study, however, the distributions of the genotypes and alleles of the PI3K RS37,30,087, RS37,30,088, and RS37,30,089 were not statistically different between the PD and control groups. There were also no significant differences in the serum PI3K levels of PD patients with different genotypes of PI3K RS37,30,087, RS37,30,088, or RS37,30,089. Lastly, the distributions of the genotypes and alleles of 3 PI3K SNPs were not significantly different between the normal cognitive function and cognitive impairment subgroups.

There are some limitations to the current study. Firstly, all participants were recruited from 1 hospital and the sample size was relatively small, which may result in insufficient statistical power. Future studies with a larger number of participants and a multi-center design are needed to validate the current findings. Secondly, although 2 common assessment tools (i.e., MoCa and MMSE) were used to evaluate the cognitive function of patients with PD, the lack of assessment of each cognitive domain

remains a limitation to this study. Thirdly, correlation analysis was not performed in this study. Whether PI3K polymorphisms are correlated with the incidence and clinical phenotypes of PD warrants further investigation.

5. Conclusion

In conclusion, our study showed that the serum PI3K level significantly varied in PD patients with different levels of disease severity, disease duration, and cognitive function. However, the PI3K levels of patients with different genotypes of PI3K RS37,30,087, RS37,30,088, or RS37,30,089 were not significantly different. Additionally, the distribution of the genotypes and alleles of 3 PI3K SNPs were not significantly different between patients with normal or impaired cognitive function. These data provide preliminary evidence of the potential roles of PI3K and SNPs of the *PI3K* gene in PD.

Author contributions

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Writing – review & editing: Benchi Cai, Xiuying Zhao, Tao Chen.

