Original Article

Evaluating white matter alterations in Parkinson's disease-related *parkin* S/N167 mutation carriers using tract-based spatial statistics

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Background: Genetic susceptibility plays an important role in the pathogenesis of Parkinson's disease (PD). *parkin* S/N167 mutations may increase the risk of PD and affect white matter fibers in the brain. This cross-sectional study explored the effects of gene polymorphisms on white matter fiber damage in PD.

Methods: In all, 54 cases were enrolled in the study, including PD patients carrying *parkin* gene S/N167 mutations (G/A), PD patients without gene S/N167 mutations (G/G), and healthy controls (HC). The whole-brain white matter fiber skeleton was analyzed using the tract-based spatial statistics (TBSS) method. Two-way analysis of variance (ANOVA) and post hoc tests were used for data analyses.

Results: Two classification methods were used; one was based on disease classification, with 26 patients in the PD group (n=12 G/G, n=14 G/A) and 28 in the HC group (n=15 G/G, n=13 G/A), and the other was based on genetic classification, with 27 patients in the G/G group and 27 in the G/A group. In the G/A group, there was a wide range of significant changes in fractional anisotropy (FA), radial diffusivity (RD), and mean diffusivity (MD) values ($P<0.05$). There was also a significant decrease in FA in the PD-G/A group compared with the PD-G/G and HC-G/A groups ($P<0.05$).

Conclusions: There were more extensive brain white matter fiber damage and changes in PD patients; the G/A polymorphism may cause more extensive brain white matter damage.

Keywords: Diffusion tensor imaging (DTI); *parkin* gene S/N 167 polymorphism; Parkinson's disease (PD); white matter alteration

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting approximately 1% of the global population aged >60 years (1-3). Genetic susceptibility plays an important role in the pathogenesis of PD, and family linkage analysis and mutation detection have confirmed that *parkin* gene is an important genetic pathogenic factor leading to PD (4). The *parkin* gene is the most common causative gene in Chinese patients with sporadic early-onset PD, and notably, exon deletion was the most common type of mutation (5). With advances in research, the role of *parkin* mutations in the onset of sporadic and late-onset PD patients has also received attention. Polymorphisms of S/N167 at the genotype and allele levels may increase the risk of PD (2,6). Within a cohort of 278 families, *parkin* mutations were identified in 11.2% of cases (50/448) with PD onset at >50 years of age (7). Due to the G to A mutation in exon 4 of the *parkin*, the serine (S) of the 167th codon is replaced by asparagine (N), thus forming the S/N167 polymorphism that may result in insufficient parkin protein production or insufficient activity of parkin protein (2,5,8).

Imaging genetics is a new discipline that links imaging and genetics to explore the effects of genetic variation on brain structure and function (9-12). Diffusion tensor imaging (DTI) technology has been widely used in the field of neurology in investigations of Alzheimer's disease, PD, and multiple sclerosis (12-14). White matter fibers transmit essential cerebral nerve impulses. There is evidence that the frontal and occipital lobes of patients with early PD may have extensive white matter microstructural damage, leading to changes in brain morphology and a series of clinical symptoms, such as motor and non-motor symptoms (15). The DTI method quantifies the amount and direction of diffused water molecules to reflect the spatial directivity and integrity of the structure of brain white matter and uses the fiber-tracking technique for three-dimensional reconstruction, which then intuitively reflects the trend, loss, and density of fasciculi in the white matter. This can then be used to estimate the integrity of the axons and the extent of microstructural damage (16). Tract-based spatial statistics (TBSS) is an automated whole-brain analysis method based on the white matter fiber skeleton that has recently been developed and become popular in white matter studies. The TBSS is a common alignment method based on fasciculi and can automatically and accurately analyze data from DTI (16,17). The most commonly used DTI parameters include fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD).

The FA values are primarily used to measure the isotropic diffusion ability of water molecules in the tissue and to characterize the directional distribution of the random movement of water molecules. A decrease in FA values may be due to demyelination, axon loss, or changes in axon size, and indicates that the arrangement of white matter fiber bundles is not regular and has lost integrity (18,19). The MD parameter is primarily used to describe the unidirectional diffusion capacity of water molecules in organic tissue and represents the overall movement trend of water molecules. Increased MD values indicate a poor capacity to retain water molecules in tissues, indicating tissue degradation (19). Meanwhile, TBSS can accurately align the major white matter tracts (17-20). It accurately positions the white matter through a white matter skeleton-based registration method and can quantitatively observe changes in the brain white matter diffusion index in patients. Thereby, TBSS can effectively reduce the image distortion caused by registration and smoothing (10,17), and has high sensitivity, objectivity, and interpretability in evaluating white matter fiber bundle damage (17).

In the present study, we explored differences in the white matter between PD and healthy control (HC) groups, as well as between patients carrying a *parkin* S/N167 mutation (G/A) and those not carrying the mutation (G/G), and analyzed the correlations between white matter fiber damage and PD cognition or motor function in patients. Our aims were to understand the pathological process of PD, to explore the effects of gene polymorphisms on white matter fiber damage in PD, and to provide more evidence for the disease mechanism in PD using genetic imaging. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1007/rc).

Methods

Study design

This cross-sectional study included 54 participants was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Fujian Medical University Union Hospital, and all patients provided written informed consent. The flow diagram of inclusion process for PD and HC group presented in Figure S1.

