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Association of *GBA* Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease

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Abstract

IMPORTANCE—Parkinson disease (PD) is heterogeneous in symptom manifestation and rate of progression. Identifying factors that influence disease progression could provide mechanistic insight, improve prognostic accuracy, and elucidate novel therapeutic targets.

OBJECTIVE—To determine whether *GBA* mutations and the E326K polymorphism modify PD symptom progression.

DESIGN, SETTING, AND PARTICIPANTS—The entire *GBA* coding region was screened for mutations and E326K in 740 patients with PD enrolled at 7 sites from the PD Cognitive Genetics Consortium. Detailed longitudinal motor and cognitive assessments were performed with patients in the on state.

MAIN OUTCOMES AND MEASURES—Linear regression was used to test for an association between *GBA* genotype and motor progression, with the Movement Disorder Society–sponsored version of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) score at the last assessment as the outcome and *GBA* genotype as the independent variable, with adjustment for levodopa equivalent dose, sex, age, disease duration, MDS-UPDRS III score at the first assessment, duration of follow-up, and site. Similar methods were used to examine the association between genotype and tremor and postural instability and gait difficulty (PIGD) scores. To examine the effect of *GBA* genotype on cognitive progression, patients were classified into those with conversion to mild cognitive impairment or dementia during the study (progression) and those without progression. The association between *GBA* genotype and progression status was then tested using logistic regression, adjusting for sex, age, disease duration, duration of follow-up, years of education, and site.

RESULTS—Of the total sample of 733 patients who underwent successful genotyping, 226 (30.8%) were women and 507 (69.2%) were men (mean [SD] age, 68.1 [8.8] years). The mean (SD) duration of follow-up was 3.0 (1.7) years. *GBA* mutations (β = 4.65; 95% CI, 1.72–7.58; P = .002), E326K (β = 3.42; 95% CI, 0.66–6.17; P = .02), and *GBA* variants combined as a single group (β = 4.01; 95% CI, 1.95–6.07; $P = 1.5 \times 10^{-4}$) were associated with a more rapid decline in MDS-UPDRS III score. Combined *GBA* variants (β = 0.38; 95% CI, 0.23–0.53; P = .01) and

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E326K (β = 0.64; 95% CI, 0.43–0.86; *P* = .002) were associated with faster progression in PIGD scores, but not in tremor scores. A significantly higher proportion of E326K carriers (10 of 21 [47.6%]; *P* = .01) and *GBA* variant carriers (15 of 39 [38.5%]; *P* = .04) progressed to mild cognitive impairment or dementia.

CONCLUSIONS AND RELEVANCE—*GBA* variants predict a more rapid progression of cognitive dysfunction and motor symptoms in patients with PD, with a greater effect on PIGD than tremor. Thus, *GBA* variants influence the heterogeneity in symptom progression observed in PD.

Although Parkinson disease (PD) is a common neurodegenerative disorder, our understanding of its pathogenesis remains limited, and neuroprotective therapies have been unattainable. Furthermore, the rate of progression of symptoms is highly variable for reasons that are poorly understood.[1–3] Genetic and environmental factors likely play a role in modifying the rate of disease progression. The identification of genes that modify the rate of motor and/or cognitive decline could provide targets for the rational development of novel therapies that delay disease onset or slow progression. Individual-level genotypes for such genes might also be important to consider in the design and analysis of interventional trials for PD.

A logical first step in seeking genetic modifiers for progression in PD is to examine well-established PD susceptibility genes. Loss-of-function mutations in the glucocerebrosidase gene (*GBA* [OMIM 606463]) cause Gaucher disease, a recessive lysosomal storage disorder. Heterozygous *GBA* mutation carriers have a substantially increased risk for developing PD.[4] Three studies[5–7] have reported an association between *GBA* mutations and more rapid progression of motor symptoms by Hoehn and Yahr stage in patients with PD. However, only one of these studies observed a significant difference in progression using the Unified Parkinson's Disease Rating Scale Part III (UPDRS III),[6] which is widely considered the criterion standard for the assessment of motor symptoms in PD.[8] Furthermore, that study did not adjust for concurrent dopamine replacement therapy (DRT), which strongly influences the UPDRS III score. One of the previous studies[5] also reported that *GBA* mutation carriers with PD displayed a more rapid progression to dementia, but these results have not been replicated. In addition, the *GBA* E326K polymorphism (rs2230288), which in the homozygous state does not result in Gaucher disease, conveys a modest risk for PD,[9] but whether E326K is associated with more rapid progression of motor or cognitive symptoms is unknown.

