Original Article

Association of synuclein alpha (*SNCA*) gene polymorphisms with spontaneous brain activity in patients with Parkinson's disease

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Background: The synuclein alpha (*SNCA*) gene responsible for encoding alpha-synuclein, is believed to play a crucial role in the pathogenesis of Parkinson's disease (PD). However, the specific impact of *SNCA* gene single-nucleotide polymorphisms (SNPs) on brain function in PD remains unclear. Therefore, this cross-sectional retrospective study, particularly through use of imaging analysis, aimed to characterize the relationship between *SNCA* gene SNPs and spontaneous brain activity in PD in order to enhance our understanding of the mechanisms underlying PD pathogenesis.

Methods: A total of 63 patients with PD and 73 sex- and age-matched healthy control (HC) participants were recruited from outpatient and inpatient clinics at Fujian Medical University Union Hospital from August 2017 to November 2019, and all underwent a resting-state functional magnetic resonance imaging (rs-fMRI) scanning. All participants were also examined to determine the correlation of different genotypes with regional brain activity measured by rs-fMRI using amplitude of low-frequency fluctuation (ALFF) analysis. Multivariate regression analysis was used to calculate the correlation between the brain function data and clinical features. All rs-fMRI data were analyzed with the SPM12 software and adjusted according to the false discovery rate (FDR) at the cluster level.

Results: This study included 63 patients with PD and 73 sex- and age-matched healthy participants were included in the study. The spontaneous brain activity in the right superior cerebellum (Cerebelum_Crus1_R), vermis (Vermis_7), and left supplementary motor area (Supp_Motor_Area_L) of patients in the PD group was weak compared to that in the HC group. The z-score ALFF of left central posterior gyrus was positively correlated with the Mini-Mental State Examination score ($r=0.542$; $P<0.001$) in the PD group. For rs11931074, the main genotypic effects were found in the left inferior cerebellum (Cerebellum_9_L) and right anterior cingulate and paracingulate gyri (Cingulum_Ant_R); for rs356219 and rs356165, the main genotypic effects were found in the left caudate nucleus (Caudate_L). An interaction effect of disease with genotype was found in the right inferior parietal gyrus (Parietal_Inf_R) only for rs356219.

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Conclusions: Our study found a correlation of the *SNCA* SNPs rs11931074, rs356219, and rs356165 with brain functional alterations in patients with PD. Furthermore, an interaction effect was found in the right inferior parietal gyrus only for rs356219. This study may contribute to furthering the understanding of the influence of *SNCA* gene SNPs on brain function in patients with PD.

Keywords: Parkinson's disease (PD); resting-state functional magnetic resonance imaging (rs-fMRI); synuclein alpha gene (*SNCA* gene); single-nucleotide polymorphisms (SNPs)

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by loss of dopaminergic neuron in the substantia nigra pars compacta (SNpc) and the formation of Lewy bodies (LBs) and Lewy neurites (1-3). The synuclein alpha (*SNCA*) gene is an alpha synuclein (α-synuclein) gene and is located at 4q21-q23. The α-synuclein encoded by the *SNCA* gene is the main component of LBs, which is the characteristic pathological change of PD (4). Mutations in the *SNCA* gene lead to the misfolding and aggregation of α-synuclein, resulting in neurotoxicity and contributing to the pathogenesis and development of PD (4,5).

In the past few decades, numerous studies have focused on the relationship between single-nucleotide polymorphisms (SNPs) in the *SNCA* gene and PD susceptibility (6-8). Furthermore, it has been suggested that this association may be caused by the cis-regulation of *SNCA* gene expression. A meta-analysis that included 36 studies from different countries and regions showed that eight SNP sites of *SNCA* are related to the risk of PD. Seven SNPs, namely rs2736990, rs356220, rs356165, rs181489, rs356219, rs11931074, and rs2737029, are associated with PD risk, while rs356186 is associated with a low risk of PD. In Southeast Asian populations, rs2736990 and rs11931074 are associated with an increased risk of PD, while in European populations, rs356219, rs181489, rs2737029, rs356165, and rs11931074 are associated with an increased risk of PD, while rs356186 is linked with a lower risk of PD (6). Another study of 1,061 Chinese Han patients with PD showed that seven *SNCA* SNPs, including rs356165 and rs11931074, are related to PD (9). Other relevant studies have shown that in the Chinese population, the T allele of rs11931074 can increase the risk of developing PD (10) and is related to early-onset PD (11), while the G allele plays a protective role against development of PD (10). In a different study, *SNCA* rs11931074 was associated with α-synuclein deposition in the gastric and colonic mucosa of patients with PD (12). Another study suggested that the *SNCA* rs356219 variant may confer an increased susceptibility risk to PD in the Chinese Han population (13). In summary, SNPs rs11931074, rs356219, and rs356165 have been reported to be associated with a susceptibility risk to PD in the Chinese Han population.

Since the effects of PD on brain networks may occur early in the disease process, the findings of functional imaging studies have implications for the diagnosis of PD (14,15). As a noninvasive, repeatable imaging technique, resting-state functional magnetic resonance imaging (rs-fMRI) (16,17) is becoming an important method for the diagnosis of human functional brain disorders (18). rs-fMRI measures brain activity by detecting blood oxygen level-dependent (BOLD) signal changes. The data processing method used in this study was the amplitude of low frequency fluctuation (ALFF) analysis method. For measuring the BOLD signal of the spontaneous brain activity in the resting state, the ALFF approach was first proposed by Zang *et al.* (19) and then improved upon to the fractional ALFF (fALFF) approach by Zuo *et al.* (20). ALFF records the BOLD signal, which changes across time with the spontaneous activity of brain neurons in the resting state and uses low frequency signals to reflect the strength of the spontaneous activity of brain neurons. Fractional amplitude of low-frequency fluctuation (fALFF) is the ratio of the amplitude of the low frequency band (0.01–0.08 Hz) to the amplitude of the entire frequency band, which can effectively reduce signals from nonspecific brain areas such as ventricles and large blood vessels and improve sensitivity and specificity (20). ALFF and fALFF need to be normalized before statistical analysis through mean

standardization (dividing by the mean of the whole brain signal) and Z transformation (the deviation from the mean divided by the standard deviation of the whole brain signal), with mean ALFF (mALFF), z-score ALFF (zALFF), mean fALFF (mfALFF), and z-score fALFF (zfALFF) each being obtained to improve the normality of the data. The mALFF offers a more precise measurement of low-frequency amplitude signals by modifying the original ALFF values, while zALFF standardizes these values into z-scores for more standardized and fair comparisons across individuals. The combined use of these methods is intended to provide a more comprehensive and accurate framework for analyzing and interpreting the differences in resting-state brain activity. The rs-fMRI technique measures spontaneous brain activity to reflect brain function. Thus far, several rs-fMRI studies in patients with PD have found that changes in ALFF values in certain brain areas can distinguish patients with PD from normal control participants (21,22).

Neuroimaging genetics research has helped elucidate the relationship between genetic variations and the structure and function of the human brain (23). Several studies have reported that the Parkin RBR E3 Ubiquitin Protein Ligase (*PRKN*), Parkinsonism-associated deglycase (*PARK7*), HtrA2 serine peptidase 2 (*HTRA2*), and *SNCA* genes are significantly correlated with the imaging phenotype of PD (24,25). In contrast, fewer studies have been conducted for examining the relationship between genetic polymorphisms and brain function. Some studies have suggested that the *SNCA* SNPs rs11931074 (26) and rs894278 (27) may be related to changes in brain activity and motor symptoms in patients with PD; moreover, in Chinese patients with PD, *SNCA* rs11931074 polymorphisms may modulate altered brain function and may be associated with motor symptoms (26). Additionally, changes in brain function may precede the development of clinical symptoms. Based on these findings, we reasoned that the rs11931074, rs356219, and rs356165 polymorphisms can influence PD clinical symptoms through the abnormal expression of *SNCA* and the deposition of *SNCA* and thus hypothesized that SNPs could affect brain function in PD.

To test this hypothesis, this study aimed to characterize the relationship between resting-state brain function and the *SNCA* rs11931074, rs356219, and rs356165 genotypes in patients with PD and matched control participants. In addition, the relationship between resting-state functional brain activity and cognitive function, disease course, and severity in patients with PD was examined. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-14/rc).