References

[1] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386:896–912.
[2] Wu SL, Liscic RM, Kim SY, et al. Nonmotor symptoms of Parkinson's disease. Parkinsons Dis. 2017;2017:4382518.
[3] Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med. 2020;36:1–12.
[4] Lin WC, Tsai NW, Huang YC, et al. Peripheral leukocyte apoptosis in patients with Parkinsonism: correlation with clinical characteristics and neuroimaging findings. Biomed Res Int. 2014;2014:635923.
[5] Liu Y, Zeng X, Hui Y, et al. Activation of α7 nicotinic acetylcholine receptors protects astrocytes against oxidative stress-induced apoptosis: implications for Parkinson's disease. Neuropharmacology. 2015;91:87–96.
[6] Katsuno M, Sahashi K, Iguchi Y, et al. Preclinical progression of neurodegenerative diseases. Nagoya J Med Sci. 2018;80:289–98.
[7] Maiti P, Manna J, Dunbar GL. Current understanding of the molecular mechanisms in Parkinson's disease: targets for potential treatments. Transl Neurodegener. 2017;6:28.
[8] Ghavami S, Shojaei S, Yeganeh B, et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. Prog Neurobiol. 2014;112:24–49.
[9] Gorecki AM, Bakeberg MC, Theunissen F, et al. Single nucleotide polymorphisms associated with gut homeostasis influence risk and age-at-onset of Parkinson's disease. Front Aging Neurosci. 2020;12:603849.
[10] Taximaimaiti R, Li H. MUL1 gene polymorphisms and Parkinson's disease risk. Acta Neurol Scand. 2019;139:483–7.
[11] Ulhaq ZS, Garcia CP. Inflammation-related gene polymorphisms associated with Parkinson's disease: an updated meta-analysis. Egypt J Med Hum Genet. 2020;21:14.
[12] Li X, Zhang J, Zhu X, et al. Progesterone reduces inflammation and apoptosis in neonatal rats with hypoxic ischemic brain damage through the PI3K/Akt pathway. Int J Clin Exp Med. 2015;8:8197–203.
[13] Dou MY, Wu H, Zhu HJ, et al. Remifentanil preconditioning protects rat cardiomyocytes against hypoxia-reoxygenation injury via δ-opioid receptor mediated activation of PI3K/Akt and ERK pathways. Eur J Pharmacol. 2016;789:395–401.
[14] Cianciulli A, Porro C. Microglia mediated neuroinflammation: focus on PI3K modulation. Biomolecules. 2020;10:137.
[15] Timmons S, Coakley MF, Moloney AM, et al. Akt signal transduction dysfunction in Parkinson's disease. Neurosci Lett. 2009;467:30–5.
[16] Chung JY, Lee SJ, Lee SH, et al. Direct interaction of α-synuclein and AKT regulates IGF-1 signaling: implication of Parkinson disease. Neurosignals 2011;19:86–96.
[17] Zheng N, Zhao H, Tian H, et al. Relationship between insulin signal transduction pathway-associated gene polymorphism and Alzheimer disease. J New Med. 2017;48:550–4.
[18] Liu J. Diagnostic criteria of Parkinson's disease in China (2016 edition). Chin J Neurol. 2016;04:268–71.
[19] Hoehn-yahr (modified) grading scale for Parkinson's disease. Chinese J Microinvasive Neurosurg. 2008;2:51–2.
[20] Hu G, Zhou X, Qin P. Study on the evaluation of memory impairment in elderly patients with AD and PD using MMSE scale. Seeking Medical Treatment (2nd half of the month). 2013;08:32–3.
[21] Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
[22] Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. Cold Spring Harb Perspect Biol. 2017;9:a028035.
[23] Williams A, Sarkar S, Cuddon P, et al. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. Nat Chem Biol. 2008;4:295–305.
[24] Heras-Sandoval D, Pérez-Rojas JM, Hernández-Damián J, et al. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. Cell Signal. 2014;26:2694–701.
[25] Oh I, Cho H, Lee Y, et al. Blockage of autophagy rescues the dual PI3K/mTOR inhibitor BEZ235-induced growth inhibition of colorectal cancer cells. Dev Reprod. 2016;20:1–10.
[26] Khwanraj K, Madlah S, Grataitong K, et al. Comparative mRNA expression of eEF1A isoforms and a PI3K/Akt/mTOR pathway in a cellular model of Parkinson's disease. Parkinsons Dis. 2016;2016:8716016.
[27] Wilhelmsson U, Bushong EA, Price DL, et al. Redefining the concept of reactive astrocytes as cells that remain within their unique domains upon reaction to injury. Proc Natl Acad Sci USA. 2006;103:17513–8.
[28] Yang L, Wang H, Liu L, et al. The role of insulin/IGF-1/PI3K/Akt/GSK3β signaling in Parkinson's disease dementia. Front Neurosci. 2018;12:73.
[29] Armentero MT, Sinforiani E, Ghezzi C, et al. Peripheral expression of key regulatory kinases in Alzheimer's disease and Parkinson's disease. Neurobiol Aging. 2011;32:2142–51.
[30] Yang Y, Tang BS, Guo JF. Parkinson's disease and cognitive impairment. Parkinsons Dis. 2016;2016:6734678.
[31] Hershey LA, Peavy GM. Cognitive decline in Parkinson disease: how steep and crowded is the slope?. Neurology. 2015;85:1268–9.
[32] Fang C, Lv L, Mao S, et al. Cognition deficits in Parkinson's disease: mechanisms and treatment. Parkinsons Dis. 2020;2020:2076942.
[33] Moussaud S, Jones DR, Moussaud-Lamodière EL, et al. Alpha-synuclein and tau: teammates in neurodegeneration?. Mol Neurodegener. 2014;9:43.
[34] Sengupta U, Guerrero-Muñoz MJ, Castillo-Carranza DL, et al. Pathological interface between oligomeric alpha-synuclein and tau in synucleinopathies. Biol Psychiatry. 2015;78:672–83.
[35] Shekhar S, Kumar R, Rai N, et al. Estimation of Tau and phosphorylated Tau181 in Serum of Alzheimer's disease and mild cognitive impairment patients. PLoS One. 2016;11:e0159099.
[36] Wang Y, Liu W, He X, et al. Parkinson's disease-associated DJ-1 mutations increase abnormal phosphorylation of tau protein through Akt/GSK-3β pathways. J Mol Neurosci. 2013;51:911–8.
[37] Yin J, Liu YH, Xu YF, et al. Melatonin arrests peroxynitrite-induced tau hyperphosphorylation and the overactivation of protein kinases in rat brain. J Pineal Res. 2006;41:124–9.
[38] Le Rhun E, Bertrand N, Dumont A, et al. Identification of single nucleotide polymorphisms of the PI3K-AKT-mTOR pathway as a risk factor of central nervous system metastasis in metastatic breast cancer. Eur J Cancer. 2017;87:189–98.
[39] Xu W, Ni Z, Zhang M, et al. The role of polymorphisms in genes of PI3K/Akt signaling pathway on prostate. J Cancer. 2019;10:1023–31.
[40] Bizhani F, Hashemi M, Danesh H, et al. Association between single nucleotide polymorphisms in the PI3K/AKT/mTOR pathway and bladder cancer risk in a sample of Iranian population. Excli J. 2018;17:3–13.