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Genetic and Clinical Predictors of Deep Brain Stimulation in Young-Onset Parkinson's Disease

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Abstract

Objective—In a cohort of patients with young-onset Parkinson's disease (PD), the authors assessed (1) the prevalence of genetic mutations in those who enrolled in deep brain stimulation (DBS) programs compared with those who did not enroll DBS programs and (2) specific genetic and clinical predictors of DBS enrollment.

Methods—Subjects were participants from 3 sites (Columbia University, Rush University, and the University of Pennsylvania) in the Consortium on Risk for Early Onset Parkinson's Disease (CORE-PD) who had an age at onset < 51 years. The analyses presented here focus on *glucocerebrosidase* (*GBA*), *leucine-rich repeat kinase 2* (*LRRK2*), and *parkin* (*PRKN*) mutation carriers. Mutation carrier status, demographic data, and disease characteristics in individuals who did and did not enroll in DBS were analyzed. The association between mutation status and DBS placement was assessed in logistic regression models.

Results—Patients who had PD with either *GBA*, *LRRK2*, or *PRKN* mutations were more common in the DBS group (n = 99) compared with the non-DBS group (n = 684; 26.5% vs. 16.8%, respectively; $P = 0.02$). In a multivariate logistic regression model, *GBA* mutation status (odds ratio, 2.1; 95% confidence interval, 1.0–4.3; $P = 0.05$) was associated with DBS surgery enrollment. However, when dyskinesia was included in the multivariate logistic regression model, dyskinesia had a strong association with DBS placement (odds ratio, 3.8; 95% confidence interval, 1.9–7.3; $P < 0.0001$), whereas the association between GBA mutation status and DBS placement did not persist ($P = 0.25$).

Conclusions—DBS populations are enriched with genetic mutation carriers. The effect of genetic mutation carriers on DBS outcomes warrants further exploration.

Keywords

Parkinson's disease; glucocerebrosidase (*GBA*); leucine-rich repeat kinase 2 (*LRRK2*); parkin (*PRKN*); deep brain stimulation (DBS)

Each year, approximately 9,000 patients with Parkinson's disease (PD) in the United States electively undergo deep brain stimulator placement with the goal of improving their motor symptoms.[1] Up to 29% of patients who have PD and receive deep brain stimulation (DBS) have a mutation in 1 of 3 genes: *glucocerebrosidase* (*GBA*), *leucine-rich repeat kinase 2* (*LRRK2*), and *parkin* (*PRKN*).[2] The reason for this may be that patients with PD who receive DBS tend to have a younger age at onset (AAO) than the general PD population, which leads to an over-representation of genetic forms of PD in this population.[2] Specific mutations, like those in *GBA*, may be associated with more rapid disease progression[3]; whereas other mutations, like those in *LRRK2*, may be associated with slower disease progression.[4] However, it is unknown whether specific mutations influence the need for DBS, especially in young patients.

The Consortium on Risk for Early Onset Parkinson's Disease (CORE-PD)[5,6] recruited 1136 participants with early onset PD, defined as an AAO < 51 years, from 17 sites. We previously reported the prevalence of *GBA*, *LRRK2*, and *PRKN* mutations in this cohort.[7] The aims of the current study were: (1) to determine the prevalence of *GBA*, *LRRK2*, or

PRKN mutations in patients with PD who receive DBS compared with those who do not receive DBS in the CORE-PD cohort; and (2) to determine which variables were predictors of DBS in the 3 largest sites participating in this study.

Patients and Methods

Details of the CORE-PD study were described in previous reports.[5,8] In brief, patients with PD who were diagnosed by movement disorders specialists were recruited from 17 sites based solely on AAO < 51 years. A blood sample was sent to the National Institute of Neurologic Disorders and Stroke Human Genetics Resource Center DNA and Cell Line Repository (http://ccr.coriell.org) for DNA extraction.