Patients with PD included in this study were of Asian descent and were recruited from Fujian Medical University Union Hospital (Fujian, China) between March 2018 and December 2019. All patients underwent *parkin* S/N167 nucleotide polymorphism screening and head magnetic resonance imaging (MRI) examinations [including 3-dimensional brain volume (3D-BRAVO) and DTI imaging]. We included PD patients with the *parkin* S/N167 mutation (G/A) in the study and matched them for gender, age, number, and genotype with PD patients without the S/N167 mutation (G/G). We also recruited age- and gender-matched healthy controls (HC), including both G/A and G/G carriers, from the ShangDu Community. None of the control participants had a history or signs of neurological disorders.

Inclusion criteria

The PD patients enrolled in this study were clinically diagnosed according to the MDS clinical diagnostic criteria for Parkinson's disease (2015 edition) by two senior attending physicians (Qinyong Ye, Guoen Cai) who had received training before evaluating patients. All patients had received levodopa (L-DOPA) therapy and/or dopamine agonists on a regular basis and were taking their recommended PD drugs during the clinical evaluation. In addition, to be eligible for inclusion in this study, PD patients had to have an age of onset of >50 years and no family history of PD.

Exclusion criteria

Patients meeting any of the following criteria were excluded from the study:

(I) A clear history of brain diseases (including cerebrovascular disease, trauma, infection, poisoning, and autoimmune diseases) or obvious abnormalities in intracranial MRI (including obvious brain atrophy);
(II) Various secondary parkinsonian and parkinsonian-superimposed syndromes;
(III) Severe dementia, psychiatric diseases, neurodevelopmental diseases, anxiety, and depression;
(IV) Severe complications of diabetes and hypertension (e.g., cerebrovascular atherosclerosis, small cerebrovascular disease) that may affect the structural integrity of the brain white matter;
(V) Heavy consumption of tobacco and alcohol;
(VI) A history of exposure to heavy metals and other harmful substances;
(VII) Incomplete data, including for genetic tests, DTI, and clinical evaluations.

Clinical evaluation

All patients were clinically evaluated by neurology specialists. Cognitive function in the HC group was evaluated using the Mini-Mental State Examination (MMSE) (21). For PD patients, cognitive function was evaluated using the MMSE, the Montreal Cognitive Assessment (MoCA)-Changsha version (22), whereas motor symptoms were evaluated using Hoehn-Yahr scale (H-Y) and the Parkinson's Disease Unified Rating Scale Part III (UPDRS-III) (23).

Parkin genetic testing

Venous blood from the elbow of all participants was taken for detection of *parkin* S/N167 single nucleotide polymorphisms. The main reagent, Prime STAR HS (Premix), was purchased from Baori Medical Technology (Beijing, China) and the *parkin* gene S/N167 primers were synthesized by Inventec Trading (Shanghai, China). Sanger method sequencing was used, which included preparation of a reaction mixture (50 μL) containing 1 μL upstream primer (10 μM), 1 μL downstream primer (10 μM), 25 μL Prime STAR HS (Premix), 5 μL human genome DNA (5 ng/μL), and 18 μL ultrapure water. The amplified products were sent to Sangon Bioengineering (Shanghai, China) for Sanger DNA sequencing to determine gene polymorphisms.

MRI and image acquisition

Imaging data were acquired by a GE 3.0T dual-gradient MR scanner (GE Healthcare, Chicago, IL, USA). We used the 3D-BRAVO sequence to collect high-resolution T_1-weighted brain structure imaging data. The parameter settings were as follows: repetition time (TR) =8.7 ms, echo time (TE) =3.42 ms, flip time (TI) =400 ms, flip angle (FA) =12°, matrix =256×256, field of view (FOV) =240×240 mm, layer number =180, and slice thickness =1.1 mm. The DTI scan uses a spin-echo planar imaging [echo-planar imaging (EPI)] sequence to perform brain imaging, and echo-planar sequences in axial sections with the following settings: TR

=6,000 ms, TE =65.7 ms, FA =90°, matrix =128×128, field of view =240×240 mm, layer number =55, and layer thickness =3 mm (continuous scanning without spacing) in 16 non-linear diffusion-sensitive gradient directions with b values of 0 and 1,000 s/mm^2.

Image processing

The TBSS toolkit in FSL software (FMRIB Software Library, FMRIB, Oxford, UK) was used to construct a single FA image from the white matter skeleton for each participant (18). The TBSS toolkit uses a fitted tensor model to analyze the original diffusion data, registers the FA data of all cases into the standard space through a non-linear registration algorithm, creates an average FA skeleton, and normalizes the FA of each case. The threshold of the skeleton was set to 0.2 and the universal general linear model (Glm) is designed with age and gender as covariates. The TBSS framework with non-parametric permutation testing (5,000 permutations) was used for multiple comparisons correction and threshold-free cluster enhancement (TFCE). The results were considered significant at P<0.05(two-sided) for TFCE-corrected multiple comparisons. Brain regions with statistically significant differences between two groups on TBSS analysis were chosen as the brain regions of interest. Results were displayed as images superimposed on the MNI (Montreal Neurological Institute, Montreal, QC, Canada) template. Then, different brain regions were cut based on different white matter fibers referring to the Johns Hopkins University WM atlas (JHU-ICBM-DTI-81) distributed by FSL, and the mean FA values were extracted for statistical analysis. Brain regions that did not differ significantly were not extracted. MD, AD, and RD values were extracted using the same as the methods as used to extract FA values. The names of fiber bundles extracted were presented in Table S1.

