Title

Clinical and dopamine transporter imaging characteristics of non-manifest LRRK2 and GBA mutation carriers in the Parkinson's Progression Markers Initiative (PPMI): a cross-sectional study.

Journal

The Lancet. Neurology, 19(1)

ISSN

1474-4422

Authors

Simuni, Tanya
Uribe, Liz
Cho, Hyunkeun Ryan
et al.

Publication Date

2020

DOI

10.1016/s1474-4422(19)30319-9

Peer reviewed

Published in final edited form as:

Lancet Neurol. 2020 January ; 19(1): 71–80. doi:10.1016/S1474-4422(19)30319-9.

Correspondence to: Prof Tanya Simuni, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA, tsimuni@nmff.org.

Contributors

TS, LU, HR, CSC, ASid, JQT, ASin, DG, TF, KP, DW, BM, CMT, KK, LMC, and KM drafted and revised the manuscript (including medical writing). TS, CSC, ASid, JS, ASin, DW, BM, CMT, KM, LMC, and KM conceived or designed the study. TF, DW, BM, and CMT supervised and coordinated the study. LU, CSC, JS, AWT, and DT acquired the data. JS and AWT managed the data. TS, LU, HR, CC-G, CSC, ASid, JQT, LMS, DG, DW, BM, CMT, KK, LMC, AR, SJH, SB, and KM analysed or interpreted the data. CSC, LU, HR, and CC-G did the statistical analyses, and LU, HR, and CC-G created the figures.

*A full list of investigators is presented at the end of Article

For PPMI database see http://www.ppmi-info.org/data

For the study protocol see http://www.ppmi-info.org/study-design

For the PPMI imaging technical operations manual see http://ppmi-info.org/

Declaration of interests

CSC reports grants from the Michael J Fox Foundation, during the conduct of the study; grants from the National Institute of Neurological Disorders and Stroke and National Heart, Lung, and Blood Institute; and personal fees from the Michael J Fox Foundation, outside the submitted work. KK reports grants from the Michael J Fox Foundation, during the conduct of the study; grants from the National Institute of Neurological Disorders and Stroke, and the National Center for Advancing Translational Sciences; and personal fees from Clintrex and Hoover Brown, outside the submitted work. KM reports partial ownership of Invicro, personal fees from the Michael J Fox Foundation, Roche, Proclara, GEHC, Deanli, Prevail, Lysosomal Therapeutics, Takeda, Lundback, UCB, Invicro, Inhibikase, and Cerapsir, outside the submitted work. BM reports personal fees from the Michael J Fox Foundation and being a Parkinson's Progression Markers Initiative study eSC committee member, during the conduct of the study. WP reports personal fees from Abb Vie, Affiris, Allergan, AstraZeneca, BIAL, Biogen, Boston Scientific, Britannia, Intec, Ipsen, Lundbeck, Merz, Neuroderm, Novartis, Orion, Pharma, Roche, Prexton, Teva, Tekeda, UCBm and Zambon. KP reports grants from the Michael J Fox Foundation, during the conduct of the study; grants from AztraZeneca and Sanofi; and personal fees from Allergan and Curasen, outside the submitted work. JS reports partial owndership and consultancy work from iNVICRO; and consultancy work from Biogen, Roche, and Life Molecular Imaging, outside the submitted work. LS reports grants from the Michael J Fox Foundation, during the conduct of the study. CT reports grants from the Michael J Fox Foundation, during the conduct of the study; grants from Parkinson Foundation, Gateway LLC, Roche/Genentech, Parkinson Study Group; grants and personal fees from Biogen Idee, personal fees from Acorda, Adamas Therapeutics, Voyager Therapeutics, Intec Pharma, Grey Matter, 23andme, Neurocrine Biosciences, and CNS ratings, outside the submitted work. AT reports grants from the Michael J Fox Foundation, during the conduct of the study. DW reports salary support for serving on the Steering Committee from the Michael J Fox Foundation, during the conduct of the study.

PPMI Investigators

Steering committee: Vanessa Arnedo, Adrienne Clark, Mark Fraiser, Catherine Kopil, Sohini Chowdhury, and Todd Sherer (The Michael J Fox Foundation for Parkinson's Research, New York, NY, USA).

Study Core Centres: Nichole Daegele, Christina Salerno (Institute for Neurodegenerative Disorders, New Haven, CT, USA); Cynthia Casaceli, Ray Dorsey, Renee Wilson, and Sugi Mahes (Clinical Trials Coordination Center, University of Rochester, Rochester, NY, USA); Karen Crawford (Laboratory of Neuroimaging (LONI), University of Southern California, Los Angeles, CA, USA); Paola Casalin, Giulia Malferrari (BioRep, Milan, Italy); Mali GaniWeisz, Avi Orr-Urtreger (Tel Aviv Medical Center, Tel Aviv, Israel); Thomas Montine (Stanford University, Stanford, CA, USA); and Chris Baglieri, and Amanda Christini (Blackfynn, Philadelphia, PA, USA).

Site investigators: David Russell (Institute for Neurodegenerative Disorders, New Haven, CT, USA); Nabila Dahodwala (University of Pennsylvania, Philadelphia, PA, USA); Nir Giladi (Tel Aviv Medical Center, Tel Aviv, Israel); Stewart Factor (Emory University of Medicine, Adanta, GA, USA); Penelope Hogarth (Oregon Health and Science University, Portland, OR, USA); David Standaert (University of Alabama at Birmingham, Birmingham, AL, USA); Robert Hauser (University of South Florida, Tampa, FL, USA); Joseph Jankovic (Baylor College of Medicine, Houston, TX, USA); Marie Saint-Hilaire (Boston University, Boston, MA, USA); Irene Richard (University of Rochester, Rochester, NY, USA); David Shprecher (Banner Research Institute, Sun City, AZ, USA); Hubert Fernandez (Cleveland Clinic, Cleveland, OH, USA); Katrina Brockmann (University of Tuebingen, Tuebingen, Germany); Liana Rosenthal (Johns Hopkins University, Baltimore, MD, USA); Paolo Barone (University of Salerno, Salerno, Italy); Alberto Espay (University of Cincinnati, Cincinnati, OH, USA); Dominic Rowe (Macquarie University, Sydney, Australia); Karen Marder (Columbia University, New York, NY, USA); Anthony Santiago (The Parkinson's Institute, Sunnyvale, CA, USA); Shu-Ching Hu (University of Washington, Seattle WA, USA); Stuart Isaacson (Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL, USA); Jean-Christophe Corvol (Hospital Pitie-Salpetriere, Paris, France); Javiar Ruiz Martinez (Hospital Donostia, San Sebastian, Spain); Eduardo Tolosa (Hospital Clinic de Barcelona, Barcelona, Spain); Yen Tai (Imperial College London, London, UK); and Marios Politis (King's College London, London, UK).