In total, 1136 participants were genotyped for *PRKN*, GBA, *LRRK2*, *phosphatase and tensin homolog-induced putative kinase 1* (*PINK1*), and *DJ-1* (PD protein), as previously described.[7–10] The analyses presented here focus on the most common genetic forms of PD, namely, *GBA*, *LRRK2*, and *PRKN* mutation carriers because 20% of our patients were of Ashkenazi Jewish (AJ) ancestry. The frequency of DBS at individual sites ranged between 0% and 90.9%. To reduce site-specific biases, data from the 3 largest recruiting sites (Columbia University, Rush University, and the University of Pennsylvania) are presented. These sites collectively enrolled 814 patients.

Demographic data and disease characteristics were collected including AAO of PD, age at evaluation, disease duration, AJ ancestry, ethnicity (white, African-American, Hispanic, other), DBS status (at the time of entry into the CORE-PD), age at DBS implantation, duration in years from AAO to DBS, and duration in years from DBS to entry into the CORE-PD. Clinical evaluation included an assessment of the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS-III) in the defined on-medication condition,[11] the Mini-Mental Status Examination (MMSE),[12] and whether patients reported a history of dyskinesia (at the time of entry into the CORE-PD). Only those who had MMSE scores > 24 were enrolled. In the majority of patients who received DBS, UPDRS-III scores reflected postoperative assessments in 82 of 100 (82%).

Mutation carrier status, demographic data, disease characteristics, UPDRS-III scores, and MMSE scores of patients in the DBS and non-DBS groups were compared using the Student t test, the χ^2 test, or the Mann–Whitney test, as appropriate. Within the DBS group, demographic and disease and characteristics of *GBA*, *LRRK2*, and *PRKN* mutation carriers and noncarriers were compared using analysis of variance (ANOVA), the χ^2 test, and the Fisher exact test, as appropriate. A post-hoc Bonferroni procedure was used to perform pair-wise comparisons and identify the source of significance in the ANOVA. For replication purposes, nominal P values < 0.05 were considered statistically significant; and, for novel associations, Bonferroni-corrected P values < (0.05/number of comparisons) were considered statistically significant.

The association between mutation status and DBS placement was assessed in logistic regression models. The association was assessed first in a univariate model and then in a multivariate model, adjusting for site, AJ ancestry, AAO, disease duration (dichotomized,

<15 years and >15 years), UPDRS-III score, and MMSE score. Additional multivariate analyses were performed with the addition of prior history of dyskinesia as a covariate.

Results

There was no significant difference in the frequency of genetic mutation carriers combined in the 3 sites compared with the remaining 14 sites (18.1% vs. 17.5%; $P = 0.38$). Comparisons of the individual genetic mutations in the DBS and non-DBS groups are illustrated in Figure 1. *GBA* mutations were the most common mutations in the DBS and non-DBS groups (12.1% vs. 8.0%, respectively; $P = 0.17$). In the DBS group, 8 patients carried the *GBA* asparagine to serine substitution at position 370 (N370S) variant, and 3 carried the *GBA* leucine to proline substitution at position 444 (L444P) variant. In the non-DBS group, 65% of *GBA* mutations were of the N370s variant (n = 33), and 27% were of the L444P variant (n = 14). When examining mutations in all 3 genes combined, mutation carriers were more prevalent in the DBS group compared with the non-DBS group (26.5% vs. 16.8%, respectively; $P = 0.019$) (Table 1). *GBA*, *LRRK2*, and *PRKN* mutations were each slightly more prevalent in the DBS group than in the non-DBS group, although this difference did not reach statistical significance (Fig. 2).

Demographic and disease characteristics of patients in the DBS and non-DBS groups, including PD AAO, age at baseline evaluation, disease duration, AJ ancestry, ethnicity, UPDRS-III score, MMSE score, and prior history of dyskinesia, are presented in Table 1. Compared with the non-DBS group, patients in the DBS group were significantly older at baseline evaluation (56.7 ± 7.9 years vs. 51.6 ± 9.1 years; $P < 0.0001$) and had longer disease duration (16.5 ± 6.8 years vs. 9.9 ± 7.8 years; $P < 0.001$). A greater proportion of those in the DBS group, compared with the non-DBS group, reported a history of dyskinesia (78% vs. 38%; $P < 0.0001$) and had a higher UPDRS-III score (24.8 ± 13.1 vs. 20.3 ± 11.7; $P = 0.002$).