Statistical analysis

Case data were analyzed using IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was tested using the Shapiro-Wilk test (W test). Measurement data with a normal distribution and uniform variance, as well as data from two independent samples, were compared using independent sample *t*-tests, and measurement data are presented as the mean ± SD. Whereas measurement or grade data that did not have a normal distribution and or uniform variance were compared using the rank-sum test, and data are described with median (interquartile range). Two-way analysis of variance (ANOVA) was used to detect interactions between disease factors and genetic factors with built-in post hoc tests. Bonferroni tests were used to assess between-group differences. Pearson correlation analysis was used to calculate correlations between DTI parameters (FA, RD, MD, AD) of the PD group and the MMSE, MoCA, and UPDRS-III scores and H-Y classification. The false discovery rate (FDR) correction approach was used to correct for these correlations. Differences were considered statistically significant at P<0.05.

Results

Clinical variables

Of the 112 PD patients and 125 HCs invited to take part in the study, 54 were eligible for inclusion. Two classification methods were used; one was based on disease classification, with 26 patients in the PD group (12 G/G, 14 G/A) and 28 in the HC group (15 G/G, 13 G/A), and the other was based on genetic classification, with 27 in the G/G group and 27 in the G/A group. There were no significant differences in gender, age, or MMSE scores among the groups (*Tables 1,2*; Table S2).

TBSS analysis

Two-way ANOVA was performed based using disease and genetic factors as independent variables, and age and gender as covariates; no interaction effects were found on FA, MD, RD, or AD values (P<0.05). Group pairwise comparisons were then performed to compare the independent effects. *Figure 1A* shows FA values in brain regions of the PD and HC groups. As shown in *Figure 1B*, there were significant differences in FA values between the GG and GA groups.

Comparison of PD and HC groups

Significantly increased MD and RD and significantly decreased FA values were observed in numerous subcortical brain regions of the PD group compared with the HC group (*Figures 1A,2*, *Table 3*; Tables S3-S5). Specifically, lower FA values were seen in the PD compared with the HC group in the bilateral anterior corona radiata, bilateral anterior limb of the internal capsule, bilateral external capsules, bilateral posterior corona radiata, bilateral superior corona radiata,

Table 1 Demographic and behavioral characteristics of the included participants for HC and PD group

Characteristic	HC (n=28)	PD (n=26)	P
No. males	12	14	0.419[a]
Age	62.3±6	65.5±6.8	0.070[b]
MMSE	25.6±2.5	25±2.4	0.251[c]
Genotype (n)			
G/G	15	12	
G/A	13	14	
MoCA	–	20.2±3.1	
H-Y (%)	–		–
1.5		3.8	
2		34.6	
2.5		50	
3		11.5	
UPDRS-III	–	33.6±9.3	–

Age, Mini-Mental State Examination (MMSE) scores, and Montreal Cognitive Assessment (MoCA) scores are given as the mean ± SD. [a], Chi-square test; [b], independent sample *t*-test; c, Mann-Whitney U test. HC, healthy control; PD, Parkinson's disease; G/G, patients without parkin gene S/N167 mutations; G/A, patients carrying parkin gene S/N167 mutations; H-Y, Hoehn-Yahr Stage; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Table 2 Demographic and behavioral characteristics of the included participants for G/G and G/A group

Characteristic	G/G (n=27)	G/A (n=12)	P
No. males	14	12	0.586[a]
Age	63.9±6.6	63.8±6.6	0.951[b]
MMSE	25.6±2.4	25±2.5	0.416[c]

Unless indicated otherwise, data are given as the mean ± SD. [a], Chi-square test; [b], independent sample *t*-test; [c], Mann-Whitney U test. G/G, no S/N167 mutation; G/A, carrier of the S/N167 mutation; MMSE, Mini-Mental State Examination.

corpus callosum, and right posterior thalamic radiation. Significantly (P<0.05) higher MD values were seen in the bilateral posterior corona radiata, bilateral superior corona radiata, and the right posterior thalamic radiation of the PD compared with HC group. In addition, significantly (P<0.05) higher RD values were seen in the bilateral anterior corona radiata, bilateral anterior limb of internal capsule, bilateral external capsules, bilateral posterior corona radiata, bilateral posterior thalamic radiation, bilateral superior corona radiata, and corpus callosum of the PD versus HC group.

Comparisons between the G/G and G/A groups

Significantly increased MD and RD and significantly

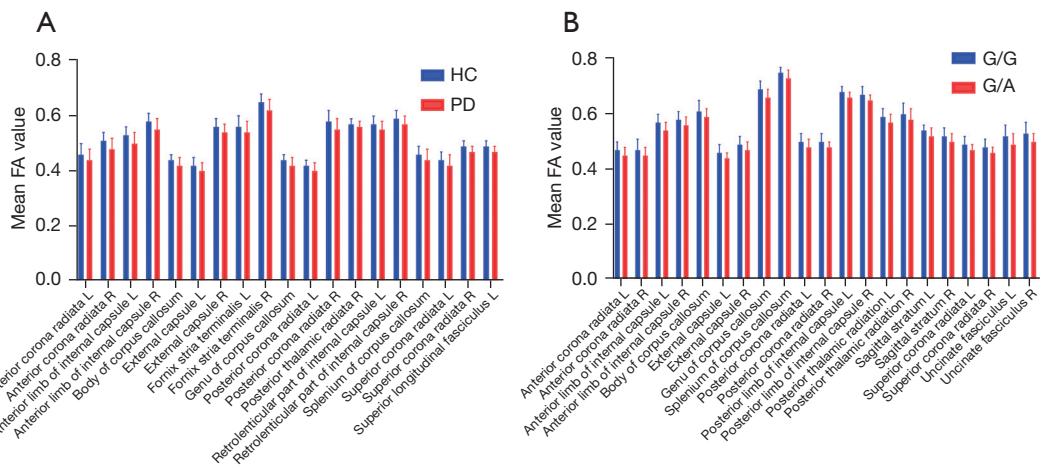

Figure 1 Brain regions showing significant differences in FA values: (A) PD versus HC; and (B) PD patients (G/A) versus PD patients (G/G). FA, fractional anisotropy; PD, Parkinson's disease; HC, healthy controls; G/G, patients without parkin gene S/N167 mutations; G/A, patients carrying parkin gene S/N167 mutations.