Coordinators: Debra Smejdir, Linda Rees (Institute for Neurodegenerative Disorders, New Haven, CT, USA); Karen Williams (University of Iowa, Iowa City, IA, USA); Farah Kausar (University of California, San Francisco, CA, USA); Karen Williams (Northwestern University, Chicago, IL, USA); Whitney Richardson (University of Pennsylvania, Philadelphia, PA, USA); Diana Willeke (Paracelsus-Elena Klinik, Kassel, Germany); Shawnees Peacock (University of California, San Diego, CA, USA); Barbara Sommerfeld (Emory University of Medicine, Atlanta, GA, USA); Alison Freed (Oregon Health and Science University, Portland, OR, USA); Katrina Wakeman (University of Alabama at Birmingham, Birmingham, AL, USA); Courtney Blair (University of South Florida, Tampa, FL, USA); Stephanie Guthrie (Baylor College of Medicine, Houston, TX, USA); Leigh Harrell (University of South

Clinical and dopamine transporter imaging characteristics of non-manifest *LRRK2* and *GBA* mutation carriers in the Parkinson's Progression Markers Initiative (PPMI): a cross-sectional study

Tanya Simuni, **Liz Uribe**, **Hyunkeun Ryan Cho**, **Chelsea Caspell-Garcia**, **Christopher S Coffey**, **Andrew Siderowf**, **John Q Trojanowski**, **Leslie M Shaw**, **John Seibyl**, **Andrew Singleton**, **Arthur W Toga**, **Doug Galasko**, **Tatiana Foroud**, **Duygu Tosun**, **Kathleen Poston**, **Daniel Weintraub**, **Brit Mollenhauer**, **Caroline M Tanner**, **Karl Kieburtz**, **Lana M Chahine**, **Alyssa Reimer**, **Samantha J Hutten**, **Susan Bressman**, **Kenneth Marek PPMI Investigators***

Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (Prof T Simuni MD); Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA, USA (L Uribe MS, HR Cho PhD, C Caspell-Garcia MS, Prof CS Coffey PhD); Departments of Neurology (Prof A Siderowf MD, Prof D Weintraub MD), Departments of Pathology and Laboratory Medicine (Prof J Q Trojanowski MD, Prof LM Shaw PhD), Departments of Psychiatry (Prof D Weintraub), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; Institute for Neurodegenerative Disorders, New Haven, CT, USA (J Seibyl MD); Laboratory of Neurogenetics, National Institute on Aging, NIH, Bethesda, MD, USA (A Singleton PhD); Laboratory of Neuroimaging (LONI), University of Southern California, Los Angeles, CA, USA (Prof AW Toga PhD); Department of Neurology, University of California, San Diego, CA, USA (Prof D Galasko MD); Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA (ProfT Foroud PhD); Department of Neurology, University of California, San Francisco, San Francisco, CA, USA (D Tosun PhD, Prof C M Tanner MD); Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA (K Poston MD); Department of Neurology, University Medical Center Goettingen, Goettingen, Germany; Paracelsus-Elena-Klinik, Kassel, Germany (B Mollenhauer MD); Department of

Florida, Tampa, FL, USA); Christine Hunter (Baylor College of Medicine, Houston, TX, USA); Cathi-Ann Thomas, Raymond James (Boston University, Boston, MA, USA); Grace Zimmerman (University of Rochester, Rochester, NY, USA) Victoria Brown (Banner Research Institute, Sun City, AZ, USA) Jennifer Mule (Cleveland Clinic, Cleveland, OH, USA); Ella Hilt (University of Tuebingen, Tuebingen, Germany); Kori Ribb (Johns Hopkins University, Baltimore, MD, USA); Susan Ainscough (University of Salerno, Salerno, Italy); Misty Wethington (University of Cincinnati, Cincinnati, OH, USA); Madelaine Ranola (Macquarie University, Sydney, Australia); Helen Mejia Santana (Columbia University, New York, NY, USA); Juliana Moreno (University of Washington, Seattle WA, USA); Deborah Raymond (Beth Israel Medical Center, New York, NY, USA); Krista Speketer (University of Washington, Seatde, WA, USA); Lisbeth Carvajal Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL, USA); Stephanie Carvalo (Hospital Pitie-Salpetriere, Paris, France); Ioana Croitoru (Hospital Donostia, San Sebastian, Spain); Alicia Garrido (Hospital Clinic de Barcelona, Barcelona, Spain); Laura Marie Payne (Imperial College London, London, UK).

Industry and Scientific Advisory Board: Veena Viswanth, Lawrence Severt (Allergan, Dublin, Ireland); Maurizio Facheris, Holly Soares (Abbvie, North Chicago, IL, USA); Mark A Mintun (Avid Radiopharmaceuticals, Inc, Philadelphia, PA, USA); Jesse Cedarbaum (Biogen Idee, Cambridge, MA, USA); Peggy Taylor (BioLegend, Dedham, MA); Kevin Biglan (Eli Lilly and Company, Indianapolis, IN, USA); Emily Vandenbroucke, Zulfiqar Haider Sheikh (GE Healthcare, Princeton, NJ, USA)Baris Bingol (Genentech, San Francisco, CA, USA); Tanya Fischer, Pablo Sardi, Remi Forrat (Genzyme Sanofi, Cambridge MA, USA); AlastairReith (GlaxoSmithKline, Brentford, UK); Jan Egebjerg, Gabrielle Ahlberg Hillert (H Lundbeck A/S, Copenhagen, Denmark); Barbara Saba (Institut de Recherches Internationales Servier, Neuilly-sur-Seine, France); Chris Min (Merck and Co, Kenilworth, NJ, USA); Robert Umek (Meso Scale Diagnostics, Rockville, MD, USA); Joe Mather (Pfizer Inc, Cambridge, MA, USA); Susan De Santi (Piramal Group, Mumbai, India); Anke Post, Frank Boess, Kirsten Taylor (F Hoffmann-La Roche Limited, Basel, Switzerland); Igor Grachev (Teva Pharmaceutical Industries, Petah Tikva, Israel); Andreja Avbersek, Pierandrea Muglia (UCB Pharma, Brussel, Belgium) Kaplana Merchant (TransThera Consulting, Portland, OR, USA); Johannes Tauscher (Takeda, Osaka, Japan).

Neurology, University of Rochester Medical Center, Rochester, NY, USA (Prof K Kieburtz MD); Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA (L M Chahine MD); The Michael J Fox Foundation for Parkinson's Research, New York, NY, USA (A Reimer BS, S J Hutten PhD); Icahn School of Medicine, Mount Sinai, New York, NY, USA (Prof S Bressman MD); and Institute for Neurodegenerative Disorders, New Haven, CT, USA (K Marek MD)

Summary

Background—The Parkinson's Progression Markers Initiative (PPMI) is an ongoing observational, longitudinal cohort study of participants with Parkinson's disease, healthy controls, and carriers of the most common Parkinson's disease-related genetic mutations, which aims to define biomarkers of Parkinson's disease diagnosis and progression. All participants are assessed annually with a battery of motor and non-motor scales, 123-I Ioflupane dopamine transporter (DAT) imaging, and biological variables. We aimed to examine whether non-manifesting carriers of *LRRK2* and *GBA* mutations have prodromal features of Parkinson's disease that correlate with reduced DAT binding.

Methods—This cross-sectional analysis is based on assessments done at enrolment in the subset of non-manifesting carriers of *LRRK2* and *GBA* mutations enrolled into the PPMI study from 33 participating sites worldwide. The primary objective was to examine baseline clinical and DAT imaging characteristics in non-manifesting carriers with *GBA* and *LRRK2* mutations compared with healthy controls. DAT deficit was defined as less than 65% of putamen striatal binding ratio expected for the individual's age. We used *t* tests, χ^2 tests, and Fisher's exact tests to compare baseline demographics across groups. An inverse probability weighting method was applied to control for potential confounders such as age and sex. To account for multiple comparisons, we applied a family-wise error rate to each set of analyses. This study is registered with ClinicalTrials.gov, number .

Findings—Between Jan 1, 2014, and Jan 1, 2019, the study enrolled 208 *LRRK2* (93% G2019S) and 184 *GBA* (96% N370S) non-manifesting carriers. Both groups were similar with respect to mean age, and about 60% were female. Of the 286 (73%) non-manifesting carriers that had DAT imaging results, 18 (11%) *LRRK2* and four (3%) *GBA* non-manifesting carriers had a DAT deficit. Compared with healthy controls, both *LRRK2* and *GBA* non-manifesting carriers had significantly increased mean scores on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (total score 4·6 [SD 4·4] healthy controls *vs* 8·4 [7·3] *LRRK2 vs* 9·5 [9·2] *GBA*, p<0·0001 for both comparisons) and the Scale for Outcomes for PD - autonomic function (5·8 [3·7] *vs* 8·1 [5·9] and 8·4 [6·0], p<0·0001 for both comparisons). There was no difference in daytime sleepiness, anxiety, depression, impulsive-compulsive disorders, blood pressure, urate, and rapid eye movement (REM) behaviour disorder scores. Hyposmia was significantly more common only in *LRRK2* non-manifesting carriers (69 [36%] of 194 healthy controls *vs* 114 [55%] of 208 *LRRK2* non-manifesting carriers; p=0·0003). Finally, *GBA* but not *LRRK2* non-manifesting carriers showed increased DAT striatal binding ratios compared with healthy controls in the caudate (healthy controls 2·98 [SD 0·63] *vs GBA* 3·26 [0·63]; p<0·0001), putamen (2·15 [0·56] *vs* 2·48 [0·52]; p<0·0001), and striatum (2·56 [0·57] *vs* 2·87 [0·55]; p<0·0001).

Interpretation—Our data show evidence of subtle motor and non-motor signs of Parkinson's disease in non-manifesting carriers compared with healthy controls that can precede DAT deficit.

Longitudinal data will be essential to confirm these findings and define the trajectory and predictors for development of Parkinson's disease.

Funding—Michael J Fox Foundation for Parkinson's Research.

Introduction

Slowing the progression of Parkinson's disease remains a major unmet goal in therapeutics. Failure of previous studies to show slowing of disability in patients with Parkinson's disease might be due to a late intervention in relation to progression of the neuropathological process. The current diagnosis is based on the set of clinical motor features that define Parkinson's disease; however, these characteristics become apparent after 50–70% of nigrostriatal dopamine function has been lost.[1,2] Therefore, intervention at the prodromal phase of the disease provides a window of opportunity. Non-manifesting gene carriers offer a unique population for potential future disease modifying and, ultimately, neuroprotective interventions. Mutations in Leucine rich kinase 2 (*LRRK2)* and heterozygous mutations in Glucosylceramidase β (*GBA*) are the two most common genetic risk factors for Parkinson's disease, responsible for up to 10% of sporadic cases globally and up to 30% in some ethnic subgroups and cases with familial disease.[3] Non-manifesting carriers represent an ideal population for disease-modifying interventions specifically targeting underlying gene-dependent biology. The challenge is that both genetic mutations have low and variable (2–30%) gene and age-dependent lifelong penetrance. Defining prodromal clinical and biological risk characteristics and establishing the trajectory change of these markers during the prodromal period and their contribution to risk of phenoconversion to motor parkinsonism are essential steps to allow therapeutics to move into the premanifesting population. The number of studies examining motor, non-motor, and imaging characteristics of non-manifesting carriers of *LRRK2* and *GBA* mutations is growing. However, data are scarce from large, controlled, prospective studies comparing non-manifesting carriers with healthy controls, and newly diagnosed participants with sporadic Parkinson's disease, as well as allowing comparison between cohorts of *GBA* and *LRRK2* non-manifesting carriers.

The primary objective of this study was to systematically assess baseline clinical and dopamine transporter (DAT) characteristics of non-manifesting carriers of *GBA* and *LRRK2* mutations compared with healthy controls enrolled in the Parkinson's Progression Markers Initiative (PPMI) study. We hypothesised that non-manifesting carriers will have several prodromal features of Parkinson's disease that will correlate with reduced DAT binding. The secondary objective was to evaluate these characteristics in non-manifesting carriers of *LRRK2* versus *GBA* mutations.

Methods

Study design

Data used in the preparation of this study were obtained from the PPMI database. PPMI is an ongoing observational, international, multicentre cohort study aiming to identify blood-based, genetic, spinal fluid, and imaging biomarkers of Parkinson's disease progression with

longitudinal follow-up in a large cohort. The aims and methodology of the study have been published elsewhere.[4,5] Study protocol and manuals and are available online.

PPMI enrolled patients with early, untreated (de novo) Parkinson's disease as well as healthy controls of similar age and sex between June 7, 2010, and May 27, 2013. The study was expanded in 2014 to include genetic cohorts with Parkinson's disease as well as non-manifesting carriers of mutations in the *SNCA, LRRK2*, and *GBA* genes. For this study, we used the baseline dataset for non-manifesting carriers of *LRRK2* and *GBA* mutations enrolled between Sept 23, 2013, and March 25, 2019, from 33 participating outpatient Parkinson's disease treatment centres worldwide.

Participants

Newly diagnosed, untreated patients with Parkinson's disease and healthy controls were enrolled in PPMI on the basis of inclusion and exclusion criteria previously published.[5] The cohort of carriers of non-manifesting *LRRK2* and *GBA* mutations comprised male and female participants aged 45 years or older at baseline with a *LRRK2* or *GBA* mutation confirmed by the genetic core. Participants were excluded if they had a clinical diagnosis of Parkinson's disease based on established diagnostic criterial or conditions that precluded safe performance of lumbar puncture. Participants who were referred to sites as non-manifesting carriers but determined to have Parkinson's disease at the screening visit by the site investigator were excluded from this analysis. Recruitment of the cohort of non-manifesting carriers was done via participating sites (existing databases) and a centralised recruitment initiative, described previously, specifically targeting first-degree relatives of patients with Parkinson's disease of Ashkenazi Jewish descent.[6] The study was approved by the Institutional Review Board at each site, and participants provided written informed consent. Data were downloaded on April 1, 2019.

Genetic testing was done by the centralised PPMI genetic testing core. All non-manifesting carriers received pretesting and post-testing genetic counselling by phone, done by certified genetic counsellors from the University of Indiana or by site-qualified personnel. The *LRRK2* genetic testing battery includes G2019S and R1441G mutations. GBA genetic testing includes N370S (in all), and L483P, L444P, IVS2+1, and 84GG (in a subset of participants) mutations. Dual mutation carriers *(LRRK2* and *GBA)* were excluded from this analysis (n=12). All PPMI participants subsequently had whole exome or genome sequencing. Two participants recruited into the cohort of healthy controls were identified to have a *GBA* or *LRRK2* mutation and were excluded from the analysis.

Outcomes

All participants enrolled in PPMI received the PPMI standard test battery of assessments described in detail previously.[7,8] In addition to mutation type, other demographic variables were collected, including sex, age, education, ethnicity, race, and family history. The clinical battery relevant to this analysis includes the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Montreal Cognitive Assessment (MOCA) for assessment of global cognitive abilities, the 15-item Geriatric Depression Scale, the Scale for Outcomes for Parkinson's Disease—autonomic function (SCOPA-AUT),

State and Trait Anxiety Scale, Modified Schwab and England Activities of Daily Living Scale, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, the Epworth Sleepiness Scale, the Rapid Eye Movement Behaviour Disorder (RBD) Questionnaire, and the University of Pennsylvania Smell Identification test (UPSIT). All participants were expected to have a DAT scan to assess DAT binding, analysed according to the PPMI imaging technical operations manual.[8] Patients were enrolled into the Parkinson's disease and healthy control cohorts on the basis of visual assessment consistent with regulatory-approved DAT read (normal *vs* abnormal). All participants had quantitative analysis using previously described methods to determine minimum putamen striatal binding ratio (SBR). Less than 65% of age-expected putamen striatal binding ratio was used as a cutoff for DAT deficit in this analysis.[5] This cutoff was also used for quantitative analysis of DAT deficit in both cohorts.[7] Quantitative data of DAT were used for this analysis; therefore, some participants might have a normal read on the visual analysis of the DAT scan and show signs of DAT deficit with quantitative analysis. PPMI also collects an array of CSF biomarkers, but these measures are available only for a small subset of participants in the genetic cohort (because they are processed in batches) and thus were not included in this report. This study is registered with ClinicalTrials.gov, number , and is closed to accrual.

Statistical analysis

Statistical analyses were done using SAS 14.3 (SAS Institute Inc, Cary, NC). We did *t* tests, χ^2 tests, and Fisher's exact tests to compare baseline demographics across groups at a significance level of 0·05. A method of inverse probability weighting was applied through the CAUSALTRT procedure, an estimation method designed primarily for use with observational data, to control for potential confounders, such as age and sex, which could affect outcome. To account for multiple comparisons reported, we applied a family-wise error rate to each set of analyses. A Bonferroni correction was made to adjust for number of comparisons of clinical characteristics and striatal binding ratios. The corrected significance level is 0·05 divided by the total number of comparisons provided for that table—ie, 0·05/49=0·001 for clinical characteristics comparisons and 0·05/9=0·005 for striatal binding ratios.

Role of the funding source

Research officers (AR and SH) at the funding institution were involved in study design, interpretation of results, review and revision of this manuscript, and the decision to submit for publication. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had the final decision to submit for publication.

Results

Of586 participants, 208 non-manifesting carriers of *LRRK2* mutations, 184 non-manifesting carriers of *GBA* mutations, and 194 healthy controls were included in the analysis. Eight participants referred to sites as non-manifesting carriers were determined to have Parkinson's disease at the screening visit by the site investigator, so they were excluded from this analysis. Participants with Parkinson's disease (n=423) are included in the tables as a

reference cohort but no comparative analyses were completed as we expected significant differences in all outcome measures. Baseline demographics, family history of Parkinson's disease, presence of DAT deficit, and type of genetic mutation (for the genetic cohorts) are presented in table 1. No difference was observed in age between non-manifesting carriers of *LRRK2* or *GBA* mutations and healthy controls. More than 50% of participants were female in both cohorts of non-manifesting carriers, compared with male predominance (65%) consistently reported in all sporadic cohort studies of Parkinson's disease.[30] As expected, non-manifesting carriers of *LRRK2* and *GBA* mutations had a high proportion of first-degree relatives with Parkinson's disease (178 [86%] of 208 and 140 [76%] of 184, respectively). Given that enrolment was focused on the Ashkenazi Jewish community, most *LRRK2* mutations were G2019S and *GBA* mutations were N370S. 195 (94%) of 208 *LRRK2* and 179 (97%) of 184 *GBA* non-manifesting carriers had a DAT scan done at baseline. However, a delay occurred between the time that the scan was collected and the SBR values became available for analysis in the primary study database. Because of this delay, 162 (78%) of 208 *LRRK2* and 124 (67%) of 184 *GBA* non-manifesting carriers had baseline DAT scan SBR values available for analysis at the time of data freeze.

The percentage of participants with DAT deficit was increased in those with *LRRK2* mutations, but decreased in those with *GBA* mutations, compared with healthy controls (18 [11%] of 162 scanned participants *vs* four [3%] of 124 *vs* 12 [6%] of 191). No difference occurred in demographics between non-manifesting carriers who had versus those who did not have DAT SBR data (appendix).

Clinical characteristics in non-manifesting carriers of *LRRK2* and *GBA* mutations were compared with healthy controls and with each other (table 2). Many variables of Parkinson's disease significantly differed between healthy controls and non-manifesting carriers. Non-manifesting carriers of *LRRK2* and *GBA* mutations had higher scores on MDS-UPDRS total score and subscores, and lower MOCA scores than healthy controls. Both cohorts of non-manifesting carriers had signs of autonomic dysfunction, as evidenced by higher SCOPA-AUT scores, but standing blood pressures remained the same. Furthermore, domains known as premotor features of Parkinson's disease, specifically olfaction, mood, anxiety, sleepiness, and RBD characteristics, were also compared with healthy controls. None of these characteristics was different in cohorts of non-manifesting carriers compared with healthy controls, aside from hyposmia that was present in non-manifesting carriers of *LRRK2* mutations but not in *GBA* mutations compared with healthy controls.

Comparison of the *GBA* versus *LRRK* cohort showed only significant differences in UP SIT score (worse in *LRRK2* group; p=0·0071). No difference occurred in RBD scores between non-manifesting carriers of *LRRK2* and *GBA* mutations.

Non-manifesting carriers of *LRRK2* mutations had no difference in SBR values compared with healthy controls (table 3, figure). Non-manifesting carriers of *GBA* mutations had significantly higher (better) SBR values in all regions than did healthy controls and non-manifesting carriers of *LRRK2* mutations. Patients were enrolled in the Parkinson's disease cohort or healthy control cohort on the basis of visual assessment, consistent with regulatory approved DAT read. As indicated in table 1, participants in both cohorts had quantitative

DAT that was not consistent with their visual assessment. Of the 12 participants in the healthy control group that had DAT deficit, which potentially could be evidence of early dopaminergic degeneration, none has converted to motor parkinsonism up to the date of data freeze for this analysis.

Discussion

We detail baseline clinical and DAT imaging characteristics of non-manifesting carriers with the two most common genetic mutations of Parkinson's disease, *LRRK2* and *GBA*, compared with healthy controls. These data have provided several novel observations and generated hypotheses that require additional longitudinal follow-up studies.

The most important observation in the study is higher prevalence of motor and non-motor features of Parkinson's disease in non-manifesting carriers of *GBA* and *LRRK2* mutations than seen in healthy controls. Although several studies have described clinical and biological features of Parkinson's disease manifesting in genetic cohorts, few reports are available in non-manifesting carriers. Our data are in line with previously published results in cohorts of non-manifesting carriers of *LRRK2* mutations.[8–13] Only Pont-Sunyer and colleagues[9] had a similarly large sample size, and, like our data, they reported higher MDS-UPDRS motor scores in non-manifesting carriers than in healthy controls. However, they did not identify a difference in MOCA scores or hyposmia. Arzi and colleagues[11] reported data for quantitative imaging of non-manifesting carriers compared with healthy controls and identified marginally lower uptake (p=0·05) in the right dorsal striatum of non-manifesting carriers but no difference in clinical features, although both cohort sizes were small (n=31).

Few data are published for characterisation of *GBA* prodromal cohorts.[14–16] Beavan and colleagues[15] reported 2-year longitudinal data on clinical characterisation of heterozygous non-manifesting carriers of *GBA* mutations (n=28) versus healthy controls (n=26) and, similar to our findings, identified a difference in MOCA and UPDRS part 3 (motor) scores, but not in RBD, although they also reported higher prevalence of hyposmia, which was not seen in our cohort.