Demographic and disease characteristics of *GBA*, *LRRK2*, *PRKN* mutation carriers and nonmutation carriers with DBS were compared using ANOVA, χ^2, and Fisher exact tests, as appropriate (Table 2). Those who carried more than 1 mutation were excluded from the analysis (n = 1; a carrier of *GBA* and *LRRK2* mutations). There was a significant difference in the AAO between the groups ($P < 0.0001$). *PRKN* mutation carriers had the youngest AAO, followed by *GBA* mutation carriers, while *LRRK2* carriers had the oldest AAO. There was a significant difference in age at DBS implantation between the individual mutation carrier groups ($P = 0.005$). The largest mean difference in age at DBS implantation was between *PRKN* and *LRRK2* carriers (−13.8 ± 4.4 years; $P = 0.014$). *PRKN* carriers had the youngest age at DBS implantation (47.0 ± 11.5 years), and *LRRK2* carriers were the oldest group to undergo DBS surgery (60.8 ± 9.0 years).

In a univariate logistic regression model, having a mutation in any of these 3 genes was associated with DBS placement (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1–2.9; $P = 0.021$). This association between mutation carrier status and DBS placement persisted when adjusted for site, AJ ancestry, AAO, disease duration, UPDRS-III score, and MMSE score (OR, 1.8; 95% CI, 1.0–3.2; $P = 0.036$). Additional analyses for specific genes showed that *GBA* mutation status (OR, 2.1; 95% CI, 1.0–4.3; $P = 0.05$) and disease duration (OR, 1.1; 95% CI, 1.0–1.1; $P < 0.001$) were the main factors associated with DBS surgery enrollment (Table 3). Thus, *GBA* mutation carriers are 2-fold more likely to be identified in the DBS group and are not more likely to be of AJ ancestry. Regarding disease duration, every year increase in PD duration increases the odds of DBS by a factor of 1.1. We repeated the same multivariate logistic regression model with history of dyskinesia as an additional covariate. Our data regarding dyskinesia were not complete, so the number of subjects included in the analyses was reduced from 690 to 479. In this new model, the association between *GBA* mutation status and DBS placement did not persist ($P = 0.25$), but disease duration (OR, 1.1; 95% CI, 1.0–1.1; $P = 0.001$) and history of dyskinesia (OR, 3.8; 95% CI, 1.9–7.3; $P < 0.0001$) were associated with DBS placement.

Discussion

Our results demonstrate that carriers of mutations in specific genes present with characteristic phenotypes and provide insight into disease progression. In the multivariate logistic regression model, *GBA* mutation carrier status was significantly associated with DBS surgery. The reason for this may be that *GBA* mutations are the most common genetic risk factor for PD.[13] Interestingly, the time from disease onset to DBS was shortest for *GBA* carriers (10.9 ± 6.0 years), which may suggest that *GBA* mutation carriers have a more rapid disease progression compared with other mutation carriers and nonmutation carriers,[14–16] ultimately resulting in *GBA* mutation carriers pursuing DBS earlier. However, the difference in disease duration among *GBA* mutation carriers did not reach statistical significance compared with other groups, which may be due to the small sample size, so additional studies are needed to elucidate this finding. It is important to note that, when prior history of dyskinesia was included as a covariate, the association between *GBA* mutation status and DBS placement did not persist. Instead, a history of dyskinesia was strongly associated with DBS placement. This is not surprising considering that dyskinesia is 1 of the key reasons patients with PD obtain DBS. This highlights the need for additional studies to explore predictors of DBS and the correlation between mutation status and DBS outcomes.

