Neuromelanin Magnetic Resonance Imaging of the Substantia Nigra in *LRRK2*-Related Parkinson's Disease

Specific T_1-weighted MRI sequences are able to detect SN neuromelanin (NM) signal changes and accurately discriminate Parkinson's disease (PD) patients from controls.[1,2]

The study of NM-MRI in PD patients carrying a *LRRK2* gene mutation (*LRRK2*-PD) could contribute to further uncover *LRRK2*-associated phenotype. Albeit considered to largely overlap idiopathic PD (iPD),[3] differences have been described.[4] Furthermore, the identification of a biomarker of

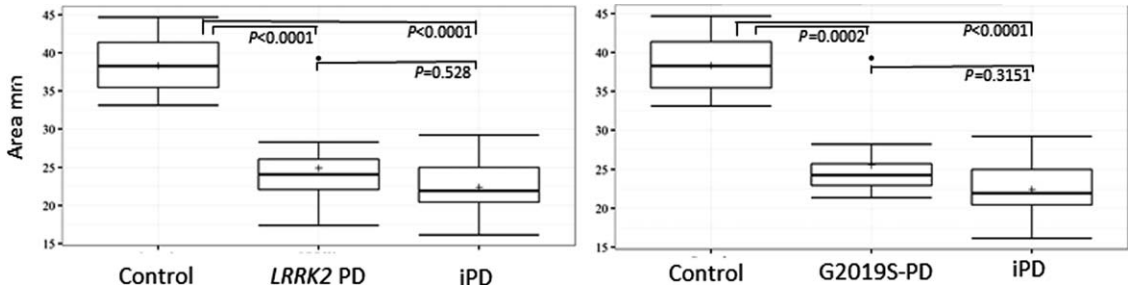

FIG. 1. Area of the SN in LRRK2-PD, G2019S-PD, iPD and control individuals. *LRRK2*-PD: all PD patients carrying a *LRRK2* mutation (G2019S and R1441H); G2019S-PD: PD patients carrying a G2019S mutation.

neurodegeneration in *LRRK2*-PD can eventually support studies in asymptomatic carriers. Castellanos and colleagues[5] found NM-MRI SN volumes significantly reduced in both idiopathic and *LRRK2*-PD (3 G2019S and 4 R1441G PD patients).

Our study aimed to further investigate neuromelanin imaging in *LRRK2*-PD. We performed a cross-sectional study including *LRRK2*-PD patients, control individuals with no signs or family history of a neurodegenerative disorder, and PD patients with no *LRRK2* mutations identified (referred as iPD). Our primary outcome was SN neuromelanin high signal area obtained with semiautomated methods.

LRRK2-PD and iPD patients were identified through previous[6] and recent genetic studies. Clinical assessments were performed in best *On*. Imaging was acquired using a 3.0 Tesla scanner and NM-sensitive pulse sequence was used as previously described.[1] OsiriX software[7] was used for imaging postprocessing. Data analysis was blinded to clinical and genetic status. Kruskal-Wallis, with pair-wise comparisons (Bonferroni method applied), and Mann-Whitney U tests were used as appropriate ($P < 0.05$). Nonparametric receiver operating characteristic curves were constructed for calculating NM imaging area sensitivity and specificity for discriminating groups.

Thirteen *LRRK2*-PD patients (10 G2019S, 3 R1441H), 10 controls, and 13 iPD patients were included. No significant differences between groups were identified concerning sex, age at disease onset (59.7 ± 12.3 *LRRK2*-PD vs. 61.8 ± 11.8 iPD), disease duration (7.7 ± 3.5 *LRRK2*-PD vs. 10.7 ± 4.3 iPD), MDS-UPDRS I, III (36.8 ± 13.0 *LRRK2*-PD; 41.2 ± 16.2 iPD), and IV scores, or levodopa equivalent daily dose. Mean age at examination in *LRRK2*-PD (67.4 ± 12.9), control (61.2 ± 7.4), and iPD (72.5 ± 12.7) groups were different. Although when comparing *LRRK2*-PD versus controls ($P = 0.1640$) and *LRRK2*-PD versus iPD ($P = 0.3220$) mean age at examination was not statistically significantly different, iPD group presented a significantly higher mean age at examination when compared to controls ($P = 0.0211$), limiting results interpretation. The H & Y (2.0 ± 0.1 *LRRK2*-PD vs. 3.0 ± 0.9 iPD) and MDS-UPDRS II scores were significantly worse in iPD.

Median SN NM area was significantly decreased in the *LRRK2*-PD group compared to controls (Fig. 1). Furthermore, when only considering G2019S *LRRK2*-PD, median SN NM signal area was also significantly decreased compared to controls. No differences were found between *LRRK2*-PD and iPD groups. High signal area showed 92.3% sensitivity and 100% specificity for discriminating *LRRK2*-PD patients from controls (cut off: 28.24 mm^2).

In our study, NM-MR imaging of the SN was able to differentiate *LRRK2*-PD patients from controls, and NM signal area reductions in *LRRK2*-PD and iPD groups did not show statistically significant differences. Our results present the most extensive data on NM-MRI in *LRRK2*-related PD and support NM imaging as a potential biomarker of SN degeneration in *LRRK2*-related PD. ■

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