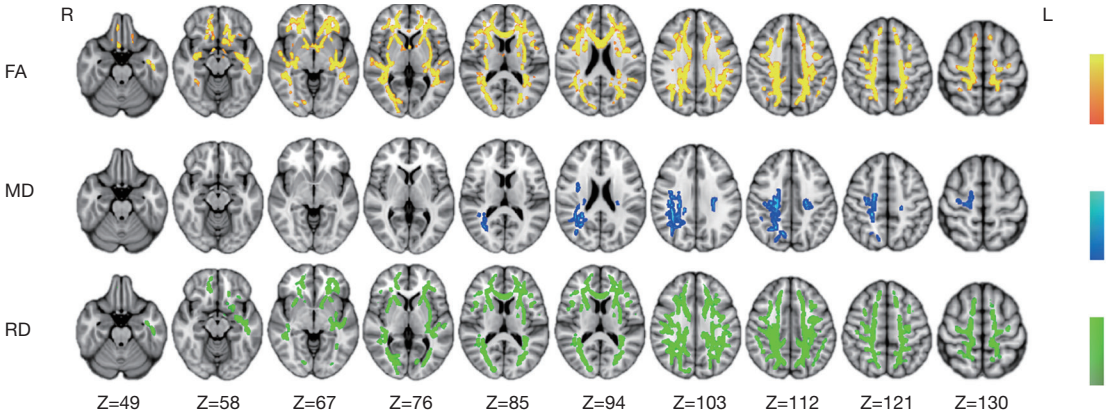

Figure 2 Comparison of diffusion tensor imaging indices (FA, MD, RD) between HC and patients with PD. Significant differences are indicated by the yellow regions overlaid on the mean FA skeleton, the blue regions overlaid on the mean MD skeleton, and the green regions overlaid on the mean RD skeleton. L, left; R, right; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; HC, healthy controls; PD, Parkinson's disease.

Table 3 Tract-based spatial statistics analysis of diffusion tensor imaging indices between groups

Modality	Group comparisons	Anatomical region
FA	HC > PD	acr-L, acr-R, alic-L, alic-R, Bcc, ec-L, ec-R, fst-L, fst-R, gcc, pcr-L, pcr-R, ptr-R, rlic-L, rlic-R, scc, scr-L, scr-R, slf-L
MD	HC < PD	pcr-L, pcr-R, ptr-R, scr-L, scr-R, slf-R
RD	HC < PD	acr-L, acr-R, alic-L, alic-R, bcc, ec-L, ec-R, fst-L, gcc, pcr-L, pcr-R, ptr-L, ptr-R, rpic-L, rpic-R, ss-L, scc, scr-L, scr-R, sfof-L
FA	G/G > G/A	acr-L, acr-R, alic-L, alic-R, boca, cp-L, cp-R, ccg-L, ct-L, ec-L, ec-R, fst-L, fst-R, gocc, icp-L, icp-R, ml-L, ml-R, mcp, pct, pcr-L, pcr-R, ploic-L, ploic-R, ptr-L, ptr-R, rpic-L, rpic-R, ss-L, ss-R, socc, scp-L, scr-L, scr-R, sfof, uf-L, uf-R
MD	G/G < G/A	acr-L, aloic-L, aloic-R, boca, cp-R, ct-R, ec-L, ec-R, fst-L, fst-R, ploic-L, ploic-R, ptr-R, rpic-L, rpic-R, ss-L, ss-R, scr-L, scr-R, slf-L
RD	G/G < G/A	acr-L, acr-R, aloic-L, aloic-R, boca, cp-L, cp-R, ct-L, ct-R, ec-L, ec-R, fst-L, goca, icp-R, ml-R, mcp, pct, pcr-L, pcr-R, ploic-L, ploic-R, ptr-L, ptr-R, rpoic-L, rpoic-R, ss-L, ss-R, soca, scr-L, scr-R, sfof-L, slf-L, slf-R, uf-R
FA	PD-G/G > PD-G/A	ct-L, ec-L, ec-R, fst-L, gocc, mcp, rpoic-L
FA	HC-G/G > HC-G/A	acr-L, cp-L, cp-R, mcp, ploc-L, ploc-R, scr-L, scr-R
MD	PD-G/G > PD-G/A	aloc-L, ct-R, ec-L, fst-L
MD	HC-G/G > HC-G/A	alic-L, alic-R, bocc, ct-R, scr-R
RD	PD-G/G > PD-G/A	aloic-L, cp-L, cp-R, ec-R, fst-L, gocc, rpoic-L
RD	HC-G/G > HC-G/A	cp-L, cp-R, icp-R, ploic-L, ploic-R

acr, anterior corona radiata; aloic, anterior limb of internal capsule; boca, body of the corpus callosum; ccg, cingulum cingulate gyrus; ch, cingulum hippocampus; cp, cerebral peduncle; ct, corticospinal tract; ec, external capsule; FA, fractional anisotropy; fst, fornix stria terminalis; G/G, patients without parkin gene S/N167 mutations; G/A, patients carrying parkin gene S/N167 mutations; goca, genu of the corpus callosum; HC, healthy control; icp, inferior cerebellar peduncle; L, left; mcp, middle cerebellar peduncle; MD, mean diffusivity; ml, medial lemniscus; pcr, posterior corona radiata; pct, pontine crossing tract; PD, Parkinson's disease; ploic, posterior limb of the internal capsule; ptr, posterior thalamic radiation; rpoic, retrolenticular part of the internal capsule; R, right; RD, radial diffusivity; scp, superior cerebellar peduncle; scr, superior corona radiata; sfof, superior fronto-occipital fasciculus; socc, splenium of the corpus callosum; ss, sagittal stratum; uf, uncinate fasciculus.