Methods

Participants

In this cross-sectional study, data were retrospectively collected from 63 patients with PD and 73 sex- and age-matched healthy control (HC) participants who attended the outpatient and inpatient clinics at Fujian Medical University Union Hospital from August 2017 to November 2019. The patients with PD enrolled were clinically diagnosed according to the Movement Disorder Society (MDS) clinical diagnostic criteria for PD (2015 edition) by two neurology specialists (28). All participants were clinically evaluated by two senior attending physicians who had more than 20 years of relevant experience in neurology department. The exclusion criteria for this study were as follows: (I) secondary parkinsonism and Parkinson-plus syndrome; (II) severe dementia, psychiatric diseases, neurodevelopmental diseases, anxiety, or depression; (III) incomplete data, including for MRI images and clinical evaluations; (IV) brain tumors, hydrocephalus, or other brain diseases found in brain MRI images; (V) severe complications of diabetes and hypertension; and (VI) poor MRI image quality. MRI scans and clinical examinations of patients with PD were performed at least 12 h after withdrawal of their pharmacological treatment. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Ethics Committee of Fujian Medical University Union Hospital (No. 2019K013). The requirement for individual consent in this retrospective analysis was waived.

Clinical assessments

The general and clinical data of participants, including name, age, education, and medication, were collected from both groups. The Unified Parkinson's Disease Rating Scale Part III (UPDR-III) (29), Hoehn-Yahr (H-Y) stage (30), and the Mini-Mental State Examination (MMSE) score (31) were used to assess the severity of motor symptoms and cognitive impairment in patients with PD. We implemented a standardized training session for all evaluators before the study began and blinded the evaluators to the study hypotheses and group assignments to ensure consistency in the measurement process.

SNCA genotyping

Elbow venous blood (5 mL) was collected from all participants, DNA was extracted from blood samples using the TIANamp Blood DNA Kit (TianGen Biotech Co., Ltd., Beijing, China), and SNPs were detected via polymerase chain reaction (PCR) amplification and Sanger DNA sequencing. The specific primers used in the above PCR amplification are listed in Table S1 and were designed for *SNCA* rs356219, rs11931074, and rs356165. The PCR amplification reaction procedure is detailed in Table S2. Participants were stratified into genotype groups based on their alleles at specific SNPs to investigate the potential associations with PD and to facilitate comparison to the HC group. For the rs11931074 SNP, the genotype groups were defined as GG, GT, and TT. For rs356219 and rs356165, participants were categorized into GG, GA, and AA genotype groups.

MRI data acquisition and processing

MRI data acquisition

Images of all patients were acquired using a Discovery 750 3.0 T MRI scanner (GE HealthCare, Chicago, IL, USA), using standard HDx 8NV Head_A coil channels as transmitting and receiving coils. During scanning, participants were awake and lying quietly on the examination bed with their eyes closed and head fixed. Both groups underwent conventional brain MRI scans, including T1/T2-weighted imaging, T2 fluid-attenuated inversion recovery (FLAIR) imaging, and diffusion-weighted imaging, among others. The rs-fMRI data were collected via an echo-planar imaging (EPI) sequence under the following parameters: repetition time (TR) =2,000 ms; echo time (TE) =30 ms; flip angle =90°; matrix =64×64; field of view (FOV) =256×256 mm^2; voxel size =4×4×4 mm^3; slice thickness =4 mm; slice number =40; slice sequence, continuous ascending scanning; and scanning time point =200.

MRI data preprocessing and ALFF analysis

Functional MRI data analyses were performed using MRIcron Software (https://www.nitrc.org/projects/mricron), Connectivity Toolbox (CONN) software (https://www.nitrc.org/projects/conn), and the toolbox for Data Processing & Analysis of Brain Imaging (DPABI) implemented in the MATLAB R2013b platform (MathWorks, Natick, MA, USA) (32). The following steps were performed (as shown in Figure S1): after image preprocessing, fast Fourier transform (FFT) was performed on the filtered time series to transform the time-domain signal to the frequency threshold to obtain the power spectrum using CONN. ALFF was calculated using the DPABI tool by taking the square root of the power spectrum. The amplitude of the analysis frequency band was divided by the amplitude of the full frequency band to obtain the fALFF diagram. For standardization purposes, the ALFF or fALFF value of each voxel was divided by the global mean ALFF value to obtain the mALFF or mfALFF value via the DPABI tool. In addition, Z transformation was performed, in which the deviation of the ALFF or fALFF value of each voxel was divided by the standard deviation of the whole brain ALFF of fALFF value in order to better align the data with a normal distribution and to obtain zALFF and zfALFF, respectively. An automated anatomical labeling (AAL) brain atlas was used to mark brain areas with significant differences in ALFF values between different groups. The presentation of significant differences in brain regions was implemented using the Xjview 95 software.

Statistical analysis

The demographic and clinical data of the patients were analyzed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA), and the measurement data are expressed as the mean ± standard deviation. The Hardy-Weinberg equilibrium (HWE) of the *SNCA* rs11931074, rs356219, and rs356165 in the PD group and HC group were determined using the Chi-square test, and the linkage disequilibrium analysis was realized on the SHEsis platform (33) (http://analysis.bio-x.cn/ myAnalysis.php). For data with a normal distribution and uniform variance, a two-sample *t*-test was used to compare data of two independent samples, and an analysis of variance (ANOVA) test was used to compare data from multiple independent samples. The Wilcoxon rank sum test was used to compare data that did not conform to a normal distribution and that had uneven variance. The data from the four grid tables were analyzed using the Chi-square test for the R×C contingency tables. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

The magnetic resonance functional data were analyzed with SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/SPM12). The comparison of the brain functional data in the PD group and the HC group was performed with a two-sample *t*-test, and the covariates included age,

Table 1 Comparison of clinical data between the PD group and HC group

Characteristic	PD (n=63)	HC (n=73)	P
Age, years	63.24±7.99	63.03±6.78	0.868[a]
Sex (male/female)	37/26	33/40	0.116[b]
MMSE score	24.89±2.76	27.40±1.57	<0.001[c]***
UPDRS III score	30.67±11.34	–	–
Course of disease (months)	54.51±41.93	–	–
Hoehn-Yahr stage	2.36±0.55	–	–
Education (1/2/3/4/5)	10/16/12/17/8	3/14/25/22/9	0.075[c]
LEDD, mg/day	377.3 ±236.2	–	–

Data are presented as the mean ± standard deviation or number. [a], two-sample *t*-test; [b], Chi-square test; [c], Kruskal-Wallis test. 1, illiterate; 2, elementary school; 3, junior high school; 4, high school/technical secondary school; 5, university/college. ***, P<0.001. PD, Parkinson's disease; HC, healthy control; MMSE, Mini-Mental State Examination; UPDRS III, Unified Parkinson's Disease Rating Scale Part III; LEDD, levodopa equivalent daily dose.

gender, and MMSE score. Multivariate regression analysis was used to calculate the correlation between the brain function data and MMSE score, UPDRS III score, and disease course, with the covariates being age and gender. For the analysis of the influence of rs11931074 on brain function data, full factor analysis was used to analyze the main effects of diseases and genes and their interaction effects on functional data, with the covariates being age and gender. Post hoc comparisons were performed using the Bonferroni test. The two-sample *t*-test was used to analyze the differences in functional data between G-allele carriers and non-G allele carriers, with the covariates being age, gender, and MMSE score. The analysis process for the influence of rs356219 and rs356165 on brain functional data were the same as that for rs11931074. All rs-fMRI data analyzed with the SPM12 software were adjusted according to the false discovery rate (FDR) at the cluster level. Brain regions with a voxel level of P<0.001 and a cluster level of P<0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

Participants in this study included 63 patients with PD in the PD group and 73 sex- and age-matched healthy participants in the HC group (Figure S2). The inheritance of *SNCA* SNPs rs11931074, rs356219, and rs356165 in the PD group and the HC group was in accordance with the HWE and was constant (P>0.05; Table S3), with the three SNP sites conforming to the linkage disequilibrium (Table S4). There was no statistically significant differences in sex, age, education, or the levodopa equivalent daily dose (LEDD) between the PD and HC groups. The MMSE score of the PD group was lower than that of the HC group (P<0.001; *Table 1*). For the different genotype groups (GG, GA/GT, TT/AA) of rs11931074, rs356219, and rs356165 in the PD group, there were no significant differences in sex, age, MMSE score, UPDRS III score, disease course, H-Y stage, or LEDD. Moreover, the sex, age, and MMSE score among the genotype groups in the PD and HC group showed no statistically significant differences (*Tables 2-4*). In addition, there were no significant differences in age, sex, education, MMSE score, UPDRS III score, H-Y stage, disease course, or LEDD between the rs11931074 G-allele carriers (GG + GT group) and non-G allele carriers (TT group) in patients with PD or among all participants (Table S5).

