Substantia nigra hyperechogenicity in Parkinson disease patients with leucine-rich repeat kinase 2 variants in the Chinese Han population

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To the Editor: Parkinson disease (PD) is the second most common neurodegenerative disease, and is characterized by both motor and non-motor symptoms. The leucine-rich repeat kinase 2 (*LRRK2*) gene, characterized by different mutations among different populations, is well-known in both familial and sporadic PD. The frequency of the G2019S mutation is 20% to 40% in the Ashkenazi Jewish and North African Arab populations, while G2385R is a common risk factor associated with Asian populations. Research teams have found that G2385R is also associated with PD in the Chinese Han population, suggesting a clear contribution of this mutation to the Han population, but descriptions of clinical PD symptoms in the Chinese Han population are rare and warrant further G2385R genotype-phenotype analyses. Substantia nigra (SN) hyperechogenicity was determined by transcranial sonography (TCS) in PD patients. It is a risk marker for PD, and associated with altered microstructural changes in white matter, including those areas relevant for motor and limbic function. Previous studies of *LRRK2* variants, especially the G2019S mutation, have explored potential associations between Caucasian *LRRK2* variants and SN hyperechogenicity,[1-3] but few have addressed Asian populations. Here, we used TCS imaging to compare features of Han Chinese PD patients with and without *LRRK2* variants.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (No. JD-LK-2018-061-01). All participants provided written informed consent. Clinical evaluations, genetic analyses, and TCS methods were as previously described.[4,5] After exclusions for inadequate TCS bone windows, 198 patients were enrolled from November 2016 to September 2018. We assessed right and left SN areas, and midbrain area. Largest SN area (SNmax), total SN area (total SN), and the quotient of total SN/midbrain area (S/M) were determined. The width of the third ventricle (WTV) was also determined. An echogenic area ≥ 0.20 cm^2 was used to determine SN hyperechogenicity (SN+), echogenicity of brainstem raphe nuclei was rated as reduced when they were interrupted or not visible, and echogenicity of the lenticular nucleus was classified as hyperechogenic if it was more intense than that of the surrounding white matter [Supplementary Figure 1, http://links.lww.com/CM9/A229]. Statistical analyses were performed using SPSS software version 17.0 (Chicago, IL, USA). Data are presented as either mean ± standard deviations or frequencies (percentages). We used the Shapiro-Wilk test to determine normal data distribution. Categorical variables were analyzed using the Chi-squared test or Fisher exact test, while the Mann-Whitney *U* test or Student's *t* tests were used for continuous variables. All *P* values were two-sided, and values <0.05 were considered statistically significant.

Of the 198 PD patients included in the analysis, 12 had rare *LRRK2*-PD mutations and 37 had common mutations. For the common group, 32 were G2385R-PD and five were R1628P-PD. The *LRRK2*-PD, common *LRRK2*-PD, and G2385R-PD groups showed similar gender compositions, ages, ages at onset, courses of disease, and Unified Parkinson Disease Rating Scale III scores compared to the idiopathic PD (IPD) group ($P > 0.05$) [Table 1]. For TCS imaging, group mean SNmax areas were 0.45 ± 0.20 cm^2 for *LRRK2*-PD, 0.44 ± 0.20 cm^2 for common *LRRK2*-PD, 0.45 ± 0.20 cm^2 for G2385R-PD, and 0.43 ± 0.17 cm^2 for IPD. Prevalence of SN+ was 63.3%, 59.5%, 59.4%, and 50.3% among the same four groups, respectively. There were no significant differences between *LRRK2*-PD and IPD groups, Common *LRRK2*-PD and

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Table 1: Ecographic features in *LRRK2*-PD, common *LRRK2*-PD, G2385R-PD, and IPD in 198 patients with Parkinson disease.

Items	*LRRK2*-PD ($n = 49$)	Common *LRRK2*-PD ($n = 37$)	G2385R-PD ($n = 32$)	IPD ($n = 149$)	*P*	*P1*	*P2*
Sex, female/male	17/32	14/23	13/19	56/93	0.737‡	1.000‡	0.841‡
Age (years)	63.98 ± 7.04	63.57 ± 7.50	63.47 ± 7.32	62.08 ± 8.73	0.250†	0.420†	0.562†
AAO (years)	59.55 ± 7.17	59.53 ± 7.23	59.56 ± 7.26	57.57 ± 9.18	0.170*	0.329*	0.258*
Duration (years)	4.49 ± 3.30	4.03 ± 3.26	4.02 ± 3.27	4.45 ± 3.81	0.430†	0.566†	0.919†
UPDRS III score	27.69 ± 11.18	26.16 ± 12.06	26.03 ± 11.99	24.97 ± 12.22	0.080†	0.351†	0.522†
Right SN (cm^2)	0.36 ± 0.16	0.39 ± 0.18	0.37 ± 0.18	0.38 ± 0.18	0.675†	0.895†	0.833†
Left SN (cm^2)	0.43 ± 0.20	0.41 ± 0.20	0.41 ± 0.20	0.42 ± 0.14	0.859†	0.506†	0.445†
SNmax (cm^2)	0.45 ± 0.20	0.44 ± 0.20	0.45 ± 0.20	0.43 ± 0.17	0.737*	0.935*	0.819*
Total SN (cm^2)	0.58 ± 0.29	0.59 ± 0.33	0.62 ± 0.33	0.63 ± 0.32	0.602†	0.366†	0.597†
Midbrain (cm^2)	4.83 ± 0.66	4.85 ± 0.79	4.85 ± 0.79	4.70 ± 0.87	0.407†	0.324†	0.499†
S/M (%)	12.47 ± 6.46	12.31 ± 7.19	12.31 ± 7.19	13.33 ± 6.96	0.755†	0.336†	0.589†
SN+	31 (63.3)	22 (59.5)	19 (59.4)	75 (50.3)	0.103‡	0.359‡	0.337‡
HBR, *n* (%)	5 (10.2)	5 (13.5)	4 (12.5)	13 (8.7)	0.777‡	0.362‡	0.508§
WTV (mm)	5.89 ± 4.06	4.82 ± 1.71	4.82 ± 1.71	5.37 ± 1.96	0.874†	0.453†	0.145†
LLH, *n* (%)	4 (8.2)	2 (5.4)	2 (6.3)	8 (5.4)	0.496§	1.000§	0.691§
RLH, *n* (%)	3 (6.1)	2 (5.4)	2 (6.3)	9 (6.0)	1.000§	1.000§	1.000§

Values were shown as mean ± standard deviation or frequencies (percentages). For *P* values: *P*: LRRK2-PD *vs*. IPD; *P1*: common LRRK2-PD *vs*. IPD; *P2*: G2385R-PD *vs*. IPD. * Student *t* test. † Mann-Whitney *U* test. ‡ Chi-squared test. § Fisher exact test. LRRK2-PD: Parkinson disease with LRRK2 variants; common LRRK2-PD: Parkinson disease with common LRRK2 variants; G2385R-PD: Parkinson disease with G2385R variant; IPD: Idiopathic Parkinson disease; AAO: Age at onset; UPDRS III: Unified Parkinson Disease Rating Scale III; SN: Substantia nigra; SNmax: The larger area of SN; S/M: Total SN/midbrain; SN+: SN hyperechogenicity; HBR: Hypoechogenicity of the brainstem raphe; WTV: The width of third ventricle; LLH: Left lentiform hyperechogenicity; RLH: Right lentiform hyperechogenicity.

IPD groups, and G2385R-PD and IPD groups for TCS parameters, including right SN, left SN, total SN, midbrain, S/M, SN+, hypoechogenicity of the brainstem raphe nuclei, WTV, left lentiform hyperechogenicity, and right lentiform hyperechogenicity.

This study focused on TCS features of Han Chinese PD patients carrying *LRRK2* variants, especially the G2385R variant. All data, including SN hyperechogenicity frequencies, SN areas, SNmax areas, and total SN areas were indistinguishable between *LRRK2*-PD and IPD groups, common *LRRK2*-PD and IPD groups, and G2385R-PD and IPD groups. This is consistent with previous studies in other populations. For example, Brüggemann *et al*[1] used TCS assessment in 62 PD patients of Ashkenazi descent and found that patients with the *LRRK2* G2019S mutation were not different from IPD patients in terms of right SN, left SN, and SNmax values. Similarly, Sierra *et al*,[2] who used TCS assessment in 79 PD patients from Northern Spain, also found that G2019S-PD patients were not different from IPD patients in terms of SNmax, a finding that was later confirmed in 57 more Spanish PD patients.[3] SN echogenicity is thought to be a non-invasive imaging marker for PD, but we failed to find any associations between TCS imaging and *LRRK2*-PD data. Together with previous studies that addressed associations between *LRRK2*-PD and TCS, our data suggest limited or no associations between *LRRK2* variants and TCS features in PD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient-consent forms. In those forms, patients gave their consent for their images and other clinical information to be reported in the journal. The patients understood that their names and initials would not be published and due efforts would be made to conceal their identities, but anonymity could not be guaranteed.

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Conflicts of interest

None.

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