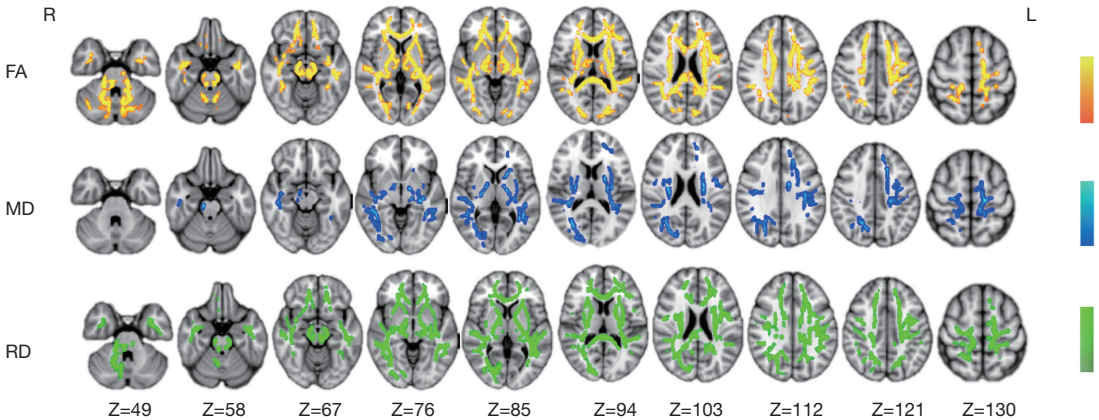

Figure 3 Comparison of diffusion tensor imaging indices (FA, MD, RD) between PD patients (G/A) and PD patients (G/G). Significant differences are indicated by the yellow regions overlaid on the mean FA skeleton, the blue regions overlaid on the mean MD skeleton, and the green regions overlaid on the mean RD skeleton. R, right L, left; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; G/A, patients carrying parkin gene S/N167 mutations; G/G, patients without parkin gene S/N167 mutations.

decreased FA values were observed in numerous subcortical brain regions of the G/A compared G/G group (*Figures 1B,3*, *Table 3*; Tables S6-S8). Specifically, FA values were lower in the G/A than G/G group in the bilateral anterior corona radiata, bilateral anterior limb of internal capsule, bilateral external capsules, bilateral posterior corona radiata, bilateral posterior limb of internal capsule, bilateral posterior thalamic radiation, bilateral sagittal stratum, bilateral superior corona radiata, and corpus callosum. These significant differences in white matter tracts between the G/G and G/A groups overlapped those seen between the PD and HC groups. There were also significant decreases in FA values in the bilateral uncinate fasciculus in the G/A group. There were increases in MD values in the G/A versus G/G group in the bilateral anterior limb of the internal capsule, bilateral external capsule, bilateral posterior thalamic radiation, bilateral sagittal stratum, and bilateral superior corona radiata. In addition, RD values were significantly ($P<0.05$) increased in the G/A versus G/G group in the bilateral anterior corona radiata, bilateral anterior limb of internal capsule, bilateral external capsules, bilateral posterior corona radiata, bilateral posterior thalamic radiation, bilateral superior corona radiata, and corpus callosum.

Comparisons within subgroups

PD-G/G versus PD-G/A

In the PD-G/A group, FA values in the corticospinal tract, bilateral external capsules, left fornix stria terminalis, genu of the corpus callosum, and middle cerebellar peduncle were significantly lower than in the PD-G/G group (*Figure 4*, *Table 3*; Table S9), whereas MD values in the left interior limb of the internal capsule, right corticospinal tract, and left external capsule were significantly higher in the PD-G/A group. RD values in the left anterior limb of the internal capsule, bilateral cerebral peduncle, left corticospinal tract, right external capsule, left fornix stria terminalis, genu of the corpus callosum, and left retrolenticular part of the internal capsule were significantly higher in the PD-G/A than PD-G/G group (*Figure 4*, *Table 1*; Tables S9-S11).

HC-G/G versus HC-G/A

The FA values in the bilateral posterior limb of the internal capsule, the left anterior limb of the internal capsule, the left posterior corona radiata, left external capsule, left anterior corona radiata, bilateral cerebral peduncle, middle cerebellar peduncle, bilateral posterior limb of the internal capsule, and bilateral superior corona radiata were significantly lower in the HC-G/A than HC-G/G group. In contrast, MD values in the bilateral anterior limb of the internal capsule, body of the corpus callosum, right corticospinal tract, and right superior corona radiata were significantly higher in the HC-G/A than HC-G/G group. The RD values were also significantly ($P<0.05$) higher in the HC-G/A than HC-G/G group in the bilateral cerebral peduncle, right inferior cerebellar peduncle, and bilateral posterior limb of the internal capsule (*Figure 4*, *Table 3*; Tables S12-S14).