ALFF analysis

ALFF analysis between the PD group and HC group

The mALFF, and zALFF values of the right superior cerebellum, cerebellar vermis, and left supplementary motor area were decreased in patients in the PD group as compared with those in the HC group (Table S6, *Figure 1A,1B*). There was no significant difference in the mfALFF or zfALFF values of brain area between the HC group and PD group.

Correlation analysis of ALFF values and the clinical data of the PD group and HC group

The zALFF values of the left central posterior gyrus of the PD group were positively correlated with the MMSE score (r=0.542; P<0.001; *Figure 1C,1D*, Table S7). The mfALFF values of the upper right margin of the HC group were negatively correlated with the MMSE score to a moderate extent (r=0.528; P<0.001; *Figure 1E,1F*, Table S7). The zALFF values of the right orbital superior frontal gyrus in the PD group was positively and weakly correlated with disease course (r=0.311; P=0.13; *Figure 1G,1H*, Table S7).

ALFF analysis of the rs11931074 group

We performed a full factorial analysis on the ALFF maps. The analysis of mALFF maps and zALFF maps showed

Table 2 Comparison of general clinical data between the genotypes of rs11931074 in the PD group and HC group

Characteristic	Group	GG	GT	TT	P
Age, years	PD	65.80±9.78	64.00±9.25	61.89±8.54	0.658[c]
	HC	60.58±9.12	64.21±5.62	62.63±6.86	0.132[c]
Sex (male/female)	PD	2/3	19/12	16/11	0.793[d]
	HC	3/9	15/19	15/12	0.206[b]
MMSE score	PD	24.80±2.86	24.84±2.61	24.96±3.01	0.871[c]
	HC	27.58±1.16	27.44±1.81	27.26±1.43	0.637[c]
UPDRS III score	PD	30.00 ±10.05	28.10±10.87	33.74±11.71	0.167[e]
Course of disease (months)	PD	40.20± 29.01	48.26±31.59	64.33±52.19	0.548[c]
Hoehn-Yahr stage	PD	2.50±0.00	2.23±0.55	2.44±0.64	0.535[c]
LEDD, mg/day	PD	250.00±165.83	365.27±221.61	414.57±259.67	0.330[c]

Data are presented as the mean ± standard deviation or number. [b], Chi-square test; [c], Kruskal-Wallis test; [d], Fisher exact test; [e], ANOVA. PD, Parkinson's disease; HC, healthy control; GG, rs11931074 GG genotype; GT, rs11931074 GT genotype; TT, rs11931074 TT genotype; MMSE, Mini-Mental State Examination; UPDRS III, Unified Parkinson's Disease Rating Scale Part III; LEDD, levodopa equivalent daily dose; ANOVA, analysis of variance.

Table 3 Comparison of the general clinical data of the rs356219 genotypes between the PD group and HC group

Characteristic	Group	GG	GA	AA	P
Age	PD	61.89±8.54	64.33±7.13	63.83±9.99	0.742[c]
	HC	62.32±6.93	64.52±5.40	60.58±9.12	0.09[c]
Sex (male/female)	PD	16/11	19/11	2/4	0.401[d]
	HC	15/13	15/18	3/9	0.250[b]
MMSE score	PD	24.96±3.01	24.90±2.63	24.50±2.67	0.819[c]
	HC	27.29±1.41	27.42±1.84	27.58±1.16	0.679[c]
UPDRS III score	PD	33.74±11.71	28.17±11.05	29.33±9.14	0.173[e]
Course of disease (months)	PD	64.33±52.19	47.87±32.05	43.50±27.25	0.581[c]
Hoehn-Yahr stage	PD	2.44±0.64	2.27±0.50	2.50±0.00	0.600[c]
LEDD, mg/day	PD	414.57±259.67	367.45± 225.06	258.33 ±149.72	0.332[c]

Data are presented as the mean ± standard deviation or number. [b], Chi-square test; [c], Kruskal-Wallis test; [d], Fisher exact test; [e], ANOVA. PD, Parkinson's disease; HC, healthy control; GG, rs356219 GG genotype; GA, rs356219 GA genotype; AA, rs356219 AA genotype; MMSE, Mini-Mental State Examination; UPDRS III, Unified Parkinson's Disease Rating Scale Part III; LEDD, levodopa equivalent daily dose; ANOVA, analysis of variance.

a significant main genotype effect on the left inferior cerebellum (*Figure 2A*, Table S8). Analysis of the mfALFF maps and zfALFF maps showed a significant main genotype effect on the right anterior cingulate and paracingulate gyri (*Figure 2B*, Table S8).

Among all participants, compared with the GG + GT group, the TT group had higher mfALFF and zfALFF values in the left caudate nucleus (*Figure 2C*, Table S8), but no significant differences in brain areas were observed between the mALFF and zALFF values. In the PD group, compared with the PD-TT group, the PD-GG + GT group had higher mfALFF and zfALFF values in the right

Table 4 Comparison of general clinical data between the genotypes of rs356165 in the PD group and HC group

Characteristic	Group	GG	GA	AA	P
Age	PD	61.89±8.54	64.33±7.13	63.83±9.99	0.742[c]
	HC	62.26±7.05	64.50±5.33	60.58± 9.12	0.089[c]
Sex (male/female)	PD	16/11	19/12	2/3	0.793[d]
	HC	14/13	16/18	3/9	0.286[b]
MMSE score	PD	24.96±3.01	24.90±2.63	24.50±2.66	0.819[c]
	HC	27.26±1.43	27.44±1.81	27.44±1.81	0.637[c]
UPDRS III score	PD	33.74±11.71	28.17±11.05	29.33±9.14	0.173[e]
Course of disease (months)	PD	64.33±52.19	47.87±32.05	43.50±27.25	0.581[c]
Hoehn-Yahr stage	PD	2.44±0.64	2.27±0.50	2.50±0.00	0.600[c]
LEDD, mg/day	PD	414.57±259.67	365.27±221.61	250.00±165.83	0.330[c]

Data are presented as the mean ± standard deviation or number. [b], Chi-square test; [c], Kruskal-Wallis test; [d], Fisher exact test; [e], ANOVA. PD, Parkinson's disease; HC, healthy control; GG, rs356165 GG genotype; GA, rs356165 GA genotype; AA, rs356165 AA genotype; MMSE, Mini-Mental State Examination; UPDRS III, Unified Parkinson' Disease Rating Scale Part III; LEDD, levodopa equivalent daily dose; ANOVA, analysis of variance.