Our results provide additional insight into disease progression based on genotype. We infer that all individuals who received DBS were not significantly cognitively impaired before surgery, because the inclusion criteria at the 3 assessment centers required successful cognitive screening to qualify for surgery and because inclusion criteria for the CORE-PD required an MMSE score of 24. Because *PRKN* mutation carriers had long disease duration at the time of DBS, these data suggest that such mutation carriers may be resistant to cognitive decline. This observation is consistent with recent reports of long-term cognitive outcomes in *PRKN* carriers.[8]

The strength of our study is that we have examined the association between genotype and DBS placement in the largest cohort to date. In these young-onset PD subjects, we documented that the frequency of mutations in 3 genes (*GBA*, *LRRK2*, and *PRKN*), considered collectively, was higher in those who received DBS compared with those who did not. This finding is consistent with a prior study that reported a high prevalence of genetic mutation carriers in the DBS population.[2] It has been hypothesized that, because PD genetic mutation carriers are relatively young in age, respond to dopaminergic therapy, and have motor fluctuations and/or dyskinesia, they are more likely to pursue DBS.[2] Given the high prevalence of PD with mutations in these 3 genes in the DBS population (particularly in those with an AAO < 51 years), large studies are needed to assess whether particular genetic mutations are associated with DBS outcomes. However, our study had some limitations. Because this study was retrospective, we did not have pre-DBS clinical data (such as UPDRS-III scores), which precludes our ability to fully compare the impact of DBS in the different mutation carriers and nonmutation carriers. As such, compared with the non-DBS group, patients in the DBS group had higher UPDRS-III scores, which may be attributed to more advanced disease, but this remains unclear. Although all GBA carriers were initially screened for common mutations and then carriers of any of 10 mutations were subsequently fully sequenced to look for additional mutations,[7] not all patients underwent full sequencing for *GBA* mutations in our study. Sidransky et al.[22] reported that full sequencing of *GBA* can increase the detection rate by up to 50% in the non-AJ population, a group that composed roughly 80% of our cohort. In the DBS group, the prevalence *GBA* mutation in non-AJ patients was 9.5%. Full sequencing of *GBA* may increase this prevalence to as much as 18%. Thus, the prevalence of *GBA* mutation reported here may be an underestimate. Furthermore, our study was limited to the young-onset PD population with an AAO < 51 years. Studies are needed to assess mutation prevalence in subjects with an AAO ≥ 51 years but < 70 years, because DBS is considered in individuals up to age 75 years.[21,23] Also, only patients with MMSE scores > 24 were included in the study; thus, it is possible that mutation carriers who developed dementia after DBS were missed in our cohort. A prospective study is needed to capture the prevalence of mutation carriers in the DBS candidate population and the impact of DBS in these individuals. Finally, there was a wide range in the frequency of DBS surgeries based on site, which may also be due to the retrospective nature of the study and to site-specific practices regarding DBS. We tried to limit this site-specific bias by selecting only the 3 largest recruiting sites from the CORE-PD cohort.

Because there is increasing emphasis on performing DBS earlier in the course of PD, the enrichment of genetic forms of PD may increase, because patients will be younger, underscoring the urgent need to define the safety and efficacy of DBS in mutation carriers. Subjects in the EARLYSTIM trial had a mean age at DBS of 52 years,[24] which is comparable to the age at DBS implantation in the *GBA* and *LRRK2* groups in our cohort. *GBA* carriers are vulnerable to cognitive decline,[13,17,19] and variants such as N370S are specifically associated with cognitive impairment.[20,25] The N370S variant was the most common *GBA* mutation identified in our cohort, regardless of DBS status. Thus, whether these patients have different cognitive outcomes after DBS based on the target (subthalamic nucleus vs. globus pallidus interna) remains to be explored[18]. There also are implications regarding DBS implantation in *LRRK2* and *PRKN* carriers. Because these patients remain relatively cognitively intact despite long disease duration, they may have a longer window of opportunity regarding DBS and early implantation may not be critical. Our long-term research goal is to define the best groups for DBS, and these genetic studies offer the potential to define candidates with a high likelihood of success and those at higher risk for long-term decline.