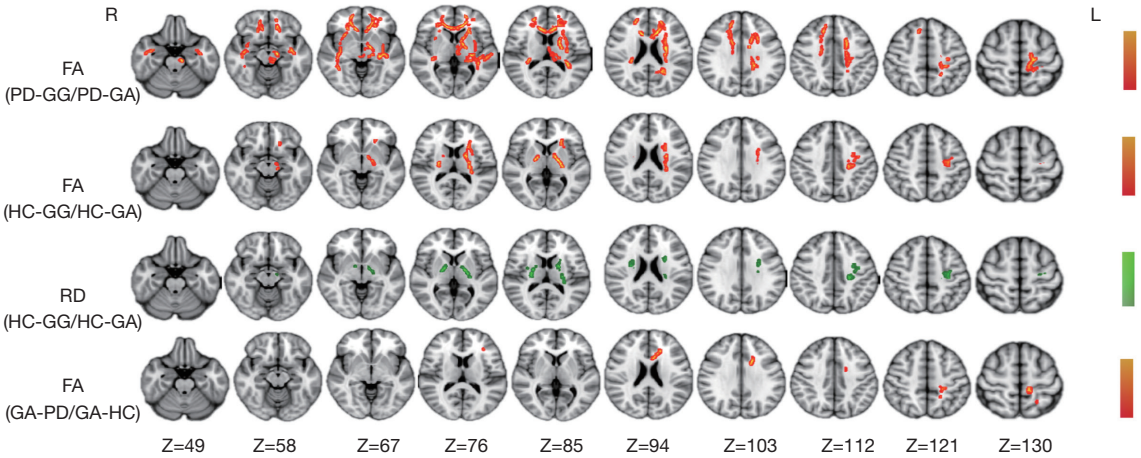

Figure 4 Comparison of diffusion tensor imaging indices (FA, RD) between groups. Significant differences are indicated by the red regions overlaid on the mean FA skeleton and the green regions overlaid on the mean RD skeleton. R, right; L, left; FA, fractional anisotropy; PD, Parkinson's disease; G/G, patients without parkin gene S/N167 mutations; G/A, patients carrying parkin gene S/N167 mutations; HC, healthy controls; RD, radial diffusivity.

G/A-HC versus G/A-PD

There were no significant differences between the G/A-PD and G/A-HC groups.

G/G-HC versus G/G-PD

There were no significant differences between the G/G-PD and G/G-HC groups.

Correlation analysis between the parameter values and clinical indicators of PD

The UPDRS-III scores were negatively correlated with FA values of the bilateral anterior corona radiata, bilateral external capsules, right fornix stria terminalis, splenium of the corpus callosum, and right superior corona radiata. There was a positive correlation between UPDRS-III scores and MD values of the bilateral superior corona radiata and the right superior longitudinal fasciculus, as well as between UPDRS-III scores and RD values of the bilateral anterior corona radiata, bilateral anterior limb of the internal capsule, bilateral external capsule, splenium of the corpus callosum, and bilateral superior corona radiata.

The MoCA scores were positively correlated with FA values of the bilateral anterior corona radiata, bilateral anterior limb of the internal capsule, body of the corpus callosum, bilateral external capsules, genu of the corpus callosum, and bilateral superior corona radiata. The MoCA scores were negatively correlated with RD values of the anterior limb of the internal capsule, bilateral external capsule, and body of the corpus callosum (*Tables 4-6*, *Figure 5*).

The MoCA scores were positively correlated with FA values of the left posterior corona radiata and the MD value of the right superior corona radiata (*Tables 4-6*).

Discussion

This study evaluated abnormalities in white matter tracts on diffusion-weighted MRI based on TBSS. Compared with the HC group, the PD group had extensive white matter fiber damage in many brain areas on the FA and RD maps. The difference in the MD map involved a smaller brain area. These findings are similar to those reported previously (9,14,24,25). Extensive areas of white matter fiber damage were found in the PD group, which may contribute to the diversity of PD clinical symptoms. Although ANOVA did not reveal a significant interaction between genotype and disease status, multiple comparisons revealed that there may be more pronounced damage in the G/A than in the G/G group. Similarly, there was serious damage in the G/A-PD compared with the G/G-PD group. However, there were no significant differences identified between the GG/HC and GG/PD groups. This suggests that the G/A polymorphism can cause more serious white matter fiber damage.

Some *parkin* mutations lead to the production of an abnormally small and non-functional parkin protein and cause functional defects of the parkin protein (5,26,27). The

Table 4 Clinical correlations of fractional anisotropy with white matter changes

Anatomical region	H-Y		UPDRS-III		MoCA		MMSE	
	r	P value	r	P value	r	P value	r	P value
Anterior corona radiata L	–0.107	0.603	–0.643	0.000	0.560	0.011	0.172	0.4
Anterior corona radiata R	–0.154	0.453	–0.538	0.013	0.456	0.022	–0.001	0.997
Anterior limb of internal capsule L	–0.281	0.164	–0.328	0.102	0.546	0.011	0.012	0.954
Anterior limb of internal capsule R	–0.323	0.107	–0.282	0.162	0.498	0.018	–0.09	0.66
Body of the corpus callosum	–0.269	0.183	–0.213	0.296	0.537	0.011	0.159	0.439
External capsule L	–0.083	0.686	–0.408	0.036	0.466	0.021	–0.133	0.518
External capsule R	–0.124	0.545	–0.410	0.036	0.481	0.02	–0.132	0.519
Fornix stria terminalis L	–0.151	0.462	–0.188	0.359	0.193	0.346	0.103	0.617
Fornix stria terminalis R	–0.247	0.224	–0.412	0.036	0.294	0.145	–0.071	0.729
Genu of the corpus callosum	–0.304	0.131	–0.251	0.216	0.531	0.011	0.108	0.599
Posterior corona radiata L	–0.022	0.915	–0.036	0.862	0.09	0.663	0.420	0.032
Posterior corona radiata R	–0.244	0.23	–0.204	0.319	0.204	0.318	–0.386	0.052
Posterior thalamic radiation R	–0.323	0.107	–0.321	0.109	0.331	0.098	–0.132	0.521
Retrolenticular part of internal capsule L	–0.257	0.206	–0.108	0.599	0.047	0.82	–0.275	0.174
Retrolenticular part of internal capsule R	–0.262	0.197	–0.284	0.16	0.25	0.218	–0.12	0.559
Splenium of the corpus callosum	–0.173	0.397	–0.391	0.036	0.326	0.104	–0.041	0.841
Superior corona radiata L	–0.181	0.375	–0.361	0.07	0.594	0.011	0.094	0.648
Superior corona radiata R	–0.204	0.319	–0.397	0.036	0.415	0.037	–0.086	0.677
Superior longitudinal fasciculus L	0.031	0.881	–0.249	0.22	0.21	0.304	–0.283	0.162