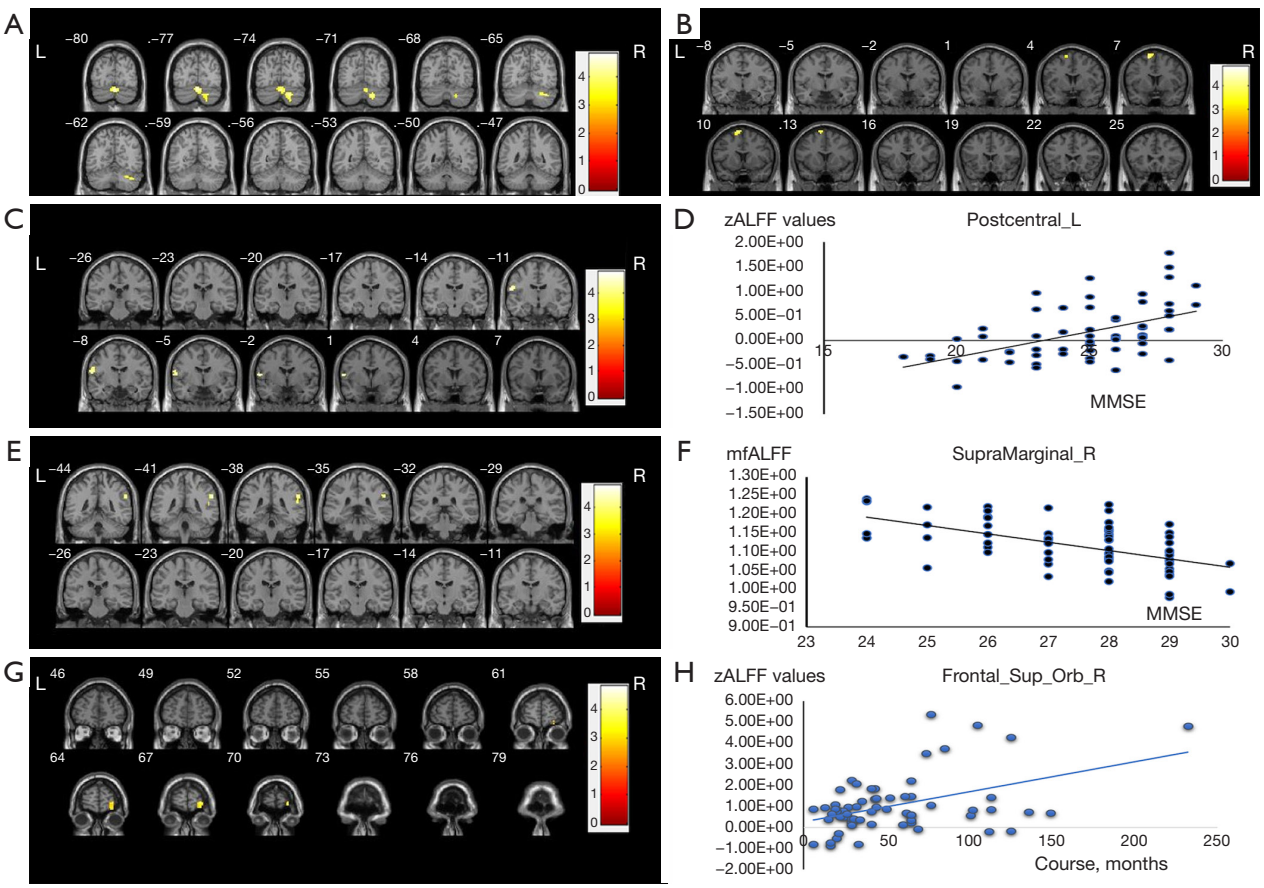

Figure 1 ALFF analysis of patients in the PD group and participants in the HC group and the correlation analysis of brain function data and clinical data. (A) Significant differences in mALFF and zALFF values in the right superior cerebellum (Cerebellum_Crus1_R) and vermis

(Vermis_7) between the PD group and the HC group. (B) Significant differences in mALFF and zALFF values in the left supplementary motor area (Supp_Motor_Area_L) between the brain areas in the PD group and HC group. (C) The zALFF values in the left postcentral gyrus (Postcentral_L) were positively correlated with the MMSE score in the PD group. (D) Correlation analysis between zALFF values of Postcentral_L and MMSE score in the PD group. (E) The mfALFF values of the right supramarginal gyrus (SupraMarginal_R) were negatively correlated with the MMSE score in the HC group. (F) Correlation analysis of mfALFF values of SupraMarginal_R and the MMSE score in the HC group. (G) The zALFF values of the right superior frontal gyrus, orbital part (Frontal_Sup_Orb_R) were positively correlated with the disease course in the PD group. (H) Correlation analysis of zALFF values of the Frontal_Sup_Orb_R and the disease course in the PD group. The yellow area in the figure represents the significant differences in brain regions, the color bar in (A) and (B) shows the *t* value range of the two-sample *t*-test, and the color bar in the (C), (E), and (G) shows the *t* value range of the multiple regression analysis. All data were corrected by the FDR at the block level, with a voxel level of P<0.001 and clump level P<0.05 being considered statistically significant brain regions. L, left; R, right; zALFF, z-score amplitude of low-frequency fluctuation; MMSE, Mini-Mental State Examination; mfALFF, mean fractional amplitude of low-frequency fluctuation; ALFF, amplitude of low-frequency fluctuation; PD, Parkinson's disease; mALFF, mean amplitude of low-frequency fluctuation; HC, healthy control; zfALFF, z-score fractional amplitude of low-frequency fluctuation; FDR, false discovery rate.

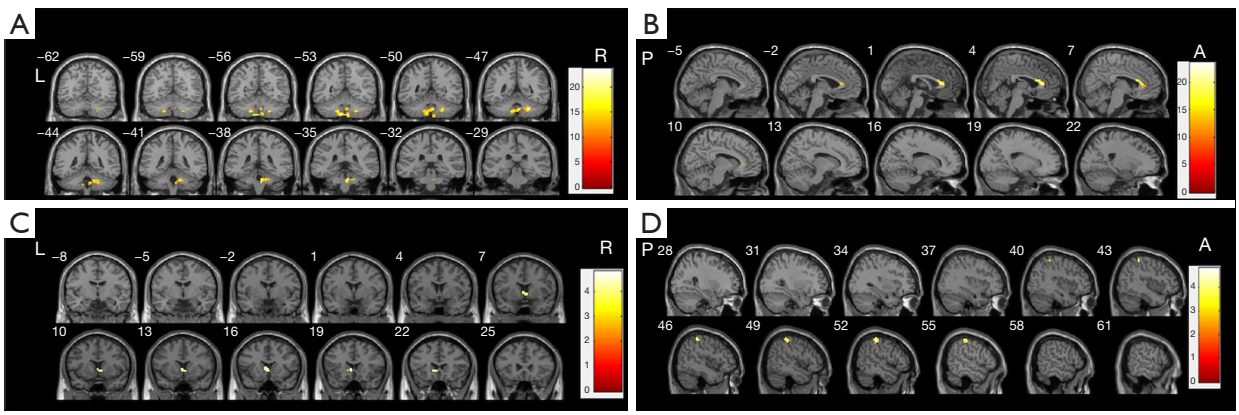

Figure 2 ALFF analysis of the rs11931074 group. (A) A significant genotype main effect was observed in left inferior cerebelum (Cerebelum_9_L) for mALFF and zALFF values. (B) A significant main genotype effect was observed in the right anterior cingulate and paracingulate gyri (Cingulum_Ant_R) for the mfALFF and zfALFF values. (C) The left caudate nucleus (Caudate_L) was found to be a significantly different brain region between the rs11931074 GG + GT group and TT group in all participants (mfALFF and zfALFF values). (D) The right postcentral gyrus (Postcentral_R) was found to be a significantly different brain region between the rs11931074 PD-GG + GT group and PD-TT group (mfALFF and zfALFF values). The color bar in (A) and (B) shows the *F* value range of the full factorial analysis, and the color bar in (C) and (D) shows the *t* value range of the two-sample *t*-test. All data were corrected via the FDR at the block level, with a voxel level of P<0.001 and a clump level of P<0.05 being considered statistically significant brain regions. L, left; R, right; P, posterior; A, anterior; ALFF, amplitude of low-frequency fluctuation; mALFF, mean amplitude of low-frequency fluctuation; zALFF, z-score amplitude of low-frequency fluctuation; mfALFF, mean fractional amplitude of low-frequency fluctuation; zfALFF, z-score fractional amplitude of low-frequency fluctuation; GG, rs11931074 GG genotype; GT, rs11931074 GT genotype; TT, rs11931074 TT genotype; PD, Parkinson's disease; FDR, false discovery rate.

postcentral gyrus (*Figure 2D*, Table S8).