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Appendix. Consortium on Risk for Early Onset Parkinson's Disease (CORE-PD) Investigators

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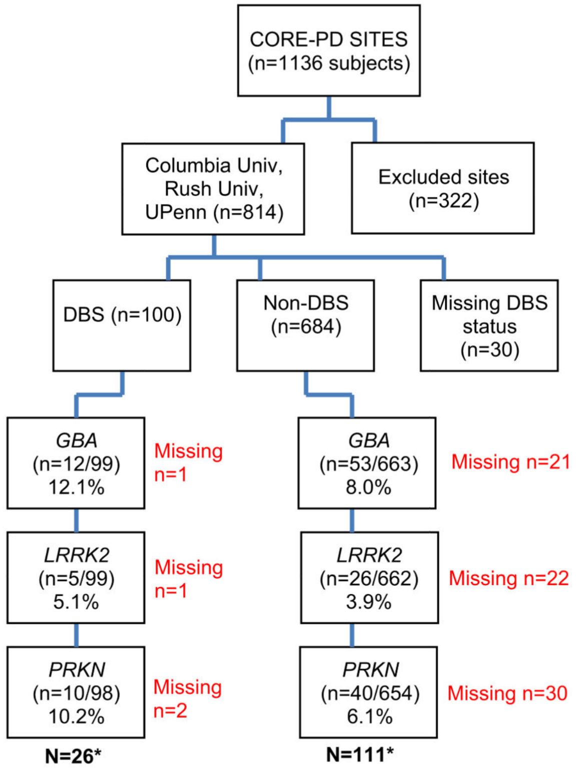

Figure 1.

Consortium on Risk for Early Onset Parkinson's Disease (CORE-PD) enrollment and frequency of mutation carriers in the deep brain stimulation (DBS) and non-DBS groups. *GBA*, glucocerebrosidase; *LRRK2*, leucine-rich repeat kinase 2 (all individuals with *LRRK2* had the glycine-to-serine mutation at codon 2019 [G2019S]); *PRKN*, parkin. Asterisks indicate values that reflect the total number of unique subjects with mutations.

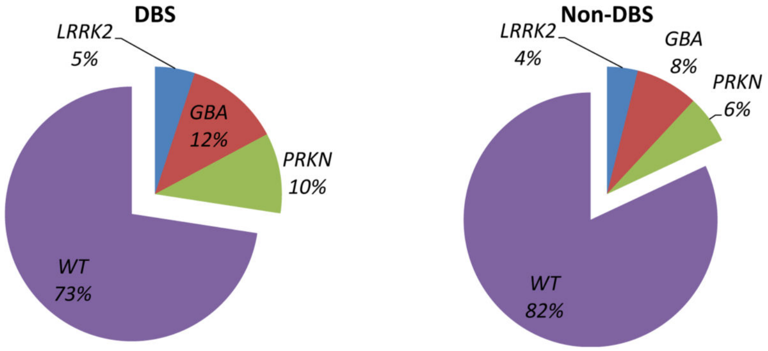

Figure 2.

Frequency of mutation carriers in the deep brain stimulation (DBS) and non-DBS groups. *LRRK2*, leucine-rich repeat kinase 2; *GBA*, glucocerebrosidase; *PRKN*, parkin; WT, wild-type (*GBA*: DBS vs. non-DBS, $P = 0.26$; *LRRK2*: DBS vs. non-DBS, $P = 0.58$; PRKN: DBS vs. non-DBS, $P = 0.13$).

Table 1

Demographic and Disease Characteristics of Subjects with and Without Deep Brain Stimulation. Values reported are mean ± SD

Variable	DBS Group (n = 100)	Non-DBS Group (n = 684)	*P*
Age of onset	40.3 ± 7.1	41.7 ± 6.9	0.06
Age at baseline evaluation	56.7 ± 7.9	51.6 ± 9.1	<0.0001
Disease duration, y	16.5 ± 6.8	9.9 ± 7.8	<0.0001
AJ ancestry, % of subjects	15.0	15.8	0.81
Ethnicity, %[a]			
White	83.0	82.0	0.51
African-American	0.0	15.0	
Hispanic	13.0	12.3	
Other	4.0	3.51	
UPDRS-III[b]	24.8 13.1	20.3 11.7	0.002
MMSE[c]	28.8 ± 1.9	28.9 ± 2.1	0.22
Prior history of dyskinesia, % of subjects[d]	78.3	37.9	<0.0001
Prevalence of mutation carriers, %[e]	26.5	16.8	0.019

[a] Non-DBS, n = 683.