H-Y, Hoehn-Yahr Stage scale; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; R, right; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Table 5 Clinical correlations of mean diffusivity with white matter changes

Anatomical region	H-Y		UPDRS-III		MoCA		MMSE	
	r	P value	r	P value	r	P value	r	P value
Posterior corona radiata L	0.08	0.697	0.228	0.262	–0.033	0.875	0.278	0.169
Posterior corona radiata R	–0.059	0.776	0.382	0.054	–0.124	0.545	0.295	0.144
Posterior thalamic radiation R	–0.067	0.744	0.327	0.103	–0.117	0.57	0.241	0.235
Superior corona radiata L	0.129	0.528	0.544	0.013	0.1	0.626	0.343	0.086
Superior corona radiata R	0.026	0.899	0.447	0.023	–0.059	0.774	0.430	0.028
Superior longitudinal fasciculus R	–0.116	0.574	0.500	0.014	–0.104	0.612	0.376	0.058

H-Y, Hoehn-Yahr Stage scale; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; R, right; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Table 6 Clinical correlations of radial diffusivity with white matter changes

Anatomical region	H-Y		UPDRS-III		MoCA		MMSE	
	r	P value	r	P value	r	P value	r	P value
Anterior corona radiata L	–0.063	0.759	0.667	0.004	–0.377	0.058	0.171	0.404
Anterior corona radiata R	0.097	0.639	0.517	0.004	–0.510	0.008	0.121	0.557
Anterior limb of the internal capsule L	0.078	0.704	0.401	0.015	–0.452	0.021	0.09	0.663
Anterior limb of the internal capsule R	0.106	0.606	0.364	0.068	–0.438	0.025	–0.084	0.683
Body of the corpus callosum	–0.028	0.893	0.504	0.005	–0.457	0.019	0.263	0.195
External capsule L	0.045	0.827	0.522	0.004	–0.473	0.015	0.236	0.245
External capsule R	0.063	0.759	0.323	0.107	–0.236	0.246	0.025	0.902
Fornix stria terminalis L	0.143	0.486	0.299	0.138	–0.448	0.022	–0.047	0.821
Genu of the corpus callosum	–0.056	0.785	0.244	0.229	–0.036	0.862	0.377	0.058
Posterior corona radiata L	0.03	0.884	0.343	0.086	–0.152	0.458	0.334	0.095
Posterior corona radiata R	0.023	0.909	0.388	0.016	0.006	0.976	0.183	0.37
Posterior thalamic radiation L	0.198	0.333	0.359	0.072	–0.228	0.262	0.141	0.491
Posterior thalamic radiation R	0.181	0.377	0.176	0.391	–0.115	0.575	0.382	0.054
Retrolenticular part of the internal capsule L	0.091	0.658	0.311	0.122	–0.226	0.268	0.191	0.351
Retrolenticular part of the internal capsule R	0.109	0.598	0.399	0.015	–0.283	0.161	0.038	0.854
Sagittal stratum L	0.089	0.664	0.561	0.004	–0.273	0.177	0.241	0.236
Splenium of the corpus callosum	0.054	0.793	0.535	0.004	–0.258	0.203	0.298	0.139
Superior corona radiata L	–0.125	0.544	0.383	0.054	–0.159	0.438	–0.052	0.8
Superior corona radiata R	–0.118	0.565	0.341	0.089	–0.024	0.909	0.116	0.574
Superior fronto-occipital fasciculus L	–0.054	0.795	0.460	0.008	–0.088	0.669	0.374	0.06

H-Y, Hoehn-Yahr Stage scale; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; R, right; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

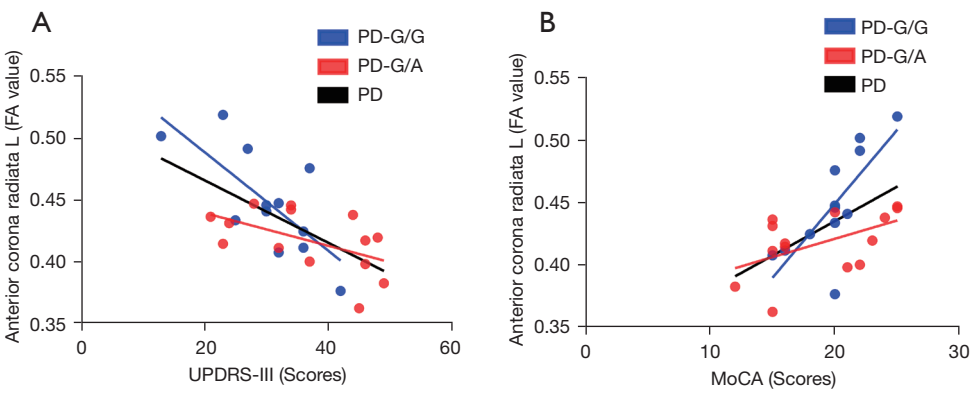

Figure 5 Correlation between FA values of the anterior corona radiata left and (A) UPDRS-III and (B) MoCA scores. FA, fractional anisotropy; PD, Parkinson's disease; G/G, patients without parkin gene S/N167 mutations; G/A, patients carrying parkin gene S/N167 mutations; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; MoCA, Montreal Cognitive Assessment.