ALFF analysis of the rs356219 group

The full factorial analysis revealed significant genotype effects in the left caudate nucleus for mfALFF values in the PD group (*Figure 3A*, Table S9). A significant interaction effect was found in the right inferior parietal gyrus for zfALFF values (*Figure 3B*, Table S9). Further post hoc comparison showed that the zfALFF values of the right inferior parietal gyrus of the PD-GG group were lower than those of the PD-GA group and PD-AA group, while the

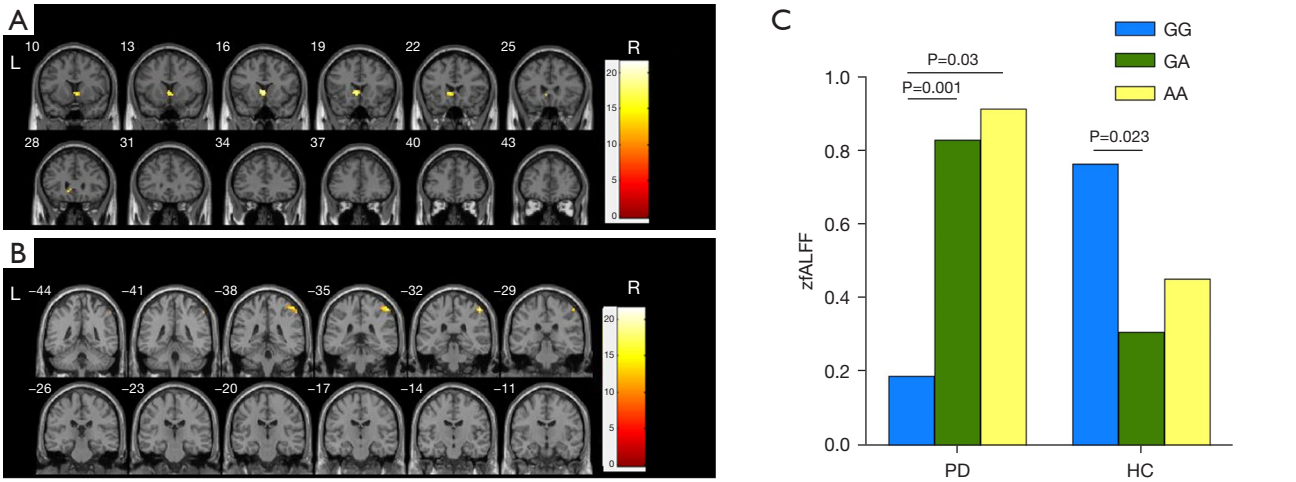

Figure 3 ALFF analysis of the rs356219 group. (A) A significant genotype main effect was observed in the left caudate nucleus (Caudate_L) for mfALFF values. (B) A significant main interaction effect was observed in the right inferior parietal gyrus (Parietal_Inf_R) for zfALFF values. (C) The post hoc comparison of the genotypes and disease interaction effect of the zfALFF values in the Parietal_Inf_R according to the Bonferroni test. The color bar in (A) and (B) shows the *F* value range of the full factorial analysis. All data were corrected according to FDR at the block level, with a voxel level of P<0.001 and a clump level of P<0.05 indicating statistically significant brain regions. L, left; R, right; zfALFF, z-score fractional amplitude of low-frequency fluctuation; PD, Parkinson's disease; HC, healthy control; GG, rs356219 GG genotype; GA, rs356219 GA genotype; AA, rs356219 AA genotype; ALFF, amplitude of low-frequency fluctuation; mfALFF, mean fractional amplitude of low-frequency fluctuation; FDR, false discovery rate.

zfALFF values of the right inferior parietal gyrus (Parietal_Inf_R,) of the HC-GG group was higher than that of the HC-GA group and HC-AA group (*Figure 3C*).

ALFF analysis of the rs356165 group

The full factorial analysis revealed that the mfALFF and zfALFF values of the left caudate nucleus had significant genotype main effects (*Figure 4*, Table S10), but there was no significant disease main effect or interaction effect found for the mfALFF and zfALFF values.

Discussion

The aim of the this study was to investigate the association of *SNCA* SNPs rs11931074, rs356219, and rs356165 using ALFF in patients with PD and HCs. We found that the mALFF values and zALFF values of the right cerebellum, cerebellar vermis, and the left supplementary motor area in the PD group were lower than those in the HC group. Additionally, the zALFF values of the left central posterior gyrus of the PD group were positively correlated with the MMSE score. The zALFF values of the superior frontal gyrus of the right orbit were positively correlated with the course of PD. The rs11931074 genotype main effect brain areas were the left cerebellum, the right anterior cingulate gyrus, and the paracingulate gyrus. The rs356219 and rs356165 genotype main effect brain area was the left caudate nucleus, and the disease × rs356219 genotype interaction effect brain area was the right inferior parietal gyrus. Spontaneous functional brain activity was enhanced in the right central posterior gyrus in patients with PD carrying the rs11931074 G allele. These findings provide evidence to support the notion that the *SNCA* SNPs rs11931074, rs356219, and rs356165 are involved in brain function in both patients with PD and HC participants.

The preclinical and prodromal stage of PD can precede the onset of typical motor symptoms in patients with PD by several years (14). People with a known genetic risk of developing PD and without motor symptoms are suitable candidates for studying the preclinical and prodromal stages of PD. A study using ALFF analysis found that in the PD group, this index showed a decrease in activity in a number of regions, including the supplementary motor cortex, the mesial prefrontal cortex, the right middle frontal gyrus, and the left cerebellum (21). Another rs-fMRI study showed that, compared to baseline, the fALFF values of the right cerebellum, right thalamus, right striatum, left superior parietal lobule, left inferior parietal lobule, left central

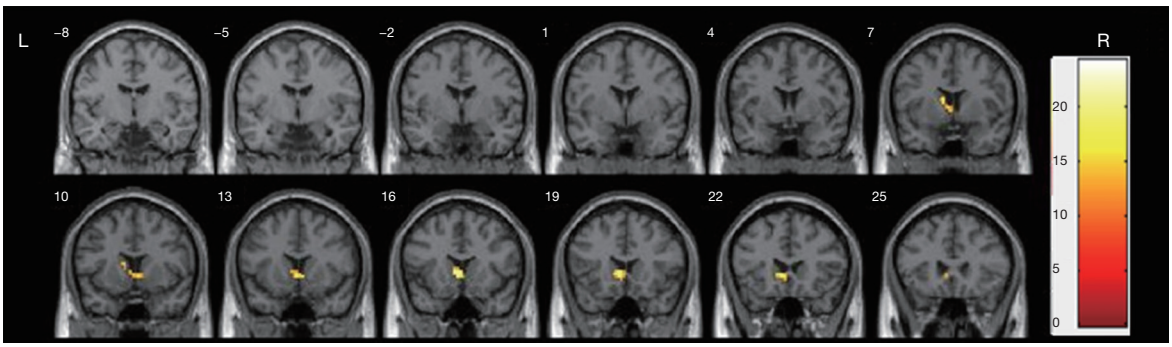

Figure 4 ALFF analysis of the rs356165 group. A significant genotype main effect was observed in the left caudate nucleus for mfALFF value. The yellow region in the plot indicates the left caudate nucleus, and the right color bar shows the range of *F* values for the full factorial analysis. All data were corrected according to the FDR at block level, with a voxel level of P<0.001 and a clump level of P<0.05 indicating a statistically significant brain region. L, left; R, right; ALFF, amplitude of low-frequency fluctuation; mfALFF, mean fractional amplitude of low-frequency fluctuation; FDR, false discovery rate.

anterior gyrus, and left central posterior gyrus were lower in the PD group than in the control group after two years. Further correlation analysis revealed that the fALFF values of the right cerebellum were positively correlated with the UPDRS score. It has been suggested that the cortical-basal ganglia-thalamic-cortical loop and cerebellar-thalamic-cortical loop dysfunctions are involved in the development of PD, and the spontaneous neural activity of the cerebellum may play an important role in cognitive function and movement in patients with PD (34). This is speculated to be related to dopaminergic neuron degeneration, abnormal signal transmission from the basal ganglia, and dopamine replacement therapy. Our study found that the spontaneous neurological activity of the left supplementary motor area, the right cerebellum, and cerebellar vermis were weakened in patients of the PD group, which is similar to the findings of previous studies (34). However, we found no abnormality in certain brain areas, such as the right thalamus and right striatum, which may be attributed to the fact that different studies may employ different samples, imaging techniques, and data-processing methods. Specifically, mALFF accurately measures brain activity by focusing on low-frequency amplitudes, while zALFF standardizes these measurements for consistent comparisons across individuals. Combining both methods, we aimed to gather a detailed and comparable overview of brain activity during rest.