In the present study, we examined the association of *GBA* mutations and E326K with progression of motor symptoms, as measured by the Movement Disorder Society–sponsored version of the UPDRS III (MDS-UPDRS III),[10] and cognitive decline, as indicated by conversion to mild cognitive impairment (MCI) or dementia, in a large multicenter longitudinal cohort of patients with PD.

Methods

Patients

We performed detailed longitudinal assessments of 740 patients with PD who were volunteer research participants enrolled at 7 sites for the PD Cognitive Genetics Consortium,

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including University of Pennsylvania, Philadelphia; Feinstein Institute for Medical Research, Manhasset, New York; The Johns Hopkins University, Baltimore, Maryland; Mayo Clinic, Jacksonville, Florida; Pacific Northwest Udall Center (PANUC), Portland, Oregon, and Seattle, Washington (all 6 are Morris K. Udall Centers of Excellence for Parkinson's Disease Research); and Rush University Medical Center, Chicago, Illinois. All patients met UK Parkinson Disease Society Brain Bank clinical diagnostic criteria for PD (modified so that having >1 affected relative with PD was not considered an exclusion criterion).[11] The institutional review boards at each of the participating sites approved all study procedures. We obtained standard protocol approvals, registrations, and written informed consent from all study participants.

We examined all individuals in the on state (defined as the period of time during which a patient's motor symptoms improve after DRT) if they were receiving DRT. The UPDRS III was administered at all visits to all patients at the University of Pennsylvania and the Feinstein Institute for Medical Research and at the baseline visit for 9 patients at the PANUC in Seattle. These scores were converted to MDS-UPDRS III equivalents using a calibration formula.[12] The MDS-UPDRS III was administered to all other patients. We calculated the levodopa equivalent dose at each assessment for individuals receiving PD medications as previously described.[13] Clinical evaluations were performed at approximately 1- to 2-year intervals.

All patients also underwent detailed cognitive testing as previously described (eMethods in the Supplement).[14,15] At 5 of the 7 sites, these data were reviewed at diagnostic consensus conferences and patients were classified as having no cognitive impairment, MCI, or dementia using previously reported diagnostic procedures.[16–18]

Genotyping

Genomic DNA was extracted from peripheral blood samples or saliva samples using standard methods. The entire *GBA* coding region was sequenced in all patients to capture all known pathogenic mutations (defined as those reported in patients with Gaucher disease) and nonsynonymous polymorphisms, including rs2230288 (E326K). Seven patients failed genotyping, for a sequencing success rate of 99.1%. All sequencing was performed at a single laboratory at the PANUC in Seattle using previously described methods.[14]

Statistical Analysis

Several clinical and demographic factors influence performance on the MDS-UPDRS III, particularly DRT. Furthermore, medication dosage and response often vary over time for each patient. Thus, adjusted scores that account for dosage and response to DRT at each assessment are required to evaluate changes in MDS-UPDRS III performance within and across individuals. To assess the association between *GBA* genotype and motor symptom progression while accounting for the effects of DRT, we performed a 2-stage, adjusted-outcome regression. In the first stage, we modeled the association between the MDS-UPDRS III score and levodopa equivalent dose using a linear mixed-effects model that controlled for sex, age, and disease duration at each assessment. The residuals from the model yielded adjusted MDS-UPDRS III scores. In the second stage, we used multiple

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linear regression to test for the association between *GBA* genotype and the adjusted MDS-UPDRS III score at the last assessment, using the adjusted MDS-UPDRS III score at the first assessment, the duration of follow-up (interval between assessments), and study site as covariates. The resulting regression coefficient for genotype is the estimated difference in the adjusted MDS-UPDRS III score at the last assessment comparing *GBA* carriers and noncarriers with the same adjusted MDS-UPDRS III score at the first assessment and the same interval between assessments. Additional details of the analysis are provided in the eMethods in the Supplement.

We subsequently performed post hoc analyses to examine the association of *GBA* genotype with progression in tremor and postural instability and gait difficulty (PIGD) scores using the items from each category that overlap between the UPDRS III and MDS-UPDRS III. The tremor score was calculated as the sum of items 3.16 and 3.17 from the MDS-UPDRS III or items 3.20 and 3.21 from the UPDRS III; the PIGD score was calculated as the sum of items 3.10 and 3.12 from the MDS-UPDRS III or items 3.29 and 3.30 from the UPDRS III. We used the same 2-stage, adjusted-outcome regression approach described above to test for the association of *GBA* genotype with progression of tremor and PIGD scores.

