Phenotypic effect of GBA1 variants in individuals with and without Parkinson’s disease: The RAPSODI study

Marco Toffoli a,b, Harneek Chohan c, Stephen Mullin a,d, Aaron Jesuthasan e, Selen Yalkic a,b, Sofia Koletsi a,b, Elisa Menozzi a,b, Soraya Rahall a, Naomi Limbachiya a, Nadine Loefflad a,b, Abigail Higgins a, Jonathan Bestwick c, Sara Lucas-Del-Pozo a,b, Federico Fierli a,b, Audrey Farbos a, Roxana Mezabrovschi a,b, Chiao Lee-Yin a,b, Anette Schrag a, David Moreno-Martinez a, Derralynn Hughes a, Alastair Noyce c, Kevin Colclough h, Aaron R. Jeffries a, Christos Proukakis a,b, Anthony H.V. Schapira a,b,

a Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK
b Aligning Science Across Parkinson’s (ASAP) Collaborative Research Network, Chevy Chase, MD, USA
c Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, UK
d Faculty of Health, University of Plymouth, Plymouth PL4 8AA, UK
e Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK
f Preventive Neurology Unit, Royal Free Hospital NHS Foundation Trust and University College London, London, UK
g Lysosomal Storage Disorders Unit, Royal Free Hospital NHS Foundation Trust and University College London, London, UK
h Exeter Genomics Laboratory, Royal Devon University Healthcare NHS Trust, Exeter, UK

Keywords: Parkinson; GBA; GBA1; Prodromal; Genetics

ARTICLE INFO

Background: Variants in the GBA1 gene cause the lysosomal storage disorder Gaucher disease (GD). They are also risk factors for Parkinson’s disease (PD), and modify the expression of the PD phenotype.
The penetrance of GBA1 variants in PD is incomplete, and the ability to determine who among GBA1 variant carriers are at higher risk of developing PD, would represent an advantage for prognostic and trial design purposes.

Objectives: To compare the motor and non-motor phenotype of GBA1 carriers and non-carriers.

Methods: We present the cross-sectional results of the baseline assessment from the RAPSODI study, an online assessment tool for PD patients and GBA1 variant carriers. The assessment includes clinically validated questionnaires, a tap-test, the University of Pennsylvania Smell Identification Test and cognitive tests. Additional, homogeneous data from the PREDICT-PD cohort were included.

Results: A total of 379 participants completed all parts of the RAPSODI assessment (89 GBA1-negative controls, 169 GBA1-negative PD, 47 GBA1-positive PD, 47 non-affected GBA1 carriers, 27 GD). Eighty-six participants were recruited through PREDICT-PD (43 non-affected GBA1 carriers and 43 GBA1-negative controls). GBA1-positive PD patients showed worse performance in visual cognitive tasks and olfaction compared to GBA1-negative PD patients. No differences were detected between non-affected GBA1 carriers carriers and GBA1-negative controls. No phenotypic differences were observed between any of the non-PD groups.

Abbreviations: AT30, Akiniesia Time; BRAIN, BRadykinesia Akinesia INcoordination; CRT, Choice Reaction Time; CRTACC, Choice Reaction Time – Accuracy; DPICNACC, Pattern Separation · New Stimuli · Accuracy; DPCOACC, Pattern Separation · Original Stimuli · Accuracy; GD, Gaucher Disease; HADS, Hospital Anxiety and Depression Scale; KS30, Kinesia Score; MDS-UPDRS2, Movement Disorders Society Unified Parkinson Disease Rating Scale part 2; msec, Milliseconds; NWMR, Numeric Working Memory Reaction Time; NWMRNACC, Numeric Working Memory New Stimuli · Accuracy; NWMRTOACC, Numeric Working Memory Original Stimuli · Accuracy; PD, Parkinson Disease; RBDdq, REM Sleep Behaviour Disorder Screening Questionnaire; SPMRT, Spatial Working Memory Reaction Time; SPMNACC, Spatial Working Memory New Stimuli · Accuracy; SPMOACC, Spatial Working Memory Original Stimuli · Accuracy; SRT, Simple Reaction Time; UPSIT, University of Pennsylvania Smell Identification Test; VIGRT, Digit Vigilance Reaction Time; VIGRTACC, Digit Vigilance Reaction Time · Accuracy.