Previous studies have examined the relationship between fMRI activity and genes in patients with PD, such as *COMT* gene rs4680 and *MAPT* gene rs9468 (35). Zhang *et al.* evaluated the effect of the *SNCA* SNP rs894278 site on resting-brain function in patients with PD and found that the ALFF values of the lingual gyrus and left caudate nucleus in patients with PD were lower than those in the control group (27). Some studies have shown that the T allele at rs11931074 is associated with an increased risk of developing PD in the Chinese population and that the G allele plays a protective role in patients with PD (10). Another study reported a significant interaction of disease and gene genotype in the right gyrus, suggesting that the *SNCA* rs11931074 polymorphism may modulate brain function changes in Chinese patients with PD and may be associated with motor symptoms (26,36). Our study also showed that for all participants, the mfALFF and zfALFF values in the left caudate nucleus of the non-G allele carriers of rs11931074 were higher than those of the G-allele carriers. The caudate nucleus is one of the components of the striatum, which plays an important role in the cortical-basal ganglia-thalamic-cortical loop in PD. The central posterior gyrus is located in the parietal lobe and also has a close structural and functional connection with the striatum. In our study, the mfALFF and zfALFF values in the right central posterior gyrus of the G-allele carriers were higher than those of the non-G allele carriers in the PD group. These findings suggest that the rs11931074 G allele may participate in the pathogenesis and development of PD by affecting the function of the left caudate nucleus and the right central posterior gyrus. Moreover, this points to an interaction effect of gene and disease on functional brain activity, with this association potentially being prominently implicated in the pathogenesis of PD.

In this study, rs356219 and rs356165 were found in genes

that have major effects on the left caudate nucleus, and these two SNPs exert an important effect on the spontaneous brain activity in the left caudate nucleus during the occurrence and development of PD. The angular gyrus is related to the nonmotor symptoms of PD, such as cognitive dysfunction and emotional disorder (36,37). Studies have found that patients with PD and PD with dementia (PDD) may have reduced grey matter volume (GMV) in portions of the occipital lobes, temporal lobes, and hippocampus (38). A meta-analysis of the GMV in patients with PDD reported a significantly reduced regional GMV in some brain regions including the right angular gyrus in the patients with PDD compared with HC participants (39). Additionally, in our study, significant interaction effects were observed in the right inferior parietal marginal angular gyrus, which is consistent with the findings in structural imaging studies (39). Another study showed that the functional brain activity of the posterior putamen and primary motor cortex was weakened in heathy participants with rs356219 G, and the functional connection between the posterior putamen and motor cortex was reduced when participants performed motor tasks, suggesting that carriers of the rs356219 PD-risk allele have abnormal function of the striatal-thalamic-cortical loop (40). Moreover, the study found the zfALFF value of the rs356219 locus showed a significant disease-gene interaction effect in the right parietal marginal gyrus. Further comparison revealed that the spontaneous brain activity of the right inferior parietal marginal angular gyrus of the PD-GG genotype group was weaker than that of the PD-GA and PD-AA genotype groups, while the spontaneous brain activity of the right inferior parietal marginal angular gyrus of the HC-GG genotype group was higher than that of HC-GA genotype (40). The study also indicated that in healthy participants, carrying rs356219 G can lead to abnormal functional activity in specific brain regions, which can explain the abnormal activity across the different genotypes (40). This finding suggests that the rs356219 G allele has a different effect on the functional brain activity of those with PD versus in those without PD, which further confirms that the rs356219 G allele is a PD risk allele. With consideration to previous studies and our results, we can surmise that different genes or the different loci of the same gene may have different effects on the brain function of different regions of the brain. Thus, variation in specific gene polymorphic loci may have more significant effects in brain regions with higher expression levels and less effects in other regions. The interaction of genes and environmental factors may affect various brain regions to various degrees. The phenotypic effects of specific gene polymorphism loci may be more pronounced in some brain regions when interacting with environmental factors.

It is worth noting that among the three *SNCA* SNPs (rs11931074, rs356219, and rs356165), the interaction effect of brain regions were only found for rs356219. However, how the mutation of the rs356219 gene locus affects the spontaneous functional brain activity of the right inferior parietal marginal angular gyrus remains to be further elucidated. This result also suggests that future studies can concentrate on the rs356219 locus and the related effects of gene polymorphisms on the spontaneous functional activity of the brain and further clarify its impact on functional brain activity during the development of PD.

Conclusions

We evaluated the association of *SNCA* SNPs rs11931074, rs356219, and rs356165 and ALFF in patients with PD and HC participants and found altered spontaneous activity in certain brain regions that was associated with PD status and genotype. Our results also revealed that the interaction effect of brain regions was only present for rs356219. Furthermore, changes in the functional brain activity may play a key role in the prediagnosis of PD. Overall, the findings of this study may contribute to furthering our understanding of the influence of genes on brain function and may also help arrive at deeper insights into the mechanisms underlying PD pathogenesis via imaging.

Limitations

This study involved certain limitations which should be mentioned. First, in the analysis the correlation between ALFF values and UPDRS III scores in this study, there was no correlation analysis for the "on" or "off" state of the UPDRS III scores, respectively. Therefore, in the next study, the motor assessment of the "on" and "off" state could be separately evaluated in order to study the brain network connection and neuron activity of PD in the "on and off" states, respectively. Second, we employed a cross-sectional study without follow-up and thus could not discern the changes of functional brain activity related to the progress of PD. Third, compared with ALFF, fALFF has improved sensitivity and specificity for detecting spontaneous brain activity. However, the mechanism of this signal is still unclear. The fALFF technique does not include bandpass filtering, and so similarly to ALFF, concerns

about its biological artifacts remain. Finally, our study only examined the association of the *SNCA* SNPs rs11931074, rs356219, and rs356165 with ALFF in sporadic patients with PD and matched HC participants. Brain spontaneous activity might be influenced by additional gene variants, such as other *SNCA* SNPs and other gene variants. Thus, the linkage disequilibrium between rs11931074, rs356219, and rs356165 or the others, gene-gene interactions, and more complex haplotypes should be investigated in future work.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-14/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-14/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Ethics Committee of Fujian Medical University Union Hospital (No. 2019K013). The requirement for individual consent in this retrospective analysis was waived.

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Supplementary

Table S1 *SNCA* (rs356219, rs11931074, rs356165) design-specific primers

Target site	Primer name	Primer sequence (5'→3')	Amplification length (bp)
SNCA rs356219	F1	TGCATGGGTATACTGGTGGTTCT	180
	R1	ACCCCTGCACCTTTCTTATTGC	
SNCA rs11931074	F1	GGGCCTGCACTAAAAGGGAA	157
	R1	GACAGTCAAATGGCAGCCTTC	
SNCA rs356165	F4	ACTGCCAGAAGTGTGTTTTG	410
	R4	TGTCTTATGGCTCTCTAAGGAG	

SNCA, synuclein alpha.

Table S2 PCR amplification process

Process	Temperature (℃)	Time	Cycle number
Predenaturation	98	4 min	1
Denaturation	98	10 s	40
Annealing	62	30 s	
Extend	72	40 s	
Extend	72	10 min	1
Maintain temperature	4	–	–

PCR, polymerase chain reaction.

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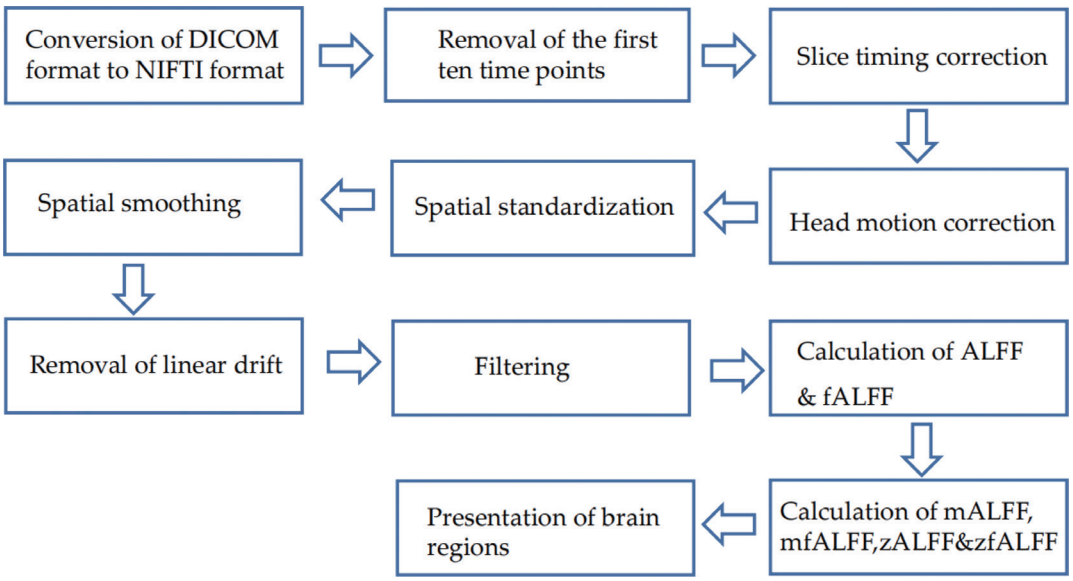