To examine the association of cognitive decline with *GBA* genotype, we first dichotomized patients with PD into those with cognitive progression and nonprogression. Individuals were categorized with progression if (1) their first cognitive diagnosis was no cognitive impairment or MCI and their last diagnosis was dementia or (2) their first diagnosis was no cognitive impairment and their last diagnosis was MCI. Individuals were considered not to have progressed if they did not progress into a more impaired category between the first and last assessments. Patients who were diagnosed with dementia at their first visit were excluded. We used logistic regression to test for the association of progression with genotype, with adjustment for sex, age, disease duration at the first assessment, duration of follow-up, years of education, and site. Unless otherwise indicated, continuous data are given as mean (SD).

We analyzed pathogenic *GBA* mutations and the E326K polymorphism in 3 different combinations. All *GBA* mutations and E326K were combined as a single group (hereinafter referred to as *GBA* variants). We also analyzed *GBA* mutations alone and E326K alone. A dominant model was used for all *GBA* variants. For all tests, $P < .05$ was considered significant. All analyses were performed using R software (version 3.2.3) with the lme4 package.[19,20]

Results

The baseline characteristics of the 733 study participants at each site who underwent successful genotyping are summarized in Table 1. Two hundred twenty-six patients (30.8%) were women, and 507 patients (69.2%) were men. In the overall cohort at the first clinical assessment, the mean age was 68.1 (8.8) years, and the mean disease duration since symptom onset was 8.6 (6.0) years. The number of visits per patient ranged from 2 to 8 (mean [SD], 3.1 [1.5]), and 321 patients (43.8%) had 3 or more visits. The raw, unadjusted mean MDS-UPDRS III score (including converted UPDRS III scores) was 27.6 (12.8), and

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the median Hoehn and Yahr stage was 2.0 (interquartile range, 2.0–3.0). Six hundred eighty-three patients (93.2%) were receiving DRT at the first assessment.

A total of 11 pathogenic mutations, 5 variants of unknown significance, and 3 nonsynonymous single-nucleotide polymorphisms were observed within the cohort (Table 2). Twenty-seven patients (3.7%) carried 1 or more pathogenic mutations; 26 of these individuals were simple heterozygotes and 1 (known to also have Gaucher disease) was a compound heterozygote. Thirty-two patients (4.4%) were heterozygous for E326K; one of these individuals also carried a pathogenic mutation and for the purpose of analysis was assigned exclusively to the mutation carrier group.

The clinical and demographic characteristics of study participants at the first clinical assessment by *GBA* genotype group are presented in Table 3. Across genotype groups, we found a significant difference in sex, age, and prevalence of dementia.

The raw, unadjusted mean change in MDS-UPDRS III score per year was 3.0 (9.9) for mutation carriers, 3.8 (5.3) for E326K carriers, 3.4 (7.7) for carriers of any *GBA* variant, and 2.0 (6.6) for noncarriers. After adjustment for important covariates, including levodopa equivalent dose at each assessment, motor progression was significantly greater in carriers of a mutation (β = 4.65; 95% CI, 1.72–7.58; $P = .002$), E326K (β = 3.42; 95% CI, 0.66–6.17; $P = .02$), or any *GBA* variant (β = 4.01; 95% CI, 1.95–6.07; $P = 1.5 \times 10^{-4}$) compared with noncarriers (Table 4). Inspection of the β coefficients in Table 4 shows that the effect size for *GBA* mutations was similar though slightly larger than for E326K.

Because *GBA* variants were associated with more rapid progression of overall motor symptoms, we then examined whether a similar association existed with progression of the symptoms that are used to define the PIGD and tremor-dominant motor subtypes.[21] We found no significant association between *GBA* mutations or E326K, individually or combined, with progression in tremor scores (Table 4). However, E326K (β = 0.64; 95% CI, 0.43–0.86; $P = .002$) and the combined *GBA* variant group (β = 0.38; 95% CI, 0.23–0.53; $P = .01$) were associated with faster progression in PIGD scores compared with noncarriers.

During the study, a higher proportion of *GBA* E326K carriers (10 of 21 [47.6%]; $P = .01$), but not mutation carriers (5 of 18 [27.8%]; $P = .69$), progressed to MCI and dementia compared with noncarriers. The association with conversion to MCI and dementia was also significant for the combined *GBA* variant group (15 of 39 [38.5%]; $P = .04$) (Table 5).