* Corresponding author at: Department of Clinical and Movement Neurosciences, University College London Institute of Neurology, Rowland Hill St., London NW3 2PF, UK.

E-mail address: a.schapira@ucl.ac.uk (A.H.V. Schapira).

https://doi.org/10.1016/j.nbd.2023.106343
Received 15 August 2023; Received in revised form 8 October 2023; Accepted 1 November 2023
Available online 3 November 2023

© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Conclusions: Our results support previous evidence that GBA1-positive PD has a specific phenotype with more severe non-motor symptoms. However, we did not reproduce previous findings of more frequent prodromal PD signs in non-affected GBA1 carriers.

1. Introduction

The GBA1 gene encodes the lysosomal enzyme glucerebrosidase. Variants in GBA1 are a risk factor for Parkinson disease (PD) (Sidransky et al., 2009), with a penetrance that is variable and ranges according to the severity of the variant (Gan-Or et al., 2015).

The clinical phenotype of PD seems to be significantly worse in patients that carry GBA1 variants compared to non-carriers, although how domains differ and to what extent are matters of debate (Alcalay et al., 2012; Simuni et al., 2020; Malek et al., 2018). GBA1 variant carriers have an earlier age of PD onset, with poorer overall cognitive function (Martinez-Martin et al., 2012; Beavan et al., 2015; Mullin et al., 2019; Avenali et al., 2016). Some data also suggests a higher prevalence of pre-clinical symptoms in healthy GBA1 variant carriers compared to non-carriers (McNeill et al., 2012; Beavan et al., 2015; Mullin et al., 2019; Avenali et al., 2019), although this has not been replicated in independent cohorts (Lopez et al., 2022).

Understanding the role of GBA1 variants in determining phenotypic characteristics is important for prognostic purposes, and to guide the design of clinical trials.

Here, we report baseline data from the RAPSODI study (rapsodistudy.com) (Higgins et al., 2021), an online cohort for the remote assessment of motor and non-motor signs of parkinsonism. We compare characteristics of PD patients with and without GBA1 variants, healthy GBA1 carriers, Gaucher disease (GD) patients and controls. To support our findings, we evaluate additional data from the PREDICT-PD (predictpd.com) cohort. We hope to provide further insight into the phenotype-genotype correlation of GBA1 variants in the pathogenesis of PD.

2. Material and methods

2.1. Recruitment of participants

Participants were recruited through RAPSODI (rapsodistudy.com) (Higgins et al., 2021). The study commenced active recruitment in January 2018 and participants are asked to repeat the assessment every year for up to 25 years. In this paper, we report data from the baseline (year 1) assessment. Participants were allowed to join the study if they were between the age of 18 and 90 and if they: had a diagnosis of GD, a GBA1 variant carrier. Exclusion criteria were the presence of dementia or any other conditions known to cause parkinsonism. Upon enrollment, all participants were required to give informed consent to be included in the study. The work was approved by the London – Queen Square Research Ethics Committee (REC reference: (Martinez-Martin et al., 2013)/LO/1155).

2.2. Assessment

A detailed description of the study design can be found in a previous publication (Higgins et al., 2021). Participants were asked to complete the the REM Sleep Behaviour Disorder Questionnaire (RBDq) (Stannny-Kolster et al., 2007), the Movement Disorders Society Unified Parkinson’s disease Rating Scale part 2 (MDS-UPDRS2) (Martinez-Martin et al., 2013) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snith, 1983). The RBDq has been validated in the general population with a cut-off of 5. However, in this study a cut-off of 6 was used, as it is considered more appropriate for people with PD (Nomura et al., 2011). Established cut-offs for the HADS scale (0–7 Normal, 8–10 Borderline and 11–21 Abnormal) were used for the sub-scores of depression and anxiety (Zigmond and Snith, 1983).