Figure S1 Flowchart of preprocessing for the rs-fMRI data. (I) Conversion of the DICOM format to NIFTI format through the dcm2niigui tool in MRIcron software. (II) Removal of the first 10 time points via CONN. The images of the first 10 time points were removed to eliminate the fluctuations in the BOLD value caused by the startup of the machine and the adaptation of the participants to the environment. (III) Slice timing was corrected to eliminate the phase difference of the scanning time of different slices. (IV) This study excluded participants whose head motion exceeded 2 mm in the x, y, and z direction and over 2° on the x-, y-, and z-axis. (V) For spatial standardization, the public EPI template was used to register the image of the participant to the standard brain space functional image template of the MNI and then resampled with a voxel size of 3×3×3 mm^3. (VI) Spatial smoothing was completed with a Gaussian kernel of 8×8×8 mm. (VII) Removal of linear drift was completed to further reduce the confounding signals caused by head movement, breathing, and heartbeat. (VIII) For filtering, the signals in the frequency range of 0.01–0.08 Hz were collected to analyze the spontaneous activities of brain neurons, and the effects of physiological noise were filtered out. (IX) The ALFF and fALFF calculation was completed with FFT as performed on the filtered time series to transform the time-domain signal to the frequency threshold to obtain the power spectrum using CONN. ALFF was calculated using the DPABI tool by taking the square root of the power spectrum. The amplitude of the current analysis frequency band was divided by the amplitude of the full frequency band to obtain the fALFF diagram. (X) The mALFF, zALFF, mfALFF, and zfALFF were calculated. For standardization purposes, the ALFF/fALFF value of each voxel was divided by the global mean ALFF value to obtain the mALFF/mfALFF value using the DPABI tool. In addition, Z transformation was performed, in which the deviation of the ALFF/fALFF value of each voxel was divided by the standard deviation of the whole brain ALFF/fALFF value in order to better align the data with a normal distribution and to obtain zALFF and zfALFF. (XI) An AAL brain atlas was used to mark the brain areas with significant differences in the ALFF values between different groups. The presentation of significant differences in brain regions was implemented using the Xjview 95 software. (XII) The rs-fMRI data were analyzed using SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/SPM12). The comparison of the brain functional data in the PD and HC groups was performed by the two-sample *t*-test, with the covariates being age, sex, and MMSE. Multivariate regression analysis was used to calculate the correlation between the brain function data and MMSE score UPDRS III score, and disease course. Full factorial analysis was used to analyze the main effects of diseases and genotypes and their interaction effects on functional data, with the covariates being age and sex. The two-sample *t*-test was used to analyze the differences in functional data between G-allele carriers and non-G allele carriers, with the covariates being age, sex, and the MMSE score. rs-fMRI, resting-state functional magnetic resonance imaging; DICOM, Digital Imaging and Communications in Medicine; NIFTI, Neuroimaging Informatics Technology Initiative; CONN, Connectivity Toolbox; BOLD, blood oxygen level-dependent; EPI, echo planar imaging; MNI Montreal neurological institute; ALFF, amplitude of low-frequency fluctuation; fALFF, fractional amplitude of low frequency fluctuation; FFT, fast Fourier transform; DPABI, Data Processing & Analysis of Brain Imaging; mALFF, mean ALFF; zALFF, z-score ALFF; mfALFF, mean fALFF; zfALFF, z-score fALFF; AAL, automated anatomical labeling; PD, Parkinson's disease; HC, healthy control; MMSE, mini-mental state examination; UPDRS III, Unified Parkinson's Disease Rating Scale Part III.

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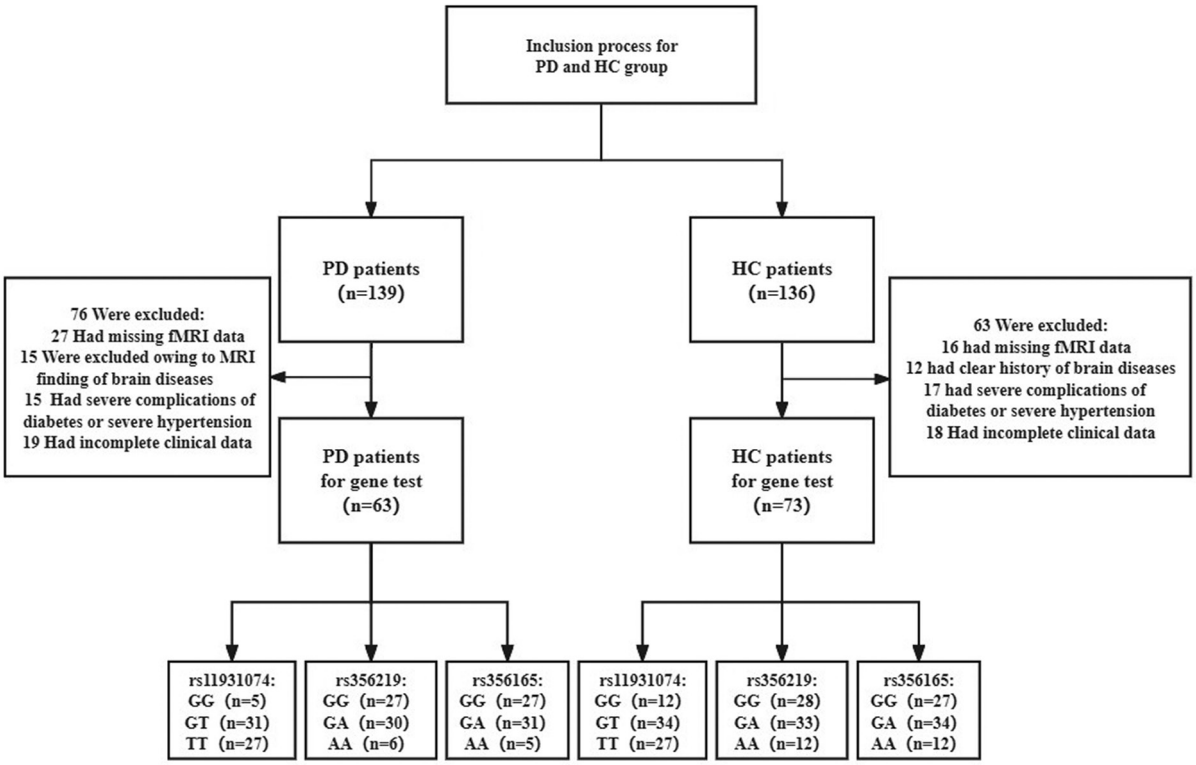

Figure S2. Flowchart of the inclusion process for the PD and HC groups. PD, Parkinson's disease; HC, healthy control; fMRI, functional magnetic resonance imaging; for rs11931074: GG, rs11931074 GG genotype; GT, rs11931074 GT genotype; TT, rs11931074 TT genotype; for rs356219: GG, rs356219 GG genotype; GA, rs356219 GA genotype; AA, rs356219 AA genotype; for rs356165: GG, rs356165 GG genotype; GA, rs356165 GA genotype; AA, rs356165 AA genotype.

Table S3 Hardy-Weinberg equilibrium of the rs11931074, rs356219, and rs356165 genotypes in the PD group and HC group

Group	GG	GT/GA	TT/AA	χ^2	P
rs11931074					
PD	5	31	27	0.92	0.63
HC	12	34	27	0.05	0.97
rs356219					
PD	27	30	6	0.32	0.85
HC	28	33	12	0.18	0.91
rs356165					
PD	27	31	5	0.92	0.63
HC	27	34	12	0.05	0.97

rs11931074 genotypes: GG, GT, and TT; rs356219, rs356165 genotypes: GG, GA, and AA. Results: P>0.05, the inheritance of the three gene loci in the PD group and the HC group was in accordance with the Hardy-Weinberg equilibrium, and the inheritance was consistent. PD, Parkinson's disease; HC, healthy control; for rs11931074: GG, rs11931074 GG genotype; GT, rs11931074 GT genotype; TT, rs11931074 TT genotype; for rs356219: GG, rs356219 GG genotype; GA, rs356219 GA genotype; AA, rs356219 AA genotype; for rs356165: GG, rs356165 GG genotype; GA, rs356165 GA genotype; AA, rs356165 AA genotype.

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Table S4 rs11931074, rs356219, and rs356165 linkage disequilibrium analysis

Polymorphic site	D'	r2
rs11931074-rs356219	0.984	0.968
rs11931074-rs356165	0.984	0.968
rs356219-rs356165	0.984	0.968

When the value of D 'and r2 is 0, the linkage is completely balanced; when the value of D' and r2 is 1, the linkage is completely unbalanced; the three loci are in line with the linkage disequilibrium.

Table S5 Comparison of the data of all participants and the rs11931074 G-allele carriers and non–G allele carriers in the PD group

Item	G-allele carrier	Non-G allele carriers	P
All participants			
Age (years)	63.70±7.09	62.26±7.69	0.266[a]
Gender: male/female	39/43	31/23	0.261[b]
Education (1/2/3/4/5)	9/18/24/21/10	4/12/13/18/7	0.428[f]
MMSE score	26.32±2.48	26.11±2.60	0.713[f]
PD group			
Age (years)	64.25±7.51	61.89±8.54	0.249[a]
Gender: male/female	21/15	16/11	0.941[c]
MMSE score	24.83±2.60	24.96±3.01	0.855[a]
UPDRS III score	28.36±10.64	33.74±11.71	0.062[a]
Course of disease (months)	47.14±30.98	64.33±52.19	0.300[f]
Hoehn-Yahr stage	2.26±0.52	2.44±0.64	0.547[f]
Education (1/2/3/4/5)	7/9/8/8/4	3/7/4/9/4	0.768[d]
LEDD, mg/day	349.26±216.50	414.57±259.67	0.259[g]

Data are shown as the mean ± standard deviation or number. [a], two-sample *t*-test; [b], Pearson Chi-square test; [c], Kruskal-Wallis test; [d], Fisher exact probability method; [e], ANOVA; [f], Mann-Whitney test; [g], Wilcoxon test. 1, illiterate; 2, elementary school; 3, junior high school; 4, high school/technical secondary school; 5, university/college. PD, Parkinson's disease; MMSE, mini-mental state examination, UPDRS III, Unified Parkinson's Disease Rating Scale Part III; ANOVA, analysis of variance.

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Table S6 Significant differences in ALFF value between the PD group and HC group

Item	Brain area (AAL template)	Clump size (voxel)	Peak point (*t* value)	Peak point MNI coordinate		
				X	Y	Z
mALFF HC-PD	Cerebelum_Crus1_R	79	4.6407	18	−75	−33
	Vermis_7	77	4.8223	0	−78	−21
	Supp_Motor_Area_L	39	4.3848	−12	6	69
zALFF HC-PD	Cerebelum_Crus1_R	71	4.5467	18	−75	−33
	Vermis_7	69	4.6799	0	−78	−21
	Supp_Motor_Area_L	36	4.3177	−12	6	69

ALFF, amplitude of low-frequency fluctuation; PD, Parkinson's disease; HC, healthy control; AAL, anatomical automatic labeling; MNI, Montreal neurological institute; mALFF, mean amplitude of low-frequency fluctuation; R, right; L, left; zALFF, z-score amplitude of low-frequency fluctuation; Cerebelum_Crus1_R, the right superior cerebellum; Vermis_7, vermis; Supp_Motor_Area_L, left supplementary motor area.

Table S7 The correlation of brain functional data in PD group and HC group with clinical scale and disease course

Item	Brain area (AAL template)	Clump size (voxel)	Peak point (*t* value)	Peak point MNI coordinate			r_s	P
				X	Y	Z		
PD zALFF & MMSE	Postcentral_L	46	4.2641	−57	−3	12	0.542	<0.001*
HC mfALFF & MMSE	SupraMarginal_R	36	−4.7196	57	−42	30	−0.528	<0.001*
PD zALFF & course	Cerebelum_Crus2_R	46	5.9361	12	−93	−39	0.194	0.129
	Hippocampus_R	43	6.0211	30	−6	−18	0.194	0.129
	Frontal_Sup_Orb_R	38	5.0201	30	66	−3	0.311	0.013*
	Parietal_Sup_R	53	4.3902	27	−51	66	0.189	0.138

*, P<0.05, significant difference. PD, Parkinson's disease; HC, healthy control; AAL, anatomical automatic labeling; MNI, Montreal neurological institute; R, right; L, left; zALFF, z-score amplitude of low-frequency fluctuation; mfALFF, mean fractional amplitude of low-frequency fluctuation; Postcentral_L, left posterior central gyrus; SupraMarginal_R, right supramarginal gyrus; Cerebelum_Crus2_R, right inferior cerebellum; Hippocampus_R, right hippocampus; Frontal_Sup_Orb_R, right superior frontal gyrus, orbital part; Parietal_Sup_R, right superior parietal gyrus.

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Table S8 Comparison of brain function indexes between the rs11931074 genotype groups and the main effect brain regions of genes

Item	Brain area (AAL template)	Clump size (voxel)	Peak point (*F*/*t* value)	Peak point MNI coordinate		
				X	Y	Z
Full factorial (main effect of genotypes)						
mALFF	Cerebelum_9_L	228	23.6754*	–9	–54	–54
mfALFF	Cingulum_Ant_R	61	23.4456*	3	30	9
zALFF	Cerebelum_9_L	131	22.1504*	–9	–54	–54
zfALFF	Cingulum_Ant_R	62	24.4574*	3	30	9
Two-sample *t*-test (PD + HC)						
mfALFF	Caudate_L	51	3.1536*	–3	15	3
zfALFF	Caudate_L	67	3.1536*	–3	15	3
Two-sample *t*-test (PD)						
mfALFF	Postcentral_R	51	3.2368*	51	–30	54
zfALFF	Postcentral_R	51	3.2368*	51	–30	54

*, P<0.05, significant difference. AAL, anatomical automatic labeling; MNI, Montreal neurological institute; R, right; L, left; PD, Parkinson's disease; HC, healthy control; ALFF, amplitude of low-frequency fluctuation; mALFF, mean amplitude of low-frequency fluctuation; zALFF, z-score amplitude of low-frequency fluctuation; mfALFF, mean fractional amplitude of low-frequency fluctuation; zfALFF, z-score fractional amplitude of low-frequency fluctuation; Cerebelum_9_L, left inferior cerebelum; Cingulum_Ant_R, right anterior cingulate and paracingulate gyri; Caudate_L, left caudate nucleus; Postcentral_R, right postcentral gyrus.

Table S9 Comparison of brain function indexes between the rs356219 genotype groups and a full factor analysis of significant brain areas

Item	Brain area (AAL template)	Clump size (voxel)	Peak point (*F*/*t* value)	Peak point MNI coordinate		
				X	Y	Z
Full factorial (main effect of genotypes)						
mfALFF	Caudate_L	49	21.6771*	–3	15	0
Groups × genotype interaction						
zfALFF	Parietal_Inf_R	44	25.2145*	54	–33	57

*, P<0.05 significant difference. AAL, anatomical automatic labeling; MNI, Montreal neurological institute; R, right; L, left; PD, Parkinson's disease; HC, healthy control; mfALFF, mean fractional amplitude of low-frequency fluctuation; zfALFF, z-score fractional amplitude of low-frequency fluctuation; Caudate_L, left caudate nucleus; Parietal_Inf_R, right inferior parietal gyrus.

Table S10 Comparison of brain function indexes in each genotype group of rs356165 and the significant brain areas of the gene main cause effects

Item	Brain area (AAL template)	Clump size (voxel)	Peak point (*F*/*t* value)	Peak point MNI coordinate		
				X	Y	Z
Full factorial (main effect of genotypes)						
mfALFF	Caudate_L	73	24.1354*	–6	18	0
zfALFF	Caudate_L	73	19.3663*	–3	15	0

*, P<0.05, significant difference. AAL, anatomical automatic labeling; MNI, Montreal neurological institute; R, right; L, left; PD, Parkinson's disease; HC, healthy control; mfALFF, mean fractional amplitude of low-frequency fluctuation; zfALFF, z-score fractional amplitude of low-frequency fluctuation; Caudate_L, left caudate nucleus.

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