Discussion

In this study, we examined the association of *GBA* variants with motor and cognitive progression in a large, multicenter PD cohort. We found that carriers of *GBA* pathogenic mutations and the E326K polymorphism had faster motor symptom progression and that a higher proportion of E326K carriers progressed to MCI and dementia. Our study is unique for 2 reasons. First, we used the MDS-UPDRS III, a much more sensitive measure of motor symptoms than the Hoehn and Yahr stage, while adjusting for important confounders that included concurrent DRT. Second, we demonstrated that a common *GBA* polymorphism that

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occurs at a frequency similar to that of all pathogenic mutations combined is associated with motor and cognitive decline.

Our results are generally consistent with those from 3 recent longitudinal studies of motor progression in *GBA*-related PD, despite significant differences in methods.[5–7] Brockmann and colleagues[6] found a significantly greater increase in UPDRS III scores during a 3-year period in 13 patients with PD and *GBA* N370S or L444P mutations compared with 26 matched noncarriers with PD. However, in contrast to our study, they did not adjust for concomitant DRT, which strongly influences UPDRS III scores. Also, although our analyses included all pathogenic *GBA* mutations, Brockmann et al[6] only included the 2 most common mutations. In a community-based incident cohort, Winder-Rhodes and colleagues[5] reported that patients with PD and a pathogenic *GBA* mutation (n = 4) or 1 of 3 single-nucleotide polymorphisms (T369M, E326K, or L119L; total, 11 patients) progressed to Hoehn and Yahr stage 3 more quickly than noncarriers (n = 106). However, they did not report analyses of individual polymorphisms, so whether E326K alone was associated with motor progression remained unclear. Although the UPDRS III was administered to patients in their cohort, it was not included in analyses of progression. Davis and colleagues[7] examined the effect of carrying the *GBA* N370S mutation on the rate of motor progression using the Hoehn and Yahr stage and the UPDRS III. In a sample of 425 patients with PD who were enrolled in studies at Washington University, St Louis, Missouri, or in the Parkinson Progression Markers Initiative and followed up for a mean of 2.7 years, Davis et al[7] found an association between N370S and faster progression in Hoehn and Yahr stage. However, in contrast to our study, Davis et al did not find a significant association between N370S and rate of progression as measured by the UPDRS III in the Washington University cohort (using data collected in the off state or in both the on and off states) or in the Parkinson Progression Markers Initiative cohort (where the on or off state was not specified). This discordance in findings might be explained by the fact that our study had substantially greater power because of the larger overall size of the cohort and our inclusion of all pathogenic *GBA* mutations rather than N370S alone.

In our PD cohort, we found that a higher proportion of *GBA*-variant carriers progressed to MCI or dementia compared with noncarriers, although this association only reached significance in the E326K group and not the mutation group. In the study by Winder-Rhodes and colleagues,[5] patients with PD who carried *GBA* mutations but not single-nucleotide polymorphisms (including E326K) progressed to dementia more rapidly than noncarriers. Overall, the findings from both studies are largely consistent with one another despite substantial differences in the analytic methods used and the manner in which patients were ascertained. We believe that the seemingly discordant findings for mutation carriers and single-nucleotide polymorphism carriers observed in the 2 studies are likely attributable to the modest sample size of each genotype group. Larger, better-powered longitudinal studies will be needed to determine whether the risk for cognitive progression varies across classes of *GBA* variants.

We found that in addition to more rapid cognitive and overall motor progression, patients with PD who carried a *GBA* variant displayed a faster decline in PIGD scores but not tremor scores. This finding is consistent with findings from a recent study of patients with PD that

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showed that after adjusting for non-PIGD items on the MDS-UPDRS III, a higher PIGD score was associated with more severe deficits in global cognition, executive function, memory, and phonemic fluency.[22]

Our data add to a growing body of literature that links *GBA* variants to multiple facets of PD. Case-control studies have shown that *GBA* mutations and E326K increase the risk for PD,[4,9] and cross-sectional studies indicate that both are associated with an earlier age at onset[14,23] and a higher prevalence of dementia with relatively greater impairment in working memory and/or executive function and visuospatial abilities.[14,24] We now demonstrate that *GBA* mutations and E326K predict more rapid progression of motor symptoms and that E326K is associated with cognitive decline. Taken together, these data suggest that the overall clinical profile is more severe in *GBA*-related PD. The fact that the magnitude of the effect of E326K on progression of motor symptoms (Table 4) and cognitive dysfunction (Table 5) is similar to or larger than that of *GBA* mutations is somewhat surprising because E326K does not cause Gaucher disease.[23,25–29] However, although E326K is a nonconserved residue and is not predicted to significantly alter glucocerebrosidase enzyme activity *in silico*, several studies expressing *GBA* constructs with E326K suggest that this polymorphism reduces enzyme activity.[27,30,31]

The mechanisms through which *GBA* influences PD pathogenesis remain unclear, but growing evidence suggests that the increased risk for PD in *GBA* carriers is due to decreased glucocerebrosidase function rather than a toxic gain of function. Glucocerebrosidase enzyme activity assayed from blood samples is decreased in *GBA* mutation and polymorphism carriers with PD, including E326K, to a greater extent than in noncarriers with PD.[32] Recent work in animal and cell culture models of glucocerebrosidase deficiency suggests that *GBA* mutations lead to impaired degradation of misfolded proteins through disruption of autophagic flux, resulting in accumulation of α-synuclein.[33–36] It is possible that *GBA* influences different molecular pathways at different stages of PD.

Our study has several limitations. Most of our cohort received DRT, and all such individuals were examined in the on state. Ideally, in studies of motor progression, individuals should be examined in the off state. However, requiring individuals to undergo assessments in the off state becomes impractical with advancing disease and motor disability and might result in dropout bias. To address this issue, we adjusted for levodopa equivalent dose for all individuals who received DRT in our analyses. Our cohort was primarily white and had a higher-than-average level of education. Thus, our sample might not be representative of all patients with PD. Finally, we combined longitudinal motor and cognitive data from multiple sites, which could have increased heterogeneity, although all of our analyses were adjusted for study site.

The identification and characterization of genetic modifiers for motor and cognitive progression in PD will not only improve our understanding of pathologic mechanisms underlying the disease and reveal novel targets for neuroprotective therapies but also could have significant clinical implications. For example, a priori genotyping of key modifying genes could be used to better predict prognosis and target patients who are at risk for faster progression for earlier interventions such as physical therapy, more aggressive medical

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therapy, or deep brain stimulation. In addition, patients with PD who are enrolled in clinical trials of potential neuroprotective therapies could be stratified based on genotype to create more homogeneous groups, thus increasing power to detect treatment effects.

Conclusions

Variants of *GBA* are associated with faster progression of motor symptoms and more rapid conversion to MCI and dementia in a multicenter cohort of patients with PD. These findings provide evidence that genetic modifiers, such as *GBA* variants, account for some of the clinical heterogeneity observed in PD. Our study provides a strong rationale for future studies of larger multicenter longitudinal cohorts using an unbiased genome-wide approach to identify additional genetic modifiers of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med. 1993; 328(3):176–183. [PubMed: 8417384]
2. Poewe W. The need for neuroprotective therapies in Parkinson's disease: a clinical perspective. Neurology. 2006; 66(10):S2–S9. (suppl 4). [PubMed: 16717249]
3. Goetz CG, Stebbins GT, Blasucci LM. Differential progression of motor impairment in levodopa-treated Parkinson's disease. Mov Disord. 2000; 15(3):479–484. [PubMed: 10830412]

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4. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009; 361(17):1651–1661. [PubMed: 19846850]
5. Winder-Rhodes SE, Evans JR, Ban M, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain. 2013; 136(pt 2):392–399. [PubMed: 23413260]
6. Brockmann K, Srulijes K, Pflederer S, et al. *GBA*-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord. 2014
7. Davis AA, Andruska KM, Benitez BA, Racette BA, Perlmutter JS, Cruchaga C. Variants in *GBA*, *SNCA*, and *MAPT* influence Parkinson disease risk, age at onset, and progression. Neurobiol Aging. 2016; 37:209.e1–209.e7.
8. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord. 2003; 18(7): 738–750. [PubMed: 12815652]
9. Pankratz N, Beecham GW, DeStefano AL, et al. PD GWAS Consortium. Meta-analysis of Parkinson's disease: identification of a novel locus, RIT2. Ann Neurol. 2012; 71(3):370–384. [PubMed: 22451204]
10. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008; 23(15):2129–2170. [PubMed: 19025984]
11. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988; 51(6):745–752. [PubMed: 2841426]
12. Goetz CG, Stebbins GT, Tilley BC. Calibration of Unified Parkinson's Disease Rating Scale scores to Movement Disorder Society–Unified Parkinson's Disease Rating Scale scores. Mov Disord. 2012; 27(10):1239–1242. [PubMed: 22886777]
13. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010; 25(15):2649–2653. [PubMed: 21069833]
14. Mata IF, Leverenz JB, Weintraub D, et al. *GBA* variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord. 2016; 31(1):95–102. [PubMed: 26296077]
15. Mata IF, Leverenz JB, Weintraub D, et al. *APOE*, MAPT, and *SNCA* genes and cognitive performance in Parkinson disease. JAMA Neurol. 2014; 71(11):1405–1412. [PubMed: 25178429]
16. Chahine LM, Qiang J, Ashbridge E, et al. Clinical and biochemical differences in patients having Parkinson disease with vs without GBA mutations. JAMA Neurol. 2013; 70(7):852–858. [PubMed: 23699752]
17. Cholerton BA, Zabetian CP, Quinn JF, et al. Pacific Northwest Udall Center of Excellence Clinical Consortium: study design and baseline cohort characteristics. J Parkinsons Dis. 2013; 3(2):205–214. [PubMed: 23938350]
18. Goldman JG, Weis H, Stebbins G, Bernard B, Goetz CG. Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. Mov Disord. 2012; 27(9):1129–1136. [PubMed: 22778009]
19. Bates DMM, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015; 67(1):1–48.
20. R Foundation for Statistical Computing. R: A language and environment for statistical computing. https://www.R-project.org/. Published 2015. Accessed January 15, 2016
21. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the Movement Disorder Society Unified Parkinson's Disease Rating Scale: comparison with the Unified Parkinson's Disease Rating Scale. Mov Disord. 2013; 28(5):668–670. [PubMed: 23408503]
22. Kelly VE, Johnson CO, McGough EL, et al. Association of cognitive domains with postural instability/gait disturbance in Parkinson's disease. Parkinsonism Relat Disord. 2015; 21(7):692–697. [PubMed: 25943529]

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23. Nichols WC, Pankratz N, Marek DK, et al. Parkinson Study Group-PROGENI Investigators. Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. Neurology. 2009; 72(4):310–316. [PubMed: 18987351]
24. Alcalay RN, Dinur T, Quinn T, et al. Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and GBA heterozygotes. JAMA Neurol. 2014; 71(6):752–757. [PubMed: 24756352]
25. Horowitz M, Pasmanik-Chor M, Ron I, Kolodny EH. The enigma of the E326K mutation in acid β-glucocerebrosidase. Mol Genet Metab. 2011; 104(1–2):35–38. [PubMed: 21831682]
26. Bras J, Paisan-Ruiz C, Guerreiro R, et al. Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Portugal. Neurobiol Aging. 2009; 30(9):1515–1517. [PubMed: 18160183]
27. Neumann J, Bras J, Deas E, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain. 2009; 132(pt 7):1783–1794. [PubMed: 19286695]
28. Kalinderi K, Bostantjopoulou S, Paisan-Ruiz C, Katsarou Z, Hardy J, Fidani L. Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Greece. Neurosci Lett. 2009; 452(2):87–89. [PubMed: 19383421]
29. Lesage S, Anheim M, Condroyer C, et al. French Parkinson's Disease Genetics Study Group. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum Mol Genet. 2011; 20(1):202–210. [PubMed: 20947659]
30. Torralba MA, Pérez-Calvo JI, Pastores GM, Cenarro A, Giraldo P, Pocoví M. Identification and characterization of a novel mutation c.1090G>T (G325W) and nine common mutant alleles leading to Gaucher disease in Spanish patients. Blood Cells Mol Dis. 2001; 27(2):489–495. [PubMed: 11259172]
31. Montfort M, Chabás A, Vilageliu L, Grinberg D. Functional analysis of 13 *GBA* mutant alleles identified in Gaucher disease patients: pathogenic changes and "modifier" polymorphisms. Hum Mutat. 2004; 23(6):567–575. [PubMed: 15146461]
32. Alcalay RN, Levy OA, Waters CC, et al. Glucocerebrosidase activity in Parkinson's disease with and without GBA mutations. Brain. 2015; 138(pt 9):2648–2658. [PubMed: 26117366]
33. Keatinge M, Bui H, Menke A, et al. Glucocerebrosidase 1 deficient Danio rerio mirror key pathological aspects of human Gaucher disease and provide evidence of early microglial activation preceding alpha-synuclein–independent neuronal cell death. Hum Mol Genet. 2015; 24(23):6640–6652. [PubMed: 26376862]
34. Du TT, Wang L, Duan CL, et al. GBA deficiency promotes CA/α-synSNuclein accumulation through autophagic inhibition by inactivated *PPP2A*. Autophagy. 2015; 11(10):1803–1820. [PubMed: 26378614]
35. Uemura N, Koike M, Ansai S, et al. Viable neuronopathic Gaucher disease model in Medaka (*Oryzias latipes*) displays axonal accumulation of alpha-synuclein. PLoS Genet. 2015; 11(4):e1005065. [PubMed: 25835295]
36. Awad O, Sarkar C, Panicker LM, et al. Altered TFEB-mediated lysosomal biogenesis in Gaucher disease iPSC-derived neuronal cells. Hum Mol Genet. 2015; 24(20):5775–5788. [PubMed: 26220978]

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Key Points

Question

Do variants in the *GBA* gene modify symptom progression in Parkinson disease (PD)?

Finding

Variants in *GBA* were associated with more rapid progression of motor symptoms in patients with PD, with a greater effect on postural instability and gait difficulty than tremor. A higher proportion of *GBA* variant carriers progressed to mild cognitive impairment and dementia.

Meaning

Variants of *GBA* influence the heterogeneity in symptom progression observed in PD, and thus, *GBA* genotype might be important to consider in the design and analysis of interventional trials. This study provides the rationale for larger-scale longitudinal analyses to identify additional genetic modifiers of PD progression.

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Table 1

Baseline Characteristics of PD Cohort

Site	No. of Patients	Female Sex, No. (%)	White Race, No. (%)	Age at First Evaluation, Mean (SD), y	Disease Duration, Mean (SD), y	MDS-UPDRS III Score, Mean (SD)[a]	Duration of Follow-up, Mean (SD), y	LED, Mean (SD), mg	DRT, No. (%)	Hoehn and Yahr Stage, Median (IQR)	Dementia, No. (%)[b]
PANUC, Seattle, Washington	321	119 (37.1)	310 (96.6)	66.6 (9.5)	8.8 (5.9)	24.8 (11.5)	2.6 (1.1)	623.4 (490.5)	293 (91.3)	2.0 (2.0–2.5)	37 (11.5)
University of Pennsylvania, Philadelphia	213	68 (31.9)	200 (93.9)	70.3 (7.5)	7.5 (5.2)	28.6 (13.0)	4.6 (1.9)	720.5 (474.4)	203 (95.3)	2.0 (2.0–2.5)	16 (7.5)
PANUC, Portland, Oregon	98	14 (14.3)	95 (96.9)	67.3 (7.5)	10.1 (6.8)	29.5 (13.9)	2.3 (0.6)	871.1 (561.0)	96 (98.0)	2.5 (2.0–2.5)	10 (10.2)
The Johns Hopkins University, Baltimore, Maryland	33	10 (30.3)	33 (100)	68.3 (8.6)	9.1 (4.9)	34.0 (11.9)	1.0 (0.1)	894.1 (563.5)	33 (100)	2.0 (2.0–3.0)	5 (15.2)
Rush University, Chicago, Illinois	37	10 (27.0)	34 (91.9)	73.4 (5.9)	10.6 (4.0)	37.7 (14.1)	2.1 (0.3)	834.9 (424.7)	37 (100)	2.0 (2.0–3.0)	6 (16.2)
Mayo Clinic, Jacksonville, Florida	18	2 (11.1)	16 (88.9)	68.0 (11.4)	11.9 (10.9)	25.4 (13.6)	1.2 (0.1)	735.3 (348.9)	18 (100)	2.0 (1.0–2.0)	NA
Feinstein Institute for Medical Research, Manhasset, New York	13	3 (23.1)	13 (100)	60.7 (8.8)	1.6 (0.8)	25.7 (8.2)	1.7 (1.9)	23.1 (43.9)	3 (23.1)	2.0 (1.5–2.0)	NA
All	733	226 (30.8)	701 (95.6)	68.1 (8.8)	8.6 (6.0)	27.6 (12.8)	3.0 (1.7)	699.7 (505.0)	683 (93.2)	2.0 (2.0–3.0)	74 (10.1)

Abbreviations: DRT, dopamine replacement therapy; IQR, interquartile range; LED, levodopa equivalent dose; MDS-UPDRS III, Movement Disorder Society–sponsored version of the Unified Parkinson's Disease Rating Scale Part III; NA, not available; PANUC, Pacific Northwest Udall Center; PD, Parkinson disease.

[a] Performed in the on state if the patient was receiving medication.

[b] Two sites (Mayo Clinic and Feinstein Institute for Medical Research) did not render a cognitive diagnosis.

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Table 2

GBA Variants Observed

Variant[a]	No. of Patients
Pathogenic mutations[b,c]	
IVS2 + 1G>A (splice site)	1
84dupG (frameshift)	2
S125N	1
R163X (premature stop)	1
S196P	1
F216Y	1
914delC (frameshift)	1
N370S	8
D409H	1
L444P	10
R496H	1
Variants of unknown significance[d]	
R(−32)T	1
P(−28)S	1
F316I	1
V460L	1
S488T	1
Nonsynonymous SNPs[e]	
K(−27)R	2
E326K	32
T369M	18

Abbreviation: SNP, single-nucleotide polymorphism.

