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Neuropsychiatric characteristics of GBA-associated Parkinson disease

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Abstract

Mutations in *GBA1* are a well-established risk factor for Parkinson disease (PD). GBA-associated PD (GBA-PD) may have a higher burden of nonmotor symptoms than idiopathic PD (IPD). We sought to characterize the relationship between GBA-PD and neuropsychiatric symptoms. Subjects were screened for common *GBA1* mutations. GBA-PD (n=31) and non-carrier (IPD; n=55) scores were compared on the Unified Parkinson Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA), Beck Depression Inventory (BDI), and the State-Trait Anxiety Index (STAI). In univariate comparisons, GBA-PD had a greater prevalence of depression (33.3%) versus IPD (13.2%) ($p<0.05$). In regression models controlling for age, sex, disease duration, motor disability, and MoCA score, GBA-PD had an increased odds of depression (OR 3.66, 95% CI 1.13–11.8) ($p=0.03$). Post-hoc analysis stratified by sex showed that, among men, GBA-PD had a higher burden of trait anxiety and depression than IPD; this finding was sustained in multivariate models. Among women, GBA-PD did not confer greater psychiatric morbidity than IPD. These results suggest that *GBA1* mutations confer greater risk of neuropsychiatric morbidity in PD, and that sex may affect this association.

Keywords

Parkinson disease; glucocerebrosidase; *GBA1*; depression; anxiety

1. Introduction

Biallelic mutations in the *glucosylceramidase beta 1* (*GBA1*) gene, which encodes the lysosomal enzyme ß-glucocerebrosidase (GCase), cause Gaucher disease. In the last two decades, both monoallelic and biallelic *GBA1* mutations have also been firmly established as strong genetic risk factors for Parkinson disease (PD) in many populations (1). The GCase pathway provides a novel focus for PD therapeutics through multiple potential mechanisms, including GCase activators, chaperones and gene therapy to increase the level and/or activity of GCase (2). As trials of promising candidate agents are imminent, it is important to better understand the phenotype of PD associated with *GBA1* mutations (GBA-PD).

The motor features of GBA-PD often resemble typical idiopathic Parkinson disease (IPD); however, converging evidence suggests that GBA-PD may encompass a greater burden of nonmotor symptoms. GBA-PD patients may experience more autonomic dysfunction (3), neuropsychiatric disturbances (3, 4), and cognitive impairment (5), with a greater tendency to develop dementia compared to IPD (6–8). *GBA1* mutations have also been strongly associated with dementia with Lewy bodies (DLB) (1, 7, 9), and GBA-PD may have a greater burden of cortical Lewy bodies than IPD (4, 10–12). Among neuropsychiatric features, anxiety and depression, which are highly prevalent in PD overall, may be even more prominent in GBA-PD (3). The presence and severity of these features may be relevant to clinical trial design, especially in randomization schema, but also as potential secondary endpoints. Therefore, we sought to further assess these features in a cohort of GBA-PD subjects.

2. Subjects and Methods

2.1 Subjects

Participants were ascertained from a tertiary care center's Parkinson disease population who were enrolled in research on the genetics of PD in Ashkenazi Jews (AJ) (13, 14): consecutive AJ patients with PD were invited to participate in research, and all who consented underwent genetic screening and research assessments. Of the 86 participants, 41, all *GBA1* non-carriers, were also cross-enrolled in the Michael J. Fox Foundation (MJFF) Ashkenazi Jewish *LRRK2* Consortium. The diagnosis of PD was made according to UK PD Society Brain Bank criteria, except that participants were not excluded if they had a family history of PD (13, 15). DNA was screened for nine of the most common *GBA1* mutations among Ashkenazim (N370S; L444P; 84GG; IVS2+1G➔A; V394L; del55bp; D409H; R496H; and A456P, a subset of whom were subsequently retested for the RecNciI allele (16)) (as previously described (17)), as well as the *LRRK2* G2019S mutation (18, 19). *GBA1* carriers were classified as heterozygous, homozygous or compound heterozygous. *LRRK2* G2019S carriers, including those who also carried *GBA1* mutations, were excluded from the current analysis. Those subjects without *GBA1* or *LRRK2* mutations were categorized as idiopathic PD (IPD). The study protocol was approved by the institutional review board at Mount Sinai Beth Israel.

2.2 Assessments

In-depth assessment included a structured history related to Parkinson disease (age of onset, disease duration, initial symptoms, present symptoms), complete Unified Parkinson's Disease Rating Scale (UPDRS) (20), Hoehn and Yahr disease staging (H&Y) (21), Schwab and England (S&E) activities of daily living scale, and formal cognitive and psychiatric assessments. Cognition was assessed by Montreal Cognitive Assessment (MoCA). A cutoff score of <26 was chosen to indicate cognitive impairment (22). Depression was assessed using the Beck Depression Inventory-II (BDI) (23, 24). A cutoff score of ≥14 was chosen for depression (24). The Spielberger State-Trait Anxiety Inventory (form Y) (STAI) (25, 26) was used to measure anxiety. The STAI employs two subscales, one assessing "state" anxiety (asking respondents to answer questions based on how they are feeling at the time of assessment), and one assessing "trait" anxiety (asking respondents to answer questions based on how they feel in general). A cutoff score of ≥55 for the STAI State subscale (STAI-S) was used to define clinical anxiety in this study (27).

Dopaminergic medication doses were converted to levodopa equivalent daily dose (LEDD) (28). Psychiatric medications were recorded by medication class, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, nonspecific monoamine oxidase inhibitors, mirtazapine, bupropion, benzodiazepines, typical antipsychotic drugs, atypical antipsychotic drugs other than clozapine or quetiapine, and clozapine or quetiapine.

2.3 Analysis

Demographic variables, UPDRS subscores (parts I–IV), H&Y stage, S&E score, and raw scores from MoCA, BDI and STAI were treated continuously; MoCA, BDI and STAI-state

scores were also treated dichotomously based on their cutoff scores. Univariate comparisons were performed using Student's t-test or Wilcoxon ranksum as appropriate (STATA 12, Statacorp, TX). Four primary models were performed: linear regressions assessing the relationship between 1) continuous BDI score and mutation status (GBA-PD or IPD), 2) continuous STAI trait score and mutation status, and 3) continuous STAI state score and mutation status; and 4) a logistic regression model assessing presence of depression as determined by cutoff score of BDI ≥14. A parallel model for STAI-state score ≥55 was not performed as few individuals met threshold. All models included covariates of age, sex, duration of disease, disease motor severity (UPDRSIII), and MoCA.

3. Results

Subjects included 55 IPD, and 31 *GBA1* mutation carriers with PD (GBA-PD), including 29 heterozygotes (24 with N370S mutations, 2 with 84GG, 2 with R496H, and 1 with L444P), and 2 compound heterozygotes (N370S/84GG; N370S/RecNciI). Demographics and group characteristics are shown in Table 1.

3.1 Primary analysis

3.1.1 Univariate comparisons—GBA-PD and IPD did not differ by age, sex, age at onset, UPDRS I–IV, H&Y, and S&E. MoCA total and cutoff scores, BDI total score, the total state and trait STAI scores, and the STAI state cutoff score did not differ between groups. However, GBA-PD had higher prevalence of depression (BDI score ≥ 14) (33.3%) vs. IPD (13.2%) ($p<0.05$) (Table 1).

3.1.2 Multivariate comparisons—In regression models (Tables 2a–d), adjusting for age, sex, PD duration, UPDRS III, and MoCA, GBA-PD had increased odds of depression compared to IPD (OR 3.66, 95% CI 1.13–11.8) ($p=0.03$) (Table 2b). This finding was sustained in additional models adjusting for antidepressant use and for antipsychotic use (data not shown). There was no difference between GBA-PD and IPD in STAI state, trait, or BDI total scores in models adjusting for age, sex, PD duration, UPDRS III, and MoCA (tables 2a, c, d); these results also did not differ when adjusting for antidepressant use and antipsychotic use (data not shown). There was no difference in STAI state and trait scores specifically, even when adjusting for BDI cutoff score (data not shown). However female sex was a significant covariate in these models (for STAI-state, ß= 8.71, 95% CI = 3.55,13.9, $p<0.01$; for STAI-trait, ß = 7.76, 95% CI = 2.35, 13.2, $p <0.01$) (tables 2c and 2d).

3.2 Post-hoc analysis by sex

As female sex was significant in the multivariate models for STAI (see 3.1.2), post hoc analysis with stratification by sex was performed.

3.2.1 Univariate comparisons—Comparisons between IPD and GBA-PD, separated by sex, are shown in Table 1. In comparison to men with IPD, men with GBA-PD had significantly higher rates of depression as determined by BDI cutoff score, and higher STAI-trait scores. Men with GBA-PD also had a younger age of onset than men with IPD. Also of note, when men with GBA-PD were compared to women with GBA-PD, there was no

difference in any of the neuropsychiatric measures; however, when men with IPD were compared to women with IPD, women with IPD had higher BDI scores (men 6.8 ± 4.6, women 13.9 ± 12.2) (p=0.03) and a greater frequency of depression as assessed by BDI cutoff score (men 5.6%, n=2, women 29.4%, n=5) (p=0.02). Compared to men with IPD, women with IPD also had higher STAI-state scores (men 32.8 ± 10.1, women 42.8 ± 13.6) (p=0.01), frequency of state anxiety as assessed by STAI-state cutoff (men 0%, women 17.7%, n=3) ($p < 0.01$), and STAI-trait scores (men 31.7 ± 9.9, women 43.4 ± 12.2) ($p < 0.01$).

3.2.2 Multivariate models—When limited to men, in models adjusting for age, PD duration, UPDRS III and MoCA, GBA-PD did not differ from IPD in STAI-state anxiety scores; however, GBA-PD had increased trait anxiety scores on average compared with IPD (OR, 95% CI) (8.48, 1.53–15.44) (p=0.02). Men with GBA-PD were also more likely to meet BDI cutoff for depression (OR, 95% CI) (9.22, 1.44–59.19) (p=0.02). These relationships were maintained even when antidepressant use and antipsychotic use were included in the models. Among women, GBA-PD and IPD did not differ in state or trait anxiety scores, or in BDI scores. The differences between men and women with IPD for both STAI ($p<0.01$) and depression ($p<0.05$) persisted in multivariate analyses controlling for age, PD duration, UPDRS III and MoCA (data not shown).

4. Discussion

While depression and anxiety are frequent features of PD overall (29–45), our data support that depression is even more common in GBA-PD than IPD (3). Further, we raise questions regarding a potential sex effect, with men with GBA-PD exhibiting higher rates of anxiety and depression than men with IPD.

Neuropsychiatric symptoms are frequent features in PD associated with both monoallelic (3, 46) and biallelic *GBA1* mutations (19). Clarifying the psychiatric phenotype of GBA-PD is important not only for clinical care and planning of clinical trials, but also in order to identify features in (motorically) asymptomatic *GBA1* mutation carriers that may be associated with development of PD and DLB, or that may suggest early neurodegeneration (47, 48). Clinically significant depression may be present in 2.7% to 89% of PD patients (30) and a population-based study found an incidence rate among PD patients of nearly 26 cases per 1000 person-years, twice the incidence rate in the non-PD population (35). Anxiety risk in PD has been studied less extensively than depression, although many studies support a prevalence of 25–35% (31, 37, 43, 49–51), with some reporting a frequency as high as 50–70% (32, 52). Risk of depression and anxiety in PD may be affected by sex (32–34, 37), age at onset (32, 53), and disease duration (35, 49, 54). The impact of PD-related genes on the risk for psychiatric complications has also been explored, though less extensively. *LRRK2* G2019S mutation carriers, for example, appear to have comparable rates of depression to non-carrier PD patients (13, 55), although carriers may have a higher burden of pre-morbid mood disorders (55). Others have suggested that rates of nonmotor symptoms in general, including depression, are comparable between genetic and non-genetic PD (56). An early description of GBA-PD found depression as a presenting symptom of GBA-PD in around 8.5%, comparable to the rate in an IPD comparison cohort (57);

however, that study did not use a validated rating scale to detect depression. A subsequent study (3) employed a more standardized approach to nonmotor symptoms, and showed that GBA-PD had significantly higher levels of anxiety, depression, apathy, and sleep disruption than IPD. Another study, however, did not demonstrate a significant difference in BDI scores between GBA-PD and IPD among early-onset Parkinson disease subjects (5).

Our observed increased frequency of depression in GBA-PD, as measured by a categorical cutoff in the Beck Depression Inventory, supports clinical observations and a study by Brockman et al. (3) that GBA-PD subjects do have higher rates of psychiatric morbidity; however, unlike the study from Brockmann et al., in which continuous BDI scores were significantly worse among GBA-PD, in our study the continuous BDI scores only trended toward being worse in the GBA-PD group compared to IPD. In addition, unlike the former study, we did not observe worse cognition among GBA-PD overall, as assessed by MoCA. Of interest, 70% of GBA-PD subjects assessed in the Brockman study had *GBA1* mutations classified as severe compared with only 13% in our study. This discrepancy might explain the cognition differences and difference in raw BDI scores between the two studies, as severity of mutations has been associated with worse disease, in particular earlier age of onset (57). Further, in a more recent study (58), there was no baseline difference in MoCA scores between GBA-PD and an IPD group matched for sex and disease duration, although there was a more rapid decline in MoCA performance over time among GBA-PD.

While we did not find an overall increase in anxiety in *GBA1* carriers, female sex was significant in the multivariate models of anxiety, prompting stratified analyses by sex. In studies of IPD, female sex is sometimes reported as a risk factor for anxiety (32, 37, 43) and depression (33, 34, 36); in addition, among those with early, drug-naïve Parkinson disease, women may demonstrate higher rates of anxiety than men (59). It is of interest, then, that in our post-hoc analysis separating GBA-PD and IPD by sex, we found that men with GBA-PD had a greater burden of trait-anxiety and of depression than men with IPD, but that there was no difference between women with GBA-PD and women with IPD. Furthermore, in univariate analysis, men and women with GBA-PD had comparable rates of neuropsychiatric symptoms, while in the IPD group, women had a higher burden of both anxiety and depression, which is more consistent with prior literature on anxiety and depression in PD. While this finding might be attributable to stochastic differences because of sample size, it may also be due to a particular *GBA1* effect in men, with mutations relatively increasing their risk of neuropsychiatric complications in PD. Alternatively, *GBA1* mutations may somehow equalize the risk for anxiety and depression between men and women, eliminating whatever factors exist in IPD that either increase the risk for neuropsychiatric symptoms in women, or decrease it in men. It is of interest, too, that in our study, men with GBA-PD had a significantly earlier age of disease onset compared to men with IPD (52 years compared to 61 years); other studies(57, 60, 61) have identified an earlier age of onset for GBA-PD overall compared to IPD. Although these gender differences need to be re-assessed in a larger sample, our findings raise the question of whether and how sex may modify expression of PD among *GBA1* mutation carriers (and, more broadly, among non-genetic IPD subjects). Male sex may increase the risk of developing PD among patients with Gaucher disease type 1 (62), although larger samples need to be studied. One recent study (63) found that, among those with dementia with Lewy bodies (DLB) both with and

without *GBA1* mutations, men were overwhelmingly represented in GBA-associated DLB, by a male:female ratio of 9:1; the ratio in DLB subjects without *GBA1* mutations was 1.1:1. Also, whereas the sex distribution for many inherited parkinsonisms, including *LRRK2* and parkin, does not demonstrate the typical increased frequency in men (56, 64), screens of *GBA1* samples suggest that GBA-PD may have a more typical 60:40 male:female predominance (61). Whether sex may otherwise have an impact on the risk of PD, or on motor or nonmotor manifestations, among heterozygous *GBA1* carriers remains an open area for investigation at the clinical and biological level.

The biological basis of increased neuropsychiatric symptoms among GBA-PD remains speculative. Anxiety and depression in PD may be related to Lewy body accumulation in brainstem structures such as the locus coeruleus and midbrain raphe (65, 66). GBA-PD subjects have greater hypoechogenicity in the midbrain raphe on transcranial sonography (3). This has been associated with depression in PD (67), and may reflect involvement of non-dopaminergic neurotransmitter systems that modulate mood. GBA-PD may have a greater burden of cortical Lewy bodies than IPD (4, 10), and anxiety and depression are frequent features of dementia with Lewy bodies (68–71), a disease that is also significantly more common in heterozygous *GBA1* mutation carriers (7, 9). It is unclear whether other, subcortical brain structures, such as the locus coeruleus or midbrain raphe, may be similarly more vulnerable to Lewy body accumulation or neurodegeneration in GBA-PD than in IPD.

Our study has several potential limitations. While psychometric instruments to assess depression in PD, including the BDI, have been widely validated, there is debate about the choice of instruments to assess anxiety. The STAI Form Y was updated from the original Form X to replace items that overlapped between depression and anxiety (25), but Form Y has not been specifically validated in PD; this may have influenced our ability to detect anxiety among participants. Despite this limitation, Movement Disorder Society expert consensus guidelines have supported the use of both the STAI (26) and the BDI (24). A strength of the STAI is its assessment of both “state” and “trait” anxiety, reflecting the dynamic nature of anxiety, which is particularly relevant to PD, although our cross-sectional design did not fully capitalize on this strength. A recently-described, PD-specific anxiety rating scale, the Parkinson Anxiety Scale, ultimately may be a superior instrument for assessing anxiety in PD, both clinically and in research settings (72).

Another limitation relates to our participants, who were recruited from among Ashkenazi Jewish patients in a tertiary referral center; thus, our findings may not be representative of PD patients in the general patient population. While we did not match for age and sex, we did adjust for these factors in the regression models, which allowed detection of a potential sex effect. We also ascertained *GBA1* mutation carriers by screening for common mutations in the Ashkenazi Jewish population, rather than by identifying mutations through complete gene sequencing; thus the number of *GBA1* mutation carriers in our sample may have been underestimated. On the other hand, if as a result of screening rather than sequencing some of the carriers were misclassified as non-carriers, this would likely lead to an underestimation of the difference in neuropsychiatric symptoms among those classified as GBA-PD; as a result, the statistically significant differences that we did identify would thus be more likely to reflect a real gene effect.

Finally, our sample is relatively small, although it is comparable to or larger than the sample size in other studies assessing neuropsychiatric symptomatology in GBA-PD. As a result of our small sample size, our study was insufficiently powered to detect differences in all measures, so there may be additional differences between GBA-PD and IPD that we could not demonstrate with statistical significance. For example, several studies have identified a greater burden of cognitive impairment in GBA-PD compared to IPD (5); we could not demonstrate this. We would have required larger numbers to obtain statistically significant results for cognition: specifically, we would have required 300 GBA-PD subjects and 300 IPD subjects to achieve sufficient power to demonstrate a significant difference ($p=0.05$) in the observed frequency of cognitive impairment as defined by MoCA score < 26. Thus we do not assert that there is no difference in cognition between GBA-PD and IPD, but that larger numbers are required to confirm such a difference. The fact that we had sufficient power to detect significant differences in anxiety and depression suggests that there is likely a more robust difference in these features. Assessment in larger cohorts with PD specific scales that perform well in cognitively impaired individuals is warranted.

Mutated GCase provides an exceptional target for disease modifying therapies in GBA-PD (2). Designing clinical trials will require a nuanced understanding of the differences between GBA-PD and IPD and of the clinical and biological impact of *GBA1* mutations on PD expression in different populations. Nonmotor symptom burden could reflect disease severity and indicate relative susceptibility of PD to disease-modifying therapies. Proper randomization or stratification schema in future trials might include nonmotor symptoms. Further, as discussions regarding pre-symptomatic trials are raised, it will be important to consider biomarkers in GBA-PD that may be present in carriers prior to phenoconversion. A recent study explored prodromal symptoms of PD, including depression, in *GBA1* mutation carriers without PD; heterozygote carriers demonstrated a significant worsening of BDI scores over the 2-year study period compared to controls (47), suggesting that depression could be a marker of premotor disease progression, and thus a potential outcome measure in the assessment of presymptomatic, disease modifying therapies. Our data support the possibility that anxiety might also be worth exploring as a marker of disease severity or treatment response, in the motor or premotor phase of GBA-associated PD.

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References

1. Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. The New England journal of medicine. 2009 Oct 22; 361(17):1651–61. Epub 2009/10/23. eng. [PubMed: 19846850]
2. Sardi SP, Cheng SH, Shihabuddin LS. Gaucher-related synucleinopathies: the examination of sporadic neurodegeneration from a rare (disease) angle. Prog Neurobiol. 2015 Feb.125:47–62. [PubMed: 25573151]
3. Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T, et al. GBA-associated PD presents with nonmotor characteristics. Neurology. 2011 Jul 19; 77(3):276–80. Epub 2011/07/08. eng. [PubMed: 21734182]
4. Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain: a journal of neurology. 2009 Jul; 132(Pt 7):1783–94. Epub 2009/03/17. eng. [PubMed: 19286695]

5. Alcalay RN, Caccappolo E, Mejia-Santana H, Tang M, Rosado L, Orbe Reilly M, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology. 2012 May 1; 78(18):1434–40. [PubMed: 22442429]

6. Seto-Salvia N, Pagonabarraga J, Houlden H, Pascual-Sedano B, Dols-Icardo O, Tucci A, et al. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Movement disorders: official journal of the Movement Disorder Society. 2012 Mar; 27(3):393–9. [PubMed: 22173904]

7. Nalls MA, Duran R, Lopez G, Kurzawa-Akanbi M, McKeith IG, Chinnery PF, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA neurology. 2013 Jun; 70(6):727–35. Epub 2013/04/17. eng. [PubMed: 23588557]

8. Oeda T, Umemura A, Mori Y, Tomita S, Kohsaka M, Park K, et al. Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. Neurobiology of aging. 2015 Dec; 36(12):3306–13. [PubMed: 26422360]

9. Mata IF, Samii A, Schneer SH, Roberts JW, Griffith A, Leis BC, et al. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Archives of neurology. 2008 Mar; 65(3):379–82. [PubMed: 18332251]

10. Choi JH, Stubblefield B, Cookson MR, Goldin E, Velayati A, Tayebi N, et al. Aggregation of alpha-synuclein in brain samples from subjects with glucocerebrosidase mutations. Molecular genetics and metabolism. 2011 Sep-Oct;104(1–2):185–8. [PubMed: 21742527]

11. Clark LN, Kartsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, et al. Association of glucocerebrosidase mutations with dementia with lewy bodies. Archives of neurology. 2009 May; 66(5):578–83. [PubMed: 19433657]

12. Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, et al. GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. Neurology. 2012 Nov 6; 79(19):1944–50. [PubMed: 23035075]

13. Alcalay RN, Mirelman A, Saunders-Pullman R, Tang MX, Mejia Santana H, Raymond D, et al. Parkinson disease phenotype in Ashkenazi Jews with and without LRRK2 G2019S mutations. Movement disorders: official journal of the Movement Disorder Society. 2013 Dec; 28(14):1966–71. [PubMed: 24243757]

14. Pankratz N, Nichols WC, Uniacke SK, Halter C, Rudolph A, Shults C, et al. Genome screen to identify susceptibility genes for Parkinson disease in a sample without parkin mutations. American journal of human genetics. 2002 Jul; 71(1):124–35. [PubMed: 12058349]

15. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of neurology, neurosurgery, and psychiatry. 1992 Mar; 55(3):181–4.

16. Balwani M, Grace ME, Desnick RJ. Gaucher disease: when molecular testing and clinical presentation disagree -the novel c.1226A>G(p.N370S)–RecNcil allele. Journal of inherited metabolic disease. 2011 Jun; 34(3):789–93. [PubMed: 21431620]

17. Alcalay RN, Levy OA, Waters CC, Fahn S, Ford B, Kuo SH, et al. Glucocerebrosidase activity in Parkinson's disease with and without GBA mutations. Brain: a journal of neurology. 2015 Sep; 138(Pt 9):2648–58. [PubMed: 26117366]

18. Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. The New England journal of medicine. 2006 Jan 26; 354(4):424–5. [PubMed: 16436782]

19. Saunders-Pullman R, Hagenah J, Dhawan V, Stanley K, Pastores G, Sathe S, et al. Gaucher disease ascertained through a Parkinson's center: imaging and clinical characterization. Movement disorders: official journal of the Movement Disorder Society. 2010 Jul 30; 25(10):1364–72. [PubMed: 20629126]

20. Fahn, S., E, R., members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn, S.M, C.Calne, DB., Goldstein, M., editors. Recent developments in Parkinson's disease 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p. 153-63.

21. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967 May; 17(5):427–42. [PubMed: 6067254]

22. Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010 Nov 9; 75(19):1717–25. [PubMed: 21060094]

23. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of general psychiatry. 1961 Jun.4:561–71. [PubMed: 13688369]

24. Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Movement disorders: official journal of the Movement Disorder Society. 2007 Jun 15; 22(8):1077–92. [PubMed: 17394234]

25. Spielberger, CD., G, R., Lushene, R., Vagg, PR., Jacobs, GA. State-Trait Anxiety Inventory for Adults. Consulting Psychologists Press, Inc; 1983.

26. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, et al. Anxiety rating scales in Parkinson's disease: critique and recommendations. Movement disorders: official journal of the Movement Disorder Society. 2008 Oct 30; 23(14):2015–25. [PubMed: 18792121]

27. Kvaal K, Ulstein I, Nordhus IH, Engedal K. The Spielberger State-Trait Anxiety Inventory (STAI): the state scale in detecting mental disorders in geriatric patients. International journal of geriatric psychiatry. 2005 Jul; 20(7):629–34. [PubMed: 16021666]

28. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2010 Nov 15; 25(15):2649–53. [PubMed: 21069833]

29. Aarsland D, Bronnick K, Alves G, Tysnes OB, Pedersen KF, Ehrt U, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry. 2009 Aug; 80(8):928–30.

30. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2008 Jan 30; 23(2):183–9. quiz 313. [PubMed: 17987654]

31. Dissanayaka NN, Sellbach A, Matheson S, O'Sullivan JD, Silburn PA, Byrne GJ, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. Movement disorders: official journal of the Movement Disorder Society. 2010 May 15; 25(7):838–45. [PubMed: 20461800]

32. Negre-Pages L, Grandjean H, Lapeyre-Mestre M, Montastruc JL, Fourrier A, Lepine JP, et al. Anxious and depressive symptoms in Parkinson's disease: the French cross-sectionnal DoPaMiP study. Movement disorders: official journal of the Movement Disorder Society. 2010 Jan 30; 25(2): 157–66. [PubMed: 19950403]

33. Riedel O, Klotsche J, Spottke A, Deuschl G, Forstl H, Henn F, et al. Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. Journal of neurology. 2010 Jul; 257(7):1073–82. [PubMed: 20140443]

34. Siri C, Cilia R, De Gaspari D, Villa F, Goldwurm S, Marco C, et al. Psychiatric symptoms in Parkinson's disease assessed with the SCL-90R self-reported questionnaire. Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2010 Feb; 31(1):35–40.

35. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Risk of incident depression in patients with Parkinson disease in the UK. European journal of neurology: the official journal of the European Federation of Neurological Societies. 2011 Mar; 18(3):448–53.

36. Dissanayaka NN, Sellbach A, Silburn PA, O'Sullivan JD, Marsh R, Mellick GD. Factors associated with depression in Parkinson's disease. Journal of affective disorders. 2011 Jul; 132(1–2):82–8. [PubMed: 21356559]

37. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE. Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross-sectional study. Movement disorders: official journal of the Movement Disorder Society. 2011 Feb 15; 26(3):484–92. [PubMed: 21312281]

38. Solla P, Cannas A, Floris GL, Orofino G, Costantino E, Boi A, et al. Behavioral, neuropsychiatric and cognitive disorders in Parkinson's disease patients with and without motor complications. Progress in neuro-psychopharmacology & biological psychiatry. 2011 Jun 1; 35(4):1009–13. [PubMed: 21324349]

39. van der Hoek TC, Bus BA, Matui P, van der Marck MA, Esselink RA, Tendolkar I. Prevalence of depression in Parkinson's disease: effects of disease stage, motor subtype and gender. Journal of the neurological sciences. 2011 Nov 15; 310(1–2):220–4. [PubMed: 21802694]
40. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE. Anxiety and motor fluctuations in Parkinson's disease: a cross-sectional observational study. Parkinsonism & related disorders. 2012 Dec; 18(10):1084–8. [PubMed: 22771284]
41. Ziropadja L, Stefanova E, Petrovic M, Stojkovic T, Kostic VS. Apathy and depression in Parkinson's disease: the Belgrade PD study report. Parkinsonism & related disorders. 2012 May; 18(4):339–42. [PubMed: 22166396]
42. Monastero R, Di Fiore P, Ventimiglia GD, Camarda R, Camarda C. The neuropsychiatric profile of Parkinson's disease subjects with and without mild cognitive impairment. Journal of neural transmission. 2013 Apr; 120(4):607–11. [PubMed: 23400362]
43. Stefanova E, Ziropadja L, Petrovic M, Stojkovic T, Kostic V. Screening for anxiety symptoms in Parkinson disease: a cross-sectional study. Journal of geriatric psychiatry and neurology. 2013 Mar; 26(1):34–40. [PubMed: 23407399]
44. Yamanishi T, Tachibana H, Oguru M, Matsui K, Toda K, Okuda B, et al. Anxiety and depression in patients with Parkinson's disease. Internal medicine. 2013; 52(5):539–45. [PubMed: 23448761]
45. Sagna A, Gallo JJ, Pontone GM. Systematic review of factors associated with depression and anxiety disorders among older adults with Parkinson's disease. Parkinsonism & related disorders. 2014 Jul; 20(7):708–15. [PubMed: 24780824]
46. Barrett MJ, Shanker VL, Severt WL, Raymond D, Gross SJ, Schreiber-Agus N, et al. Cognitive and Antipsychotic Medication Use in Monoallelic GBA-Related Parkinson Disease. JIMD reports. 2014; 16:31–8. Epub 2014/05/23. eng. [PubMed: 24850235]
47. Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA neurology. 2015 Feb; 72(2):201–8. [PubMed: 25506732]
48. McNeill A, Duran R, Proukakis C, Bras J, Hughes D, Mehta A, et al. Hyposmia and cognitive impairment in Gaucher disease patients and carriers. Movement disorders: official journal of the Movement Disorder Society. 2012 Apr; 27(4):526–32. [PubMed: 22344629]
49. Kummer A, Cardoso F, Teixeira AL. Generalized anxiety disorder and the Hamilton Anxiety Rating Scale in Parkinson's disease. Arquivos de neuro-psiquiatria. 2010 Aug; 68(4):495–501. [PubMed: 20730299]
50. Menza MA, Robertson-Hoffman DE, Bonapace AS. Parkinson's disease and anxiety: comorbidity with depression. Biological psychiatry. 1993 Oct 1; 34(7):465–70. [PubMed: 8268331]
51. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2001 May; 16(3):507–10. [PubMed: 11391746]
52. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, Garcia-Sanchez C, Gironell A, Trapecio Group S. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. Movement disorders: official journal of the Movement Disorder Society. 2008 Oct 15; 23(13):1889–96. [PubMed: 18709682]
53. Sagna A, Gallo JJ, Pontone GM. Systematic review of factors associated with depression and anxiety disorders among older adults with Parkinson's disease. Parkinsonism & related disorders. 2014 Apr 1.
54. Jasinska-Myga B, Putzke JD, Wider C, Wszolek ZK, Uitti RJ. Depression in Parkinson's disease. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2010 Jan; 37(1):61–6. [PubMed: 20169775]
55. Shanker V, Groves M, Heiman G, Palmese C, Saunders-Pullman R, Ozelius L, et al. Mood and cognition in leucine-rich repeat kinase 2 G2019S Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2011 Aug 15; 26(10):1875–80. [PubMed: 21611978]
56. Kasten M, Kertelge L, Bruggemann N, van der Vegt J, Schmidt A, Tadic V, et al. Nonmotor symptoms in genetic Parkinson disease. Archives of neurology. 2010 Jun; 67(6):670–6. [PubMed: 20558386]

57. Gan-Or Z, Giladi N, Rozovski U, Shifrin C, Rosner S, Gurevich T, et al. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. Neurology. 2008 Jun 10; 70(24):2277–83. [PubMed: 18434642]
58. Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Movement disorders: official journal of the Movement Disorder Society. 2015 Mar; 30(3): 407–11. [PubMed: 25448271]
59. Liu R, Umbach DM, Peddada SD, Xu Z, Troster AI, Huang X, et al. Potential sex differences in nonmotor symptoms in early drug-naive Parkinson disease. Neurology. 2015 May 26; 84(21): 2107–15. [PubMed: 25925983]
60. Nichols WC, Pankratz N, Marek DK, Pauciulo MW, Elsaesser VE, Halter CA, et al. Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. Neurology. 2009 Jan 27; 72(4):310–6. [PubMed: 18987351]
61. Gan-Or Z, Bar-Shira A, Mirelman A, Gurevich T, Kedmi M, Giladi N, et al. LRRK2 and GBA mutations differentially affect the initial presentation of Parkinson disease. Neurogenetics. 2010 Feb; 11(1):121–5. [PubMed: 19458969]
62. Chetrit EB, Alcalay RN, Steiner-Birmanns B, Altarescu G, Phillips M, Elstein D, et al. Phenotype in patients with Gaucher disease and Parkinson disease. Blood cells, molecules & diseases. 2013 Mar; 50(3):218–21.
63. Gamez-Valero A, Prada-Dacasa P, Santos C, Adame-Castillo C, Campdelacreu J, Rene R, et al. GBA Mutations Are Associated With Earlier Onset and Male Sex in Dementia With Lewy Bodies. Movement disorders: official journal of the Movement Disorder Society. 2016 Mar 29.
64. Orr-Urtreger A, Shifrin C, Rozovski U, Rosner S, Bercovich D, Gurevich T, et al. The LRRK2 G2019S mutation in Ashkenazi Jews with Parkinson disease: is there a gender effect? Neurology. 2007 Oct 16; 69(16):1595–602. [PubMed: 17938369]
65. Dickson DW, Fujishiro H, Orr C, DelleDonne A, Josephs KA, Frigerio R, et al. Neuropathology of non-motor features of Parkinson disease. Parkinsonism & related disorders. 2009 Dec; 15(Suppl 3):S1–5.
66. Frisina PG, Haroutunian V, Libow LS. The neuropathological basis for depression in Parkinson's disease. Parkinsonism & related disorders. 2009 Feb; 15(2):144–8. [PubMed: 18571456]
67. Walter U, Skoloudik D, Berg D. Transcranial sonography findings related to non-motor features of Parkinson's disease. Journal of the neurological sciences. 2010 Feb 15; 289(1–2):123–7. [PubMed: 19735925]
68. Klatka LA, Louis ED, Schiffer RB. Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. Neurology. 1996 Nov; 47(5):1148–52. [PubMed: 8909420]
69. Rockwell E, Choure J, Galasko D, Olichney J, Jeste DV. Psychopathology at initial diagnosis in dementia with Lewy bodies versus Alzheimer disease: comparison of matched groups with autopsy-confirmed diagnoses. International journal of geriatric psychiatry. 2000 Sep; 15(9):819–23. [PubMed: 10984728]
70. Fritze F, Ehrt U, Sonnesyn H, Kurz M, Hortobagyi T, Nore SP, et al. Depression in mild dementia: associations with diagnosis, APOE genotype and clinical features. International journal of geriatric psychiatry. 2011 Oct; 26(10):1054–61. [PubMed: 21905099]
71. Borroni B, Agosti C, Padovani A. Behavioral and psychological symptoms in dementia with Lewy-bodies (DLB): frequency and relationship with disease severity and motor impairment. Archives of gerontology and geriatrics. 2008 Jan-Feb;46(1):101–6. [PubMed: 17467082]
72. Leentjens AF, Dujardin K, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. Movement disorders: official journal of the Movement Disorder Society. 2014 Jul; 29(8):1035–43. [PubMed: 24862344]

Highlights

- *GBA1* mutations confer greater susceptibility to depression in those with Parkinson disease.
- This relationship persists when controlled for age, sex, disease duration, motor disability, and cognitive performance.
- Men with Parkinson disease due to *GBA1* mutations may be particularly susceptible to a greater burden of anxiety and depression compared to men with Parkinson disease without *GBA1* mutations.

Table 1

Summary of Demographics, Clinical Features and Primary Outcomes

	GBA-PD	IPD	p
n	31	55	—
Age	65.6 ±12.5	68.0 ± 11.4	n.s.
Men (n=54)	61.1 ± 13.0	68.2 ± 11.8	n.s.
Women (n=32)	70.5 ± 10.2	67.5 ± 10.8	n.s.
Women (%)	15 (48.4)	17 (30.9)	n.s.
Age of onset (yrs)	57.0 ± 12.7	59.7 ± 11.4	n.s.
men	52.6 ± 12.4	60.9 ± 11.9	**0.03**
women	61.7 ± 11.7	56.9 ± 9.8	n.s.
Duration of PD(yrs)	8.6 ± 5.7	8.3 ± 7.3	n.s.
men	8.5 ± 6.0	7.3 ± 5.6	n.s.
women	8.7 ± 5.6	10.6 ± 10.0	n.s.
Current Antidepressant use, n (%)	10 (32.3)	20 (36.4)	n.s.
men	4 (25.0)	12 (31.6)	n.s.
women	6 (40.0)	8 (47.1)	n.s.
Current Antipsychotic use (%) *	2 (7.41)	4 (8.16)	n.s.
men	2 (14.3)	3 (8.8)	n.s.
women	0	1 (6.7)	n.s.
UPDRS I	2.4 ± 2.0	2.4 ± 1.8	n.s.
men	2.9 ± 2.2	2.6 ± 1.9	n.s.
women	2.0 ± 1.7	1.9 ± 1.6	n.s.
UPDRS II	10.1 ± 7.0	9.4 ± 5.6	n.s.
men	10.4 ± 7.0	9.6 ± 6.1	n.s.
women	9.7 ± 7.2	8.9 ± 4.5	n.s.
UPDRS III	16.7 ± 8.7	20.4 ± 13.2	n.s.
men	18.6 ± 9.7	21.0 ± 14.1	n.s.
women	14.5 ± 7.1	19.0 ± 11.5	n.s.
UPDRS IV	2.5 ± 3.0	2.0 ± 2.3	n.s.
men	2.9 ± 3.6	1.8 ± 1.9	n.s.
women	2.1 ± 2.4	2.5 ± 2.9	n.s.
H&Y	2.3 ± 1.1	2.2 ± 0.9	n.s.
men	2.1 ± 1.0	2.2 ± 0.8	n.s.
women	2.4 ± 1.2	2.2 ± 1.0	n.s.
S&E ADL	79.1 ± 22.6	81.1 ± 18.2	n.s.
men	81.0 ± 13.7	80.3 ± 21.4	n.s.
women	77.3 ± 29	82.9 ± 8.3	n.s.
MoCA	24.5 ± 4.6	24.8 ± 4.9	n.s.
men	25.3 ± 3.3	24.3 ± 5.4	n.s.
women	23.6 ± 5.9	25.9 ± 3.6	n.s.

	GBA-PD	IPD	p
n (%) < 26	14 (51.9)	24 (44.4)	n.s.
men	7 (46.7)	19 (51.4)	n.s.
women	7 (58.3)	5 (29.4)	n.s.
BDI	11.0 ± 7.9	9.1 ± 8.4	n.s.
men	11.7 ± 9.4	6.9 ± 4.6	n.s.
women	10.3 ± 6.0	13.9 ± 12.2	n.s.
n (%) ≥ 14	10 (33.3)	7 (13.2)	<**0.05**
men	6 (37.5)	2 (5.6)	**0.007**
women	4 (28.6)	5 (29.4)	n.s.
STAI	—	—	—
State	34.6 ± 13.2	35.9 ± 12.1	n.s.
men	33.0 ± 13.0	32.8 ± 10.1	n.s.
women	36.3 ± 13.6	42.8 ± 13.6	n.s.
n (%) ≥ 55	1 (3.6)	3 (5.5)	n.s.
men	1 (7.14)	0	n.s.
women	0	3 (17.7)	n.s.
Trait	38.0 ± 13.0	35.4 ± 11.9	n.s.
men	39.9 ± 13.9	31.7 ± 10.0	**0.04**
women	36.1 ± 12.8	43.4 ± 12.1	n.s.

Results expressed as mean +/− SD.

Significant p values (<0.05) are represented; nonsignificant p values (≥0.05) denoted as “n.s.”

*Note that all subjects taking antipsychotic medications were taking either quetiapine or clozaril.

Table 2

Regression Models Describing Association with Depression and Anxiety

a: Linear regression model - BDI continuous score*			
n = 77	**Coefficient**	**95% CI**	**p**
Age	0.00	−0.14, 0.14	0.96
Sex (F)	4.36	−0.17, 8.90	0.06
PD duration	0.23	−0.12, 0.58	0.20
UPDRS III	0.03	−0.16, 0.22	0.75
GBA PD	1.35	−2.20, 4.90	0.46
MoCA	−0.23	−0.61, 0.14	0.22

b: Logistic regression model evaluating presence of depression (BDI cutoff score)*			
n = 77	**OR**	**95% CI**	**p**
Age	1.03	0.97, 1.09	0.42
Sex (F)	2.81	0.79, 10.0	0.11
PD duration	0.99	0.91, 1.08	0.90
UPDRS III	1.00	0.95, 1.06	0.87
GBA PD	3.66	1.13, 11.8	**0.03**
MoCA	0.94	0.83, 1.07	0.39

c: Linear regression model – STAI state continuous score*			
n = 77	**Coefficient**	**95% CI**	**p**
Age	0.17	−0.07, 0.41	0.16
Sex (F)	8.71	3.55, 13.9	<**0.01**
PD duration	0.11	−0.30, 0.52	0.60
UPDRS III	−0.17	−0.48, 0.15	0.30
GBA PD	0.22	−5.31, 5.76	0.94
MoCA	−0.17	−0.84, 0.50	0.62

d: Linear regression model – STAI trait continuous score*			
n = 76	**Coefficient**	**95% CI**	**p**
Age	0.10	−0.13, 0.33	0.39
Sex (F)	7.76	2.35, 13.2	<**0.01**
PD duration	0.16	−0.26, 0.58	0.46
UPDRS III	0.03	−0.29, 0.34	0.86
GBA PD	4.87	−0.55, 10.3	0.08
MoCA	0.01	−0.62, 0.64	0.98

*The significance of the terms did not change when antipsychotic and antidepressant use were included in the models (data not shown)

Neuropsychiatric characteristics of GBA-associated Parkinson disease