[b] DBS, n = 89; non-DBS, n = 641.

[c] DBS, n = 97; non-DBS, n = 664.

[d] DBS, n = 83; non-DBS, n = 475.

[e] DBS, n = 98; non-DBS, n = 661.

SD, standard deviation; DBS, deep brain stimulation; AJ, Ashkenazi Jewish; MMSE, Mini Mental Status Examination; UPDRS-III, the motor subsection of the Unified Parkinson's Disease Rating Scale.

Table 2

Demographic and Disease Characteristics of Subjects with Deep Brain Stimulation.* Values reported are mean ± SD

Variable	*GBA* (n = 11)	*LRRK2* (n = 4)	*PRKN* (n = 10)	Nonmutation Carriers (n = 72)	*P*
Age of onset, y	41.6 ± 5.3	47.5 ± 2.4	30.6 ± 9.1	41.2 ± 5.3	<0.0001
Age at baseline evaluation, y	54.9 ± 2.6	64.3 ± 11.0	51.0 ± 10.6	57.4 ± 7.6	0.019
Age at DBS implantation, y	53.9 ± 2.6 (n = 9)	60.8 ± 9.0	47.0 ± 11.5	55.2 ± 7.0	0.005
Disease duration, y	13.3 ± 4.9	16.8 ± 10.3	20.4 ± 7.3	16.1 ± 6.3	0.09
AJ ancestry, % of subjects	36.4	25.0	0.0	16.1	0.29
UPDRS-III score	27.4 ± 14.5	30.8 ± 11.7	33.8 ± 20.5 (n = 6)	23.4 ± 12.1 (n = 65)	0.37
MMSE score	28.7 ± 1.3	28.3 ± 2.4	28.2 ± 1.8	28.6 ± 2.0	0.90
Age of onset to DBS, ye	10.9 ± 6.0 (n = 9)	13.3 ± 8.5	16.4 ± 7.7	13.7 ± 5.7(n = 62)	0.29
DBS to current age, y	1.6 ± 3.0(n = 9)	3.5 ± 2.4	4.0 ± 4.2	2.4 ± 2.6 (n = 62)	0.28
Prior report of dyskinesia, % of subjects	100.0 (n = 6)	66.6 (n = 3)	80.0 (n = 8)	75.4 (n = 61)	0.55

[*] One subject who carried both *GBA* and *LRRK2* mutations was excluded.

SD, standard deviation; *GBA*, glucocerebrosidase; *LRRK2*, leucine-rich repeat kinase 2; *PKRN*, parkin; DBS, deep brain stimulation; AJ, Ashkenazi Jewish; UPDRS-III, the motor subsection of the Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental Status Examination.

Table 3

Multivariate Logistic Regression Model Predicting Deep Brain Stimulation Placement (N = 690)

Variable	**OR**	**95% CI**	***P***
GBA	2.1	1.0-4.3	0.05
LRRK2	0.6	0.2-2.0	0.50
PRKN	0.7	0.5-1.2	0.29
Site	1.1	0.9-1.7	0.17
AJ ancestry	0.9	0.5-1.6	0.74
Age of onset	1.0	1.0-1.1	0.19
Disease duration	1.1	1.0-1.1	<0.001
UPDRS-III	1.0	0.9-1.0	0.18
MMSE	1.0	0.9-1.2	0.56

OR, odds ratio; CI, confidence interval; *GBA*, glucocerebrosidase; *LRRK2*, leucine-rich repeat kinase 2; *PKRN*, parkin; AJ, Ashkenazi Jewish; UPDRS-III, the motor subsection of the Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental Status Examination.