Additionally, participants were asked 3 questions about constipation: “Does opening your bowels require a lot of effort?”, “Do you suffer from hard stools?”, “Do you ever use laxatives?”. These had multiple choice answers “Yes”, “Sometimes” and “No”.

Cognitive Tests were delivered through the ‘CogTrack’™ platform (Wesnes et al., 2017), investigating different aspects of cognition, including pattern separation ability, simple reaction time, choice reaction time, digit vigilance, spatial working memory and numeric working memory.

A summary of the tests and outcomes used can be found in supplementary table 1.

The BRadykinesia Akinesia Incoordination (BRAIN) test (Noyce et al., 2014; Hasan et al., 2019) was used to evaluate hand dexterity and bradykinesia, in which participants were asked to press the “5” and “;” keys on their keyboard in succession as fast as they could. Each hand was assessed separately for 30 s and all participants were given a preceding 5 s practice trial before data was collected. The kinesia score (KS30), corresponding to the number of taps in 30 s, as well as the akinesia time (AT30), which was the mean dwell time on each key in milliseconds (msec) were calculated.

Olfactory function was measured using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty, 2007). The cut-offs provided by the UPSIT manual identified different degrees of deficit: anosmia (0–18), severe microsmia (Noyce et al., 2014; Hasan et al., 2019; Doty, 2007; Toffoli et al., 2021; Parlar et al., 2023; Davis et al., 2016; Well et al., 2016), moderate microsmia (26–29 for males, 26–30 for females), mild microsmia (30–33 for males, 31–34 for females), and normosmia (34–40 for males, 35–40 for females). The RAPSODI database used for analysis was downloaded on the 3rd January 2023.

2.3. Collection of saliva samples and sequencing

Saliva samples were collected with the DNA OG-500 kit from DNA genotek, posted to participants upon completion of the online part of the assessment. Sequencing of the GBA1 gene was carried out at the University of Exeter Sequencing Facility with a long read, nanopore technology method previously described (Toffoli et al., 2021). The LRRK2 G2019S variant was genotyped with Kbiosciences Competitive AlleleSpecific PCR SNP genotyping system by an external laboratory (LGC Genomics, Hoddesdon, Herts).

2.4. PREDICT-PD

To seek further validation, additional non-affected GBA1 carriers and age and sex matched GBA1-negative controls were included from the PREDICT-PD study. PREDICT-PD is a web-based cohort study to identify individuals at higher risk of PD (ref Noyce et al. JNNP 2014). GBA1 variants were identified through Sanger sequencing of exons 8–11, rather than full gene sequencing (Noyce et al., Movement Disorders 2017). Questions about constipation, RBDq, HADS, UPSIT and tap-test were collected similarly to RAPSODI. For these, results show the combined data from the two cohorts. CogTrack testing was not available for PREDICT-PD and are thus only reported for the RAPSODI cohort.

2.5. Statistical analysis

R version 4.2.2 (RRID:SCR_001905, http://www.r-project.org/) was used.
used for statistical analyses.

All outcome measures were compared between the 5 groups. Additional sub-analysis were carried out comparing carriers of risk, mild and severe GBA1 variants (Parlar et al., 2023).

ANOVA was used to assess differences in age, disease duration, age at diagnosis, years of education, with Tukey multiple comparison test for post hoc analysis.

Ordinal logistic regression was used to analyse questions about constipation, MDS-UPDRS2 (after dividing the values in equal deciles), anxiety and depression subscores of HADS, and UPSIT. Logistic regression was used to analyse outcomes of the RBDsq. Linear regression was used to assess differences in KS30, AT30, SRT, CRT, VIGRT, SPMRT, NWMT. The cognitive scores for accuracy (DPICOACC, DPICNACC, CRTACC, VIGACC, SPMOACC, SPMNACC, NWMOACC, NWMNACC) represent proportions of correct answers, so they were analysed with quasibinomial regression. Age and sex were used as covariate in all analysis, and education was used as covariate in the cognitive tests. Outliers, defined as observations >3 standard deviations from the mean, were removed from the tap test and cognitive test scores.