Our study included DAT imaging for most participants (73%). Not unexpectedly, only a minority of non-manifesting carriers had DAT deficit (11% of *LRRK2 vs* 3% of *GBA* non-manifesting carriers). Considering that the number of participants with DAT deficit was small, we did not separately analyse subsets with DAT deficit versus without, but aim to do so in a future longitudinal analysis as the number of participants with DAT deficit increases. MDS-UPDRS motor scores increased in both groups of non-manifesting carriers compared with healthy controls despite low percentages of participants with DAT deficit, suggesting that early changes in MDS-UPDRS scores might be apparent even before reduction in DAT SBR. An alternative explanation might be that increases in MDS-UPDRS scores and other clinical scale scores in non-manifesting carriers are driven by examiners' and participant bias. Although the protocol stipulated that a small proportion of non-carriers would be included in the cohort of non-manifesting carriers to maintain masking, investigators were aware of the mutation-positive status of the cohort in most cases but not DAT status. However, the magnitude of change in MDS-UPDRS scores in non-manifesting carriers

compared with healthy controls is small and variable and is unlikely by itself to predict who might progress to motor Parkinson's disease.

We did not identify reduction in SBR values in non-manifesting carriers of LRRK2 mutation compared with healthy controls as was reported by other groups.[9,12,17,18] This discrepancy in findings could be attributed to the difference in demographic characteristics of cohorts, predominance of G2019S mutation carriers, or other factors to be determined with longitudinal follow-up. The size of our cohort was substantially larger than previously reported cohorts. Unexpectedly, non-manifesting carriers of *GBA* mutation had increased SBR values in all striatal regions compared with healthy controls and non-manifesting carriers of the *LRRK2* mutation; this increase was not observed in the *LRRK2* cohort. This finding might represent compensatory upregulation of tracer uptake in the early stages of the degenerative process. This hypothesis is supported by data from non-human primates showing an increase in DAT binding in monkeys treated with α-synuclein delivered via Adeno-associated virus (AAV; Kordower, J, Rush University Medical Center, IL, USA) and rodents treated with AAV showing synuclein deposition before onset of neuronal loss.[19] The biological factors that drive potential upregulation of DAT binding in non-manifesting carriers of *GBA* and not *LRRK2* mutations remain to be determined. A similar finding of significantly increased striatal binding was reported in non-manifesting carriers of the 22q11.2 mutation associated with age-related increased risk of Parkinson's disease.[20] This study used a radiotracer targeting the vesicular monoamine transporter radio ligand and reported only cross-sectional data. Alternatively, this upregulation could be a result of disruption of dopamine release before loss of dopaminergic terminals. Reduced synaptic dopamine might lead to reduced occupancy of dopamine transporters, thereby contributing to false estimation of DAT binding. Abnormal dopamine release has been shown in *GBA* transgenic mouse models.[21] Longitudinal follow-up of our and other genetic cohorts of non-manifesting carriers is crucial to further elucidate progression of DAT deficit in these groups.

Another strength of these data is the parallel ascertainment of non-manifesting carriers of *GBA* and *LRRK2* mutations with the same scope of activities (they all had the same assessments under the same protocol). Data are scarce comparing non-manifesting carriers of *LRRK2* and *GBA* mutations.[22–25] Only one previous study to our knowledge has assessed presence of premotor features in Parkinson's disease manifest *GBA* and *LRRK2* mutation cohorts and it did not identify higher prevalence of prodromal symptoms than in sporadic Parkinson's disease, although it was a retrospective analysis and did not include a healthy control group.[24] Other previous studies have largely focused on the imaging characteristics of non-manifesting carriers.[10,11,18,25]

Carriers of the *GBA* mutation with Parkinson's disease are reported to have higher incidence of cognitive dysfunction, hyposmia, and RBD, suggesting potentially rapid progression and widespread pathology.[15,26,27] However, the time course remains unclear. Although prevalence of cognitive dysfunction was higher in non-manifesting carriers of *GBA* mutations based on MOCA scores than in healthy controls in our study, we did not identify higher prevalence of hyposmia, RBD, or sleepiness in that cohort, suggesting that these changes occur later in the progression of Parkinson's disease pathology and might provide a

window of opportunity for early intervention. Additionally, the *GBA* cohort predominantly had the N370S mutation, which is a milder *GBA* mutation (ie, has less severe Parkinson's disease manifestation than other *GBA* mutations) and might not result in more rapid disease progression than does idiopathic Parkinson's disease. G2019S (*LRRK2)* cohorts generally are reported to have less disability and slower disease progression than sporadic Parkinson's disease. Our analysis identified hyposmia as the only clinical feature different between cohorts of non-manifesting carriers of *GBA* and *LRRK2* mutations, with an unexpectedly higher prevalence of hyposmia in the *LRRK2* versus the *GBA* cohort. Evidence for a higher prevalence of *GBA* mutation in RBD patients is increasing.[14,16] RBD scores remained the same in non-manifesting carriers of *GBA* mutations versus healthy controls, and in non-manifesting carriers of *GBA* versus *LRRK2* mutations. The same was reported for baseline data by Beavan and colleagues[15] of non-manifesting carriers of *GBA* mutations; however, RBD significantly increased in a 2-year follow-up. Longitudinal follow-up of the cohort and participants who develop Parkinson's disease will be essential to assess whether hyposmia and RBD occur as participants become closer to phenoconversion.

Abnormal DAT scan has been used to enrich hyposmic cohorts and was shown to successfully predict phenol-conversion to Parkinson's disease over 4 years.[7,28] It remains to be determined if the subset of non-manifesting carriers with DAT deficit will have a different longitudinal course. These data are being collected.

Both cohorts of non-manifesting carriers lack male predominance seen in cohorts of sporadic Parkinson's disease. This is consistent with previously reported data in patients with *LRRK2* and *GBA* mutations compared with sporadic Parkinson's disease.[24,29] Considering that our participants are non-manifesting carriers, it remains to be determined whether this sex distribution will persist in the subset of participants who develop Parkinson's disease. The biology of male predominance in Parkinson's disease has not been well established but lack of such might point to the genetic effect being upstream of sex.

This analysis has several limitations. The cohort of non-manifesting carriers was enrolled using different methods for the *LRRK2* group (local site enrolment targeting mostly family members of Ashkenazi Jewish patients with Parkinson's disease known to the site and centralised enrolment) and *GBA* group (mostly centralised enrolment). This change in methods might account for the difference in percentage of scans with DAT deficit. Non-manifesting carriers of *LRRK2* (predominantly G2019S) and *GBA* (predominantly N370S) mutations represent selected mutations of both genes, increasing our ability to understand the effect of these mutations, but limiting conclusions on both mutations in general.

A substantial percentage of non-manifesting carriers of *LRRK2* and *GBA* mutations did not have DAT scan SBR values (22% and 33%, respectively) at time of data freeze, which could affect the analysis and conclusions, although no difference was seen in baseline demographic characteristics between subsets with versus without DAT SBR values. Despite some missing data, to our knowledge, this study remains the largest reported cohort of non-manifesting carriers with DAT imaging results. As data are acquired, future longitudinal analysis will include a full DAT SBR dataset.

As discussed, higher MDS-UPDRS scores in both cohorts of non-manifesting carriers could be driven by bias of the investigators who, in most cases, were aware of the participant's genetic status. The same could be true regrading participant-reported outcomes. However, consistency of findings across multiple domains suggests a biologically driven result rather than ascertainment bias. This analysis does not include data from spinal fluid or blood-based biomarkers as the analysis of these were not fully available during the writing of this paper and will be reported in future publications.

Finally, we recognise that these data only report baseline observations and longitudinal follow-up is crucial to confirm these findings and test the hypothesis that it is possible to predict those at risk to develop motor symptoms of Parkinson's disease during the prodromal state. The PPMI study is committed to comprehensive longitudinal follow-up of these individuals and reporting these data as they are available.

We report baseline clinical and imaging characteristics of non-manifesting carriers of the two most common genetic mutations of Parkinson's disease, in *LRRK2* and *GBA*. Both cohorts show significant differences in several clinical variables compared with healthy controls despite a small proportion of non-manifesting carriers with DAT deficit. Interestingly, non-manifesting carriers of *GBA* mutations show increases in DAT SBR suggesting that some compensatory increase in DAT might occur early in the prodromal phase. These results provide another justification for targeting non-manifesting carriers as potential cohorts for future disease modifying interventions. Longitudinal data on the evolution of clinical and biological characteristics of both cohorts of non-manifesting carriers will be essential to define early characteristics that predict ultimate phenoconversion to Parkinson's disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Parkinson's Progression Markers Initiative (a public-private partnership) is funded by the Michael J Fox Foundation for Parkinson's Research and funding partners, including AbbVie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, Celgene, Denali, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, Voyager Therapeutics, and Golub Capital. Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

References

1. Berg D, Adler CH, Bloem BR, et al. Movement disorder society criteria for clinically established early Parkinson's disease. Mov Disord 2018; 33:1643–46. [PubMed: 30145841]
2. Kordower JH, Olanow CW, Dodiya HB, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. Brain 2013; 136: 2419–31. [PubMed: 23884810]
3. Bonifati V Genetics of Parkinson's disease—state of the art, 2013. Parkinsonism Relat Disord 2014; 20 (suppl 1): S23–28. [PubMed: 24262182]
4. Parkinson Progression Marker Initiative. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011; 95: 629–35. [PubMed: 21930184]

5. Marek K, Chowdhury S, Siderowf A, et al. The Parkinson's progression markers initiative (PPMI)—establishing a PD biomarker cohort. Ann Clin Transl Neurol 2018; 5:1460–77 [PubMed: 30564614]
6. Foroud T, Smith D, Jackson J, et al. Novel recruitment strategy to enrich for LRRK2 mutation carriers. Mol Genet Genomic Med 2015; 3: 404–12. [PubMed: 26436106]
7. Jennings D, Siderowf A, Stern M, et al. Imaging prodromal Parkinson disease: the Parkinson Associated Risk Syndrome Study. Neurology 2014; 83:1739–46. [PubMed: 25298306]
8. Mirelman A, Alcalay RN, Saunders-Pullman R, et al. Nonmotor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the LRRK2 gene. Mov Disord 2015; 30: 981–86. [PubMed: 25809001]
9. Pont-Sunyer C, Tolosa E, Caspell-Garcia C, et al. The prodromal phase of leucine-rich repeat kinase 2-associated Parkinson disease: clinical and imaging studies. Mov Disord 2017; 32: 726–38. [PubMed: 28370517]
10. Sierra M, Martinez-Rodriguez I, Sanchez-Juan P, et al. Prospective clinical and DaT-SPECT imaging in premotor LRRK2 G2019S-associated Parkinson disease. Neurology 2017; 89: 439–44. [PubMed: 28679601]
11. Artzi M, Even-Sapir E, Lerman Shacham H, et al. DaT-SPECT assessment depicts dopamine depletion among asymptomatic G2019S LRRK2 mutation carriers. PLoS One 2017; 12: e0175424. [PubMed: 28406934]
12. Bergareche A, Rodriguez-Oroz MC, Estanga A, et al. DAT imaging and clinical biomarkers in relatives at genetic risk for LRRK2 R1441G Parkinson's disease. Mov Disord 2016; 31: 335–43. [PubMed: 26686514]
13. Mirelman A, Saunders-Pullman R, Alcalay RN, et al. Application of the Movement Disorder Society prodromal criteria in healthy G2019S-LRRK2 carriers. Mov Disord 2018; 33: 966–73. [PubMed: 29603409]
14. Barber TR, Lawton M, Rolinsld M, et al. Prodromal Parkinsonism and neurodegenerative risk stratification in REM sleep behavior disorder. Sleep 2017; published online May. D01:10.1093/sleep/zsx071.
15. 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 Neurol 2015;72: 201–08. [PubMed: 25506732]
16. Gan-Or Z, Mirelman A, Postuma RB, et al. GBA mutations are associated with rapid eye movement sleep behavior disorder. Ann Clin Transl Neurol 2015; 2: 941–45. [PubMed: 26401515]
17. Vilas D, Ispierto L, Alvarez R, et al. Clinical and imaging markers in premotor LRRK2 G2019S mutation carriers. Parkinsonism Relat Disord 2015; 21:1170–76. [PubMed: 26306001]
18. Wile DJ, Agarwal PA, Schulzer M, et al. Serotonin and dopamine transporter PET changes in the premotor phase of LRRK2 parkinsonism: cross-sectional studies. Lancet Neurol 2017; 16: 351–59. [PubMed: 28336296]
19. Koprich JB, Johnston TH, Huot P, Reyes MG, Espinosa M, Brotchie JM. Progressive neurodegeneration or endogenous compensation in an animal model of Parkinson's disease produced by decreasing doses of alpha-synuclein. PLoS One 2011; 6: el7698.
20. Butcher NJ, Marras C, Pondal M, et al. Neuroimaging and clinical features in adults with a 22qll.2 deletion at risk of Parkinson's disease. Brain 2017; 140: 1371–83. [PubMed: 28369257]
21. Ginns El, Mak SK, Ko N, et al. Neuroinflammation and alpha-synuclein accumulation in response to glucocerebrosidase deficiency are accompanied by synaptic dysfunction. Mol Genet Metab 2014; 111: 152–62. [PubMed: 24388731]
22. Bregman N, Thaler A, Mirelman A, et al. A cognitive fMRI study in non-manifesting LRRK2 and GBA carriers. Brain Struct Fund 2017; 222:1207–18.
23. Chahine LM, Urbe L, Caspell-Garcia C, et al. Cognition among individuals along a spectrum of increased risk for Parkinson's disease. PLoS One 2018; 13: e0201964. [PubMed: 30125297]
24. Liu SY, Zheng Z, Gu ZQ, et al. Prevalence of pre-diagnostic symptoms did not differ between LRRK2-related, GBA-related and idiopathic patients with Parkinson's disease. Parkinsonism Relat Disord 2018; 57: 72–76. [PubMed: 30119933]

25. Thaler A, Kliper E, Maidan I, et al. Cerebral imaging markers of GBA and LRRK2 related Parkinson's disease and their first-degree unafFected relatives. Brain Topogr 2018; 31:1029–36. [PubMed: 29846835]

26. Lerche S, Schulte C, Srulijes K, et al. Cognitive impairment in Glucocerebrosidase (GBA)-associated PD: not primarily associated with cerebrospinal fluid Abeta and Tau profiles. Mov Disord 2017; 32:1780–83. [PubMed: 29094781]

27. Yahalom G, Greenbaum L, Israeli-Korn S, et al. Carriers of both GBA and LRRK2 mutations, compared to carriers of either, in Parkinson's disease: risk estimates and genotype-phenotype correlations. Parkinsonism Relat Disord 2018; 62:179–184. [PubMed: 30573413]

28. Jennings D, Siderowf A, Stern M, et al. Conversion to Parkinson disease in the PARS hyposmic and dopamine transporter-deficit prodromal cohort. JAMA Neurol 2017; 74: 933–40. [PubMed: 28595287]

29. Gan-Or Z, Leblond CS, Mallett V, Orr-Urtreger A, Dion PA,Rouleau GA. LRRK2 mutations in Parkinson disease; a sex effect or lack thereof? A meta-analysis. Parkinsonism Relat Disord 2015;21: 778–82. [PubMed: 25962553]

30. Pavon JM, Whitson HE, Okun MS. Parkinson's disease in women:a call for improved clinical studies and for comparative effectiveness research. Maturitas 2010; 65: 352–58. [PubMed: 20117891]

Research in context

Evidence before this study

We searched PubMed with the terms “Parkinson’s disease”, prodromal”, “non-manifest carriers”, “GBA”, “LRRK2” for articles published in English on or before May 25,2019, in any field. We identified a small number of studies (fewer than five) that described clinical characteristics of non-manifest *LRRK2* mutation carriers compared with healthy controls and participants with newly diagnosed Parkinson’s disease compared with those with sporadic disease, and even fewer studies in non-manifest *GBA* mutation carriers. Published data indicated presence of subtle motor features of parkinsonism in non-manifest *LRRK2* mutation carrier cohorts compared with healthy controls and no difference on cognitive screening tests. Data from small non-manifest *GBA* mutation carrier cohorts compared with healthy controls show increases in motorfeatures of parkinsonism, worse cognitive and smell identification test performances, and with no difference in REM sleep behaviour disorder. There were no publications comparing large sized cohorts of *GBA* and *LRRK2* non-manifest carriers within the same study assessed with the same clinical and imaging assessments.

Added value of this study

To our knowledge, this is the first report of comparative data from a large cohort of non-manifest carriers of *LRRK2* and *GBA* mutations versus healthy controls. We identified a significant difference in a number of motor and non-motor variables and cognitive features in both non-manifest carrier cohorts compared with healthy controls that were present despite lack of DAT deficit on DAT scans. Surprisingly smell scores were lower in *LRRK2* but not in *GBA* non-manifest carriers compared with healthy controls as hyposmia is more prevalent in GBA-related Parkinson’s disease. Additionally, there was an increased DAT uptake in *GBA* non-manifest carriers compared with healthy controls. A novel finding is that clinical features can precede DAT abnormalities.

Implications of all the available evidence

These results support the existing hypothesis that it is possible during the prodromal state to predict those at risk of developing motor parkinsonism. Longitudinal data (ongoing) will be essential to confirm our data and establish risk factors and trajectory for development of motor parkinsonism. These data will be important for future development of novel therapeutics targeting population at risk for Parkinson’s disease.

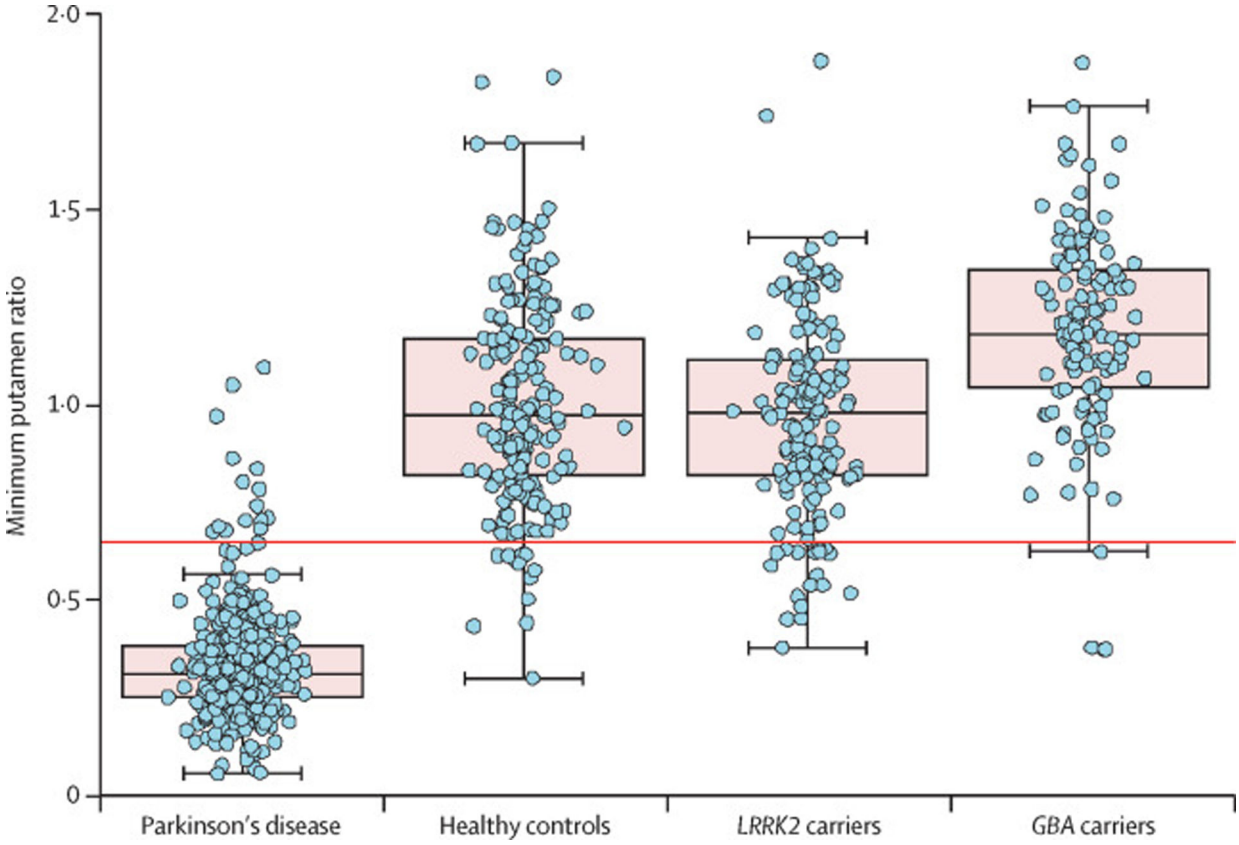

Figure: Striatal binding ratios for patients with Parkinson's disease, healthy controls, and non-manifesting *LRRK12* carriers and *GBA* carriers

The minimum putamen striatal binding ratio differed significantly between *GBA* carriers and healthy controls (p<0·0001) but did not differ between *LRRK2* carriers and healthy controls (p=0·257). The reference line indicates the cutoff for 65% age expected putamen striatal binding ratios used to define DAT deficit. DAT=dopamine transporter.

Table 1:

Demographic characteristics

	Group				p values		
	Patients with Parkinson´s disease (n=423)	**Healthy controls (n=194)**	***LRRK2* carriers (n=208)**	***GBA* carriers (n=l84)**	**Healthy controls *vs LRRK2* carriers**	**Healthy controls *vs GBA* carriers**	***LRRK2* carriers *vs GBA* carriers**
Sex							
Female	146 (35%)	69 (36%)	121 (58%)	114 (62%)	<0·0001	<0·0001	0·4455
Age							
Mean (SD)	61·7 (9·7)	60·8 (11·3)	61·6 (7·6)	61·8 (6·9)	0·3804	0·3134	0·8502
Range	33·85	31·84	46·82	45·84	··	··	··
Education							
<13 years	75 (18%)	29(15%)	36(17%)	5 (3%)	0·0218	<0·0001	<0·0001
Ethnicity							
Hispanic or Latin American	9 (2%)	3(2%)	26 (13%)	1 (1%)	<0·0001	0·3436	<0·0001
Non-Hispanic/Latino	414 (98%)	191 (98%)	181(87%)	182 (99%)	··	··	··
Missing	0	0	1 (<1%)	1 (1%)	··	··	··
Race							
White	391 (92%)	180 (93%)	193(93%)	179 (97%)	0·7182	0·0454	0·0913
Family history							
1st degree family with Parkinson´s disease	55 (13%)	0 (0%)	178(86%)	140 (76%)	<0·0001	<0·0001	0·0308
DAT deficit *							
DAT deficit	404/419 (96%)	12/191 (6%)	18/162 (11%)	4/124 (3%)	<0·0001	<0·0001	0·0032
Missing DAT scan	4	3	46	60	··	··	··
Mutation type							
G2019S	··	··	194 (93%)	0 (0%)	··	··	··
R1441G	··	··	14 (7%)	0 (0%)	··	··	··
N370S (c. 1226A>G)	··	··	0 (0%)	177 (96%)	··	··	··
L483P or L444P (c. 1448T>C)	··	··	0 (0%)	3 (2%)	··	··	··
84GG (c.84_85insG)	··	··	0 (0%)	3 (2%)	··	··	··

Data are n (%) unless otherwise stated. DAT=dopamine transporter.

* Percentages were calculated on the basis of number of participants who had DAT results.

Table 2:

Clinical characteristics

	Group				Adjusted p values		
	Patients with Parkinson ′s disease (n=423)	Healthy controls (n=194)	*LRRK2* carriers (n=208)	*GBA* carriers (n=l84)	Healthy controls *vs LRRK2* carriers	Healthy controls *vs GBA* carriers	*LRRK2* carriers *vs GBA* carriers
MDS UPDRS total score and subscores							
MDS-UPDRS total score	32·4 (13·1)	4·6 (4·4)	8·4 (7·3)	9·5 (9·2)	<0·0001	<0·0001	0·2075
MDS-UPDRS Part I	5·6 (41)	2·9 (30)	4·5 (3·8)	5·8 (51)	<0·0001	<0·0001	0·0097
MDS-UPDRS Part II	5·9 (4·2)	0·4 (10)	10 (2·1)	1·2 (2·6)	0·0009	0·0001	0·3956
MDS-UPDRS Part III	20·9 (8·9)	1·2 (2·2)	2·8 (3·8)	2·5 (37)	<0·0001	<0·0001	0·3290
Modified Schwab & England ADL score							
Mean (SD)	931 (5·9)	NA	99·7 (17)	99·5 (2·4)	··	··	0·4469
MOCA total score							
Mean (SD; range)	271 (2·3; 17–30)	28·2 (1·1; 26–30)	26·8 (2·4; 18–30)	26·8 (2·4; 16–30)	<0·0001	<0·0001	0·9571
GDS total score							
Mean (SD)	2·3 (2·4)	1·3 (21)	1·8 (2·4)	1·9 (2·4)	0·0784	0·0424	0·6042
SCOPA-AUT total score							
Mean (SD)	95 (6·2)	5·8 (3·7)	8·1 (5·9)	8·4 (6·0)	<0·0001	<0·0001	0·7663
Missing	8	2	5	1	··	··	··
Orthostatic blood pressure drop							
Systolic blood pressure	4·6 (12·7)	2·2 (12·3)	−07 (11·0)	0·9 (11·1)	0·0061	0·2093	01624
Diastolic blood pressure	−1·8 (8·4)	−3·5 (8·2)	−3·8 (7·5)	−3·3 (6·9)	0·6711	0·7734	0·6055
State trait anxiety score							
Mean (SD)	65·3 (18·3)	57·1 (14·2)	61·6 (17·5)	60·9 (17·6)	0·0222	0·0992	0·6737
QUIP							
Mean (SD)	0·3 (06)	0·3 (0·7)	0·3 (07)	0·4 (0·6)	0·2706	0·0800	0·3227
Urate							
Mean (SD)	58 (3·5)	5·6 (3·4)	5·3 (3·4)	5·2 (3·4)	0·0697	0·0577	0·8704
UPSIT raw score							
Mean (SD; range)	22·4 (8·2; 1–40)	34·0 (4·9; 11–40)	32·8 (4·3; 14–40)	34·1 (4·7; 13–40)	0·0041	0·9566	0·0071
UPSIT categories							

	Group				Adjusted p values		
	Patients with Parkinson ′s disease (n=423)	**Healthy controls (n=194)**	***LRRK2* carriers (n=208)**	***GBA* carriers (n=l84)**	**Healthy controls *vs LRRK2* carriers**	**Healthy controls *vs GBA* carriers**	***LRRK2* carriers *vs GBA* carriers**
Hyposmia	237 (56%)	69 (36%)	114 (55%)	67 (36%)	0·0003	0·8354	0·0004
Anosmia	147 (35%)	5 (3%)	3 (1%)	4 (2%)	··	··	··
Epworth sleepiness scale							
Sleepy (>9)	66 (16%)	23 (12%)	22 (11%)	18 (10%)	0·7365	0·9581	0·8079
RBD questionnaire							
Positive (>4)	158 (37%)	39 (20%)	42 (20%)	38 (21%)	0·7241	0·9038	0·9453

Data are mean (SD; range [where available]) or n (%). Fewer than five participants in each group missed any one assessment. Significance level for comparisons is p<0001 (after Bonferroni correction). MDS-UPDRS=Movement Disorders Society Unified Parkinson's Disease Rating Scale. ADL=Activities of Daily Living. MOCA=Montreal Cognitive Assessment. GDS=Geriatric Depression Scale. SCOPA-AUT=Scales for Outcomes in Parkinson's Disease. QUIP=Questionnaire for Impulsive-Compulsive Disorders. UPSIT=University of Pennsylvania Smell Identification Test. RBD=rapid eye movement sleep behaviour disorder.

Lancet Neurol. Author manuscript; available in PMC 2021 January 01.

Table 3:

Comparison of DAT striatal binding ratios

	Group				Adjusted p values		
	Patients with Parkinson′s disease (n=419)	**Healthy controls (n=191)**	***LRRK2* carriers (n=l62)**	***GBA* carriers (n=124)**	**Healthy controls *vs* *LRRK2* carriers**	**Healthy controls *vs* *GBA* carriers**	***LRRK2* carriers *vs* *GBA* carriers**
Caudate							
Mean (SD)	200 (0·56)	2·98 (0·63)	2·93 (0·59)	3·26 (0·63)	0·1780	<0·0001	<0·0001
Range	0·39–3·71	1·32–5·20	1·38–4·51	1·10–4·89	··	··	··
Putamen							
Mean (SD)	0·83 (0·30)	2·15 (0·56)	2·07 (0·51)	2·48 (0·52)	0·0918	<0·0001	<0·0001
Range	0·24–2·17	0·64–3·89	0·96–3·70	0·80–3·84	··	··	··
Striatum							
Mean (SD)	1·41 (0·40)	2·56 (0·57)	2·50 (0·53)	2·87 (0·55)	0·1176	<0·0001	<0·0001
Range	0·31–2·64	0·98–4·24	1·17–4·00	0·95–4·37	··	··	··

DAT imaging results were missing for four patients with Parkinson’s disease, three healthy controls, 46 *LRRK2* carriers, and 60 *GBA* carriers. Significance level for comparisons is p<0·005 (after Bonferroni correction).