parkin protein may function similarly to ubiquitin family members, and defects in the parkin protein in autosomal recessive juvenile parkinsonism may interfere with the ubiquitin-mediated proteolytic pathway leading to the death of neurons in the nigra (28). This causes intracellular protein metabolism disorders, the accumulation of toxic substrates, and ultimately cell death, or disrupts normal cell activities, such as the synthesis and release of dopamine synaptic vesicles. Therefore, the *parkin* S/N167 polymorphism may disrupt expression of the parkin protein, leading to the onset of PD and affecting the clinical symptoms of PD. To a certain extent, we can speculate that this genetic polymorphism can increase the risk of PD onset and affect disease progression (5).

No significant differences were found between the G/G-PD and the G/G-HC groups. This may be due to the milder damage to the white matter tracts in the G/G-PD group. However, it may also be due to the small sample size of the two groups. Based on FA maps, compared with the G/A-HC group, the G/A-PD group had more severe damage in the left brain. This may be related to the laterality of PD, with the left cerebral hemisphere, which is more closely related to primary brain networks such as movement and sensory networks, being the predominantly affected hemisphere. Then, the occurrence of clinical symptoms is more strongly related to the degree of damage in the left cerebral hemisphere (29).

The UPDRS-III and MoCA scores of the PD group were significantly correlated with FA, MD, and RD values of the white matter fibers in multiple, significantly different brain regions compared with the HC group. The white matter fibers related to cognitive function include the corpus callosum and peduncles, the anterior, superior, and posterior corona radiatas, and the external capsule. Those related to movement are the corpus callosum and compression, anterior and superior corona radiata, external capsule, forelimb of the internal capsule, and superior longitudinal tract.

Sisti *et al.* (25) found that cognitive decline is not only related to lesions in local brain regions, but may also be related to the destruction of white matter fibers and impaired connection function associated with these brain regions. Information transfer between two regions is transformed, and this plays an important role in the formation and retrieval of memories, as well as in the process of cognition (22,30). It is also related to cognitive impairment, such as in affective disorder and executive function (18).

The corona radiata connects the internal capsule and the ipsilateral cerebral cortex, including the premotor area, the motor center, and the sensory center. There is also a close connection between the corona radiata and cognitive function (31). The anterior corona radiata is connected to the prefrontal lobe and affects cognitive function through the prefrontal lobe–basal ganglia loop. Researchers have found that white matter lesions play an important role in cognitive decline (19,32,33). Patients with PD who have white matter lesions have a higher risk of developing cognitive dysfunction, and the severity of destruction of brain white matter fiber integrity is closely related to the severity of cognitive dysfunction in PD patients (34). The anterior limb of the internal capsule is related to the connection function of the thalamus, pons, and frontal lobe, and is closely associated with the functions of cognitive processing, emotion, and motivational decision-making (35). The external capsule is mainly comprised of cortical tegmental fibers and cortical striatal fibers that are sent from the insula to the midbrain and hypothalamus (24). The impaired mobility of PD patients is related to a decline in their ability to perceive the outside world (36). Through a series of complex brain network connections, external capsule lesions can affect cognitive function and movement ability through functional connections of striatal or visual pathways. Some studies have found that the fibers connecting the temporal and occipital lobes, such as the superior longitudinal fasciculus, are also related to decreased exercise capacity and impairments in goal-oriented behavior (24,37,38). A study on freezing gait (39) found that it is related not only to damage to motor fibers, such as the corticospinal tract and cerebrum, but also to damage to the superior longitudinal tract.

A mouse PD model showed that after 1-methyl-4-phenyl 1-1,2,3,6-tetrahydropyridine (MPTP) intoxication, cell loss in brain regions involved in pathology reflects reduced FA in white matter projections in these regions (40). The decrease in FA indicates the loss of white matter integrity due to the destruction of the directed axonal membrane, whereas the increase in MD reflects the reduced membrane density that hinders diffusion (15).

In the present study, TBSS analysis revealed that the white matter fibers of many brain areas related to movement and cognition in PD patients were damaged. The FA map revealed lower FA values in many white matter brain areas in the PD-G/A group, suggesting that PD patients with point mutations in the *parkin* S/N167 gene (G/A) have more severe brain white matter fiber damage,

which may indicate disruption of white matter fibers that, in turn, affects fiber connectivity, causing motor function and cognitive dysfunction.

Limitations

This study had some limitations. First, this was a single-center study, and all participants were Asian. Future multicenter, multi-ethnic cohort studies are needed to reduce bias due to case inclusion. Second, there is the potential for paradoxically significant results to emerge after splitting the dataset in multiple ways. Finally, this study was a cross-sectional study with a small sample size; a prolonged cohort study is needed to further explore the relevant effects of *parkin* S/N167 gene mutations.

Conclusions

There were more extensive brain white matter fiber damage and changes in PD patients compared with HCs, with the G/A polymorphism being associated with more extensive brain white matter damage. This study may provide more imaging information to reveal the etiology and pathogenesis of PD gene mutations. More longitudinal clinical studies are needed in the future to confirm our findings.

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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-21-1007/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1007/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of Fujian Medical University Union Hospital and all participants provided written informed consent.

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