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Increased Substantia Nigra Echogenicity in *LRRK2* Family Members Without Mutations

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Among Parkinson's disease (PD) cases with a genetic etiology (such as mutations in leucine-rich repeating kinase [*LRRK2*]), additional genetic or environmental factors likely influence penetrance and expression. Recently, it was shown that genetic PD cases are twice as likely as controls to demonstrate additional rare variants in Mendelian PD genes.¹ In *LRRK2* PD, there is heterogeneity of neuropathology and incomplete penetrance among G2019S mutation carriers. Further, there are "phenocopies," PD cases in non-mutation-carrying family members (NCFs) of *LRRK2* families.² We postulate that if additional factors influence the development of PD, these would also affect NCFs of genetic PD patients, and these individuals would have biomarkers suggestive of PD-related abnormalities.

One such biomarker is hyperechogenicity of the substantia nigra (SN) on transcranial sonography (TCS). This likely represents iron deposition and is a marker present in PD, PD gene carriers without PD, and a small percentage of controls.³ We previously reported on TCS in *LRRK2* G2019S PD and their family members; however, NCFs were not included.⁴ Here we expand on that study by reporting additional PD, non-manifesting carriers (NMCs) and controls and adding an NCF group.

We examined TCS in 82 idiopathic PD (IPD) patients, 58 PD patients with G2019S *LRRK2* mutations (*LRRK2* PD), 46 non-PD family members with G2019S mutations (NMCs), 23

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NCFs, and 113 unrelated controls. TCS acquisition, rating, and analysis were as previously described, with raters blinded to genetic status.⁴ Clinical characteristics and echogenicity among groups are summarized in Figure 1. Controls were younger than *LRRK2*PD and IPD patients; NMCs were younger than IPD patients. Hyperechogenicity among groups was compared using linear mixed-effects models to account for possible correlations among members of the same family, adjusting for age and sex. NCFs demonstrated larger areas of hyperechogenicity (aSNmax) than controls ($P = 0.003$), but did not differ from NMCs, *LRRK2*PD patients, or IPD patients (for additional results, see Fig. 1). The proportion of subjects with pathologic SN hyperechogenicity (area > 0.25 cm²) was also examined. NCFs were significantly more likely to show pathologic hyperechogenicity compared with controls (56.52% vs 24.78%; OR, 4.86; 95% CI, 1.86–12.67).

These results strengthen the findings of a prior *LRRK2* study that showed a higher proportion of NCFs with pathologic hyperechogenicity versus controls,⁵ and ours is the first to also show larger areas of substantia nigra hyperechogenicity (aSNmax) in NCFs, as measured continuously. This study builds on previous findings of increased hyperechogenicity in NCFs versus controls in *PINK1* families⁶ and worse olfaction scores in NCFs versus controls in a *LRRK2* study.⁷ Abnormal biomarkers in NCFs suggest that non-*LRRK2* factors contribute to pathology and raise the question of the optimal control group for *LRRK2* family studies. If the study goal is solely to detect *LRRK2*-specific effects, comparison between NMCs and NCFs is warranted. If it is to capture any biomarker in *LRRK2*PD families, evaluation of NMCs versus unrelated controls may be suggested. Further, evaluating NCFs relative to controls could be key to identifying additional oligogenic or environmental factors separate from *LRRK2*, which may be important for understanding idiopathic PD as well.

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FIG. 1.

Clinical characteristics and echogenicity. NCFs, non-carrier family members; NMCs, non-manifesting G2019S carriers; *LRRK2* PD, PD with G2019S *LRRK2* mutations; IPD, idiopathic PD; aSNMax, maximum area (right or left side) of substantia nigra hyperechogenicity. All continuous-variable results reported as mean (SD). Superscripts denote significant differences from the superscripted group ($P < 0.05$) in the linear mixed-effects model. Twenty-eight IPD, 32 *LRRK2* PD, 15 NMC, and 40 controls were included in the original study.⁴ Three hundred fifteen of the total 325 subjects had sufficient data to be included in the model. *Age at onset, disease duration available for 67 IPD, 55 *LRRK2* PD.