[a]Only individuals who carried a pathogenic *GBA* mutation or the E326K polymorphism were included in analyses.

[b]One individual carried 2 separate pathogenic mutations and 1 individual carried a pathogenic mutation and E326K.

[c]Defined as a variant that has been reported to cause Gaucher disease.

[d]Indicates variants not linked to Gaucher disease with a minor allele frequency of less than 0.01 in controls.

[e]Indicates an amino acid–altering variant not linked to Gaucher disease with a minor allele frequency of greater than 0.01 in controls.

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Table 3

Baseline Characteristics of *GBA* Carriers and Noncarriers

Characteristic	Carriers		Noncarriers (n = 675)	*P* Value[a]
	Mutation (n = 27)	E326K (n = 31)		
Female sex, No. (%)	10 (37.0)	16 (51.6)	200 (29.6)	.03
White race, No. (%)	26 (96.3)	28 (90.3)	645 (95.6)	.60
Age, mean (SD), y	64.0 (9.0)	65.5 (11.1)	68.4 (8.6)	.009
MDS-UPDRS III, mean (SD)	31.8 (10.6)	26.5 (12.4)	27.5 (12.9)	.20
Disease duration, mean (SD), y	9.5 (4.9)	7.5 (5.4)	8.7 (6.1)	.46
Duration of follow-up, mean (SD), y	2.8 (1.4)	2.7 (1.5)	3.0 (1.7)	.36
LED, mean (SD), mg	969.7 (505.7)	695.2 (476.3)	696.7 (505.7)	.70
Hoehn and Yahr stage, median (IQR)	2 (2.0–2.5)	2 (2.0–2.75)	2 (2.0–2.5)	.97
Dementia, No. (%)[b]	9 (33.3)	7 (24.1)	58 (9.0)	2×10^{-4}

Abbreviations: IQR, interquartile range; LED, levodopa equivalent dose; MDS-UPDRS III, Movement Disorder Society–sponsored version of the Unified Parkinson's Disease Rating Scale Part III.

[a] Calculated from the χ^2 test for categorical variables and 1-way analysis of variance for continuous traits.

[b] A cognitive diagnosis was not available for 2 E326K carriers and 29 noncarriers.

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Table 4

Association of *GBA* Variants With Motor Progression

		Measure, β Coefficient (95% CI)					
***GBA* Genotype**	**Carrier Frequency**	**Total MDS-UPRDS III Score[a]**	***P* Value**	**PIGD Score[a,b]**	***P* Value**	**Tremor Score[a,c]**	***P* Value**
Mutations	0.04	4.65 (1.72 to 7.58)	.002	0.10 (−0.11 to 0.31)	.62	0.16 (−0.44 to 0.03)	.83
E326K	0.04	3.42 (0.66 to 6.17)	.02	0.64 (0.43 to 0.86)	.002	0.37 (0.07 to 0.67)	.22
Mutations and E326K	0.08	4.01 (1.95 to 6.07)	1.5×10^{-4}	0.38 (0.23 to 0.53)	.01	0.16 (−0.06 to 0.38)	.46

Abbreviations: MDS-UPDRS III, Movement Disorder Society–sponsored version of the Unified Parkinson's Disease Rating Scale Part III; PIGD, postural instability and gait difficulty; UPDRS III, Unified Parkinson's Disease Rating Scale Part III.

[a]Based on levodopa equivalent dose–adjusted scores.

[b]Calculated from the sum of items 3.10 and 3.12 of the MDS-UPDRS III or items 3.29 and 3.30 of the UPDRS III.

[c]Calculated from the sum of items 3.16 and 3.17 of the MDS-UPDRS III or items 3.20 and 3.21 of the UPDRS III.

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Table 5

Association of *GBA* Variants With Progression to MCI or Dementia

***GBA* Genotype**	**Patients With Progression, No. (%)[a]**	**Odds Ratio (95% CI)**	***P* Value**
Mutations	5 of 18 (27.8)	1.26 (0.40–3.91)	.69
E326K	10 of 21 (47.6)	3.34 (1.30–8.55)	.01
Mutations and E326K	15 of 39 (38.4)	2.18 (1.05–4.54)	.04

Abbreviation: MCI, mild cognitive impairment.

[a]A cognitive diagnosis was not available for 2 E326K carriers and 29 noncarriers.