3. Results

Anonymised participant-level data are reported as supplementary material.

3.1. Size, demographics and genotype

Size and demographics of the cohort of participants that completed the whole assessment are reported in supplementary table 2. One participant had both GD and PD and was excluded from the analysis. Two PD participants were found to carry the LRRK2 p.G2019S variant and were also excluded from the analysis. Not all participants completed all steps of the assessment, so numbers vary for each test.

Age at recruitment for GBA1-negative PD patients was significantly higher than for GBA1-negative controls, GD patients and non-affected GBA1 carriers (all p-values <0.01). No other significant differences in age at recruitment were observed. Sex was significantly different between the groups (p-value <0.001).

There were no significant differences in disease duration or age at diagnosis among the PD groups. Years of education were similar between the groups. Genotypes of GBA1 positive participants are reported in Table 1 and in more details in supplementary table 3. (See Fig. 1.)

3.2. UPSIT score is lower in GBA1-positive PD patients

The two PD groups performed worse than all the non-PD groups in the questions about constipation (all p-values <0.05), in the MDS-UPDRS2 (all p-values <0.001), anxiety subscores of HADS (all p-values <0.05), RBDsq (all p-values <0.05), UPSIT (all p-values <0.001).

The depression sub-score of HADS showed worse outcomes for the two PD groups compared to non-affected GBA1 carriers and GBA1-negative controls (p-values all <0.05), but no differences between the PD groups and GD patients.

GBA1-positive PD patients scored worse than GBA1-negative PD patients in UPSIT (p-value 0.015, OR 0.47, CI 0.25–0.86).

No differences were observed between any of the non-PD groups for any of the questionnaires or UPSIT.

No differences were observed between risk, mild and severe variant carriers among GBA1-positive PD and non-affected GBA1-carriers.

Results did not change when analysing the RAPSODI cohort separately.

Questionnaire results are reported in Supplementary Table 4 and in Fig. 2.

3.3. The tap test can readily identify people with PD and is slightly worse in GBA1-positive PD

KS30 for both dominant and non-dominant hands were worse in the two PD groups compared to all the non-PD groups (all p-values <0.001).

AT30 scores for dominant and non-dominant hands were lower in the two PD groups compared to non-affected GBA1 carriers and GBA1-negative controls (all p-values <0.01) but were not significantly different from those of GD patients.

KS30 scores were marginally worse in GBA1-positive PD patients compared to GBA1-negative PD patients for the dominant hand (β = −3.34, p-value = 0.12) and non-dominant hand (β = −3.79, p-value = 0.05).

AT30 score for the non-dominant hand was marginally worse in GBA1-positive PD patients compared to GBA1-negative PD patients (β = 21.8, p-value = 0.09).

No differences were observed between any of the non-PD groups for KS30 or AT30.

No differences were observed between risk, mild and severe variant carriers among GBA1-positive PD and non-affected GBA1-carriers.

Results did not change when analysing the RAPSODI cohort separately.

Tap test results are reported in supplementary table 5 and in Fig. 3.

3.4. GBA1-positive PD show worse performance in picture recognition and choice reaction time

The scores of the pictures recognition test (DPICOACC and DPICNACC) and reaction time (SRT, CRT, SPMRT, NWMT, VIGRT) were worse in the two PD groups compared to the non-PD groups (all p-values <0.05).

When comparing GBA1-positive and GBA1-negative PD patients only, GBA1-positive PD patients showed a significantly worse performance for DPICOACC, DPICNACC and CRTM (p-values 0.015, 0.039 and 0.0246, respectively – shown in Fig. 4).

There were no statistically significant differences between the two PD groups for CRTACC, VIGACC, SPMOACC, SPMNACC, NWMOACC, NWMNACC.

Moreover, no significant differences were observed between the non-PD groups for any of the tests.

No differences were observed between risk, mild and severe variant carriers among GBA1-positive PD and non-affected GBA1-carriers.

Results of the cognitive tests are reported in supplementary table 6, Table 1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPSDONI  Non-affected GBA1 carriers</td>
<td>16</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>16</td>
<td>17</td>
<td>16</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>GBA1-positive PD patients</td>
<td>5</td>
<td>3</td>
<td>20</td>
<td>7</td>
<td>12</td>
<td>6</td>
<td>10</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>PREDICT-PD Non-affected GBA1 carriers</td>
<td>8</td>
<td>0</td>
<td>21</td>
<td>12</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>GBA1-positive PD patients</td>
<td>24</td>
<td>6</td>
<td>28</td>
<td>14</td>
<td>18</td>
<td>25</td>
<td>18</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Unified cohorts GBA1-positive PD patients</td>
<td>5</td>
<td>3</td>
<td>20</td>
<td>7</td>
<td>12</td>
<td>6</td>
<td>10</td>
<td>27</td>
<td>4</td>
</tr>
</tbody>
</table>

* One individual is a homozygous carrier for p.E365K.

* One individual is a homozygous carrier for p.T408M.
4. Discussion

The objective of this study was to investigate potential early signs of parkinsonism in non-affected GBA1 variants carriers, as well as to explore phenotypic differences between individuals with GBA1-positive and GBA1-negative PD. Our study approach has several strengths compared to previous research (Simuni et al., 2020; Avenali et al., 2019). First, in RAPSODI we adopted a long-read sequencing methodology, which has demonstrated superiority in detecting GBA1 variants compared to whole-genome short-read sequencing (Toffoli et al., 2021). Second, our study cohort encompasses a diverse range of GBA1 variants, in contrast to a larger study on prodromal parkinsonian features in i carriers, where 96% of the 184 non-manifesting carriers had the p. N409S variant (Simuni et al., 2020). Additionally, our study includes a comparable but larger number of GBA1 non-manifesting carriers when compared to two previously reported cohorts (Avenali et al., 2019; Lopez et al., 2022). Lastly, our assessment employs a computer-based method for measuring hand dexterity and cognition, thereby eliminating the issue of inter-rater variability and producing good quality continuous data (Hasan et al., 2019).

For most of the captured outcomes, both groups of PD patients performed significantly worse compared to people without PD, suggesting that the assessment tools are appropriate for capturing differences between these two populations. Analysis of longitudinal data will clarify whether the assessment is also able to detect subtle changes in currently unaffected individuals that might then develop PD.

We showed a difference in the PD phenotype of GBA1 carriers compared to non-carriers in UPSIT, tap test and cognitive tests for pattern recognition and reaction time. For some of the other scores, even when not statistically significant, the data suggested a trend toward a worse performance of GBA1-positive PD patients compared to GBA1-negative PD patients (constipation, anxiety and depression, RBD, working memory).

A previous study similarly showed a worse cognitive profile in 26 GBA1-positive PD compared to 39 GBA1-negative PD, but no differences in UPSIT (Alcalay et al., 2012), and another study showed a more pronounced progression of cognitive dysfunction in 59 GBA1-positive PD compared to 684 GBA1-negative PD (Davis et al., 2016). On the other hand, a recent study showed no differences in the cognitive profile in PD patients with or without GBA1 variants and duration of disease <3.5 years (193 GBA1-PD vs 1700 GBA1-negative PD) (Malek et al., 2018). Recent analysis of the large Parkinson’s Progression Markers Initiative (PPMI) cohort showed no difference in olfaction between GBA1 positive and GBA1 negative PD patients.

Our findings support the notion that cognition is more affected in GBA1-positive PD patients and suggest that olfaction is also worse in GBA1-positive PD patients, calling for additional confirmation in independent cohorts.

Of interest is the difference between the two PD groups in the pattern recognition test, which involves visual memory and visuospatial skills, supporting previous evidence that visual functions are more affected in GBA1-positive PD (Alcalay et al., 2012; Weil et al., 2016; Mata et al., 2016).

We did not observe a significantly different age at onset of PD or a different prevalence of males and females, as has been reported in other studies (Malek et al., 2018).

Moreover, we did not detect a phenotypical effect of GBA1 variants severity when stratifying them as risk, mild and severe (Parlar et al., 2023). Given the small sample size, this exploratory analysis was likely underpowered.

It remains uncertain as to whether non-affected GBA1 variant carriers show a higher prevalence of prodromal PD features than the general population.

A previous cohort study from our group showed worse olfaction, cognition and motor signs of PD at baseline, and a steeper progression, in GBA1 variant carriers compared to non-carrier controls. That cohort
had a smaller sample size, and most of the differences between the groups were already present at baseline (Avenali et al., 2019). A recent study showed no significant deterioration of UPSIT scores in 117 unaffected GBA1 variants carriers compared to controls (Lopez et al., 2022).

The cross-sectional analysis presented in our paper did not highlight any significant differences between heterozygous and biallelic GBA1 variant carriers and GBA1-negative controls. The longitudinal assessment will clarify whether the two groups show a different rate of progression of prodromal PD symptoms or conversion to PD. Whether this hypothetical difference in prodromal symptoms simply reflects the GBA1 genotype status or truly represents an early manifestation of PD, will also remain an open question that longitudinal studies will address.

The combination of biochemical and imaging markers of PD in addition to clinical features, might help better define of the potential risk of progression of prodromal PD symptoms or conversion to PD. Whether this might be connectivity issues hindering the assessment, some in unsupervised, with an intrinsic risk of introducing unreliable observations (participants might ask for help to complete some tasks, there might be connectivity issues hindering the assessment, some instructions on how to carry out the tests might be misunderstood). We addressed these issues by using the median response times in the cognitive tests, a parameter that is less affected by extreme outliers.

Another potential limitation of this study is the selection of hypothetical difference in prodromal symptoms simply reflects the GBA1 genotype status or truly represents an early manifestation of PD, will also remain an open question that longitudinal studies will address. The combination of biochemical and imaging markers of PD in addition to clinical features, might help better define of the potential risk of progression of prodromal PD symptoms or conversion to PD. Whether this might be connectivity issues hindering the assessment, some in unsupervised, with an intrinsic risk of introducing unreliable observations (participants might ask for help to complete some tasks, there might be connectivity issues hindering the assessment, some instructions on how to carry out the tests might be misunderstood). We addressed these issues by using the median response times in the cognitive tests, a parameter that is less affected by extreme outliers.

In this cross-sectional analysis, we were able to show a different phenotype in GBA1 positive PD patients compared to GBA1 negative PD patients, with the former having worse olfaction and cognitive performance (visual function and reaction time). We did not show any meaningful differences between GBA1-negative controls and non-affected GBA1 carriers.

The analysis of the longitudinal data will provide additional insight into differences in progression between these groups.

5. Conclusions

In this cross-sectional analysis, we were able to show a different phenotype in GBA1 positive PD patients compared to GBA1 negative PD patients, with the former having worse olfaction and cognitive performance (visual function and reaction time). We did not show any meaningful differences between GBA1-negative controls and non-affected GBA1 carriers.

The analysis of the longitudinal data will provide additional insight into differences in progression between these groups.

Funding

This research was funded in part by Aligning Science Across Parkinson’s (ASAP-000420) through the Michael J. Fox Foundation for Parkinson’s Research (MJFF). For the purpose of open access, the author has applied a CC BY public copyright license to all Author Accepted Manuscripts arising from this submission.

The work was supported by the EU Joint
Programme–Neurodegenerative Disease Research (JPND) project (GBA-PaCTS, 01ED2005B) and MR/T046007/1. The PREDICT-PD study was funded by Parkinson’s UK.

Authors roles

Toffoli M Conceptualization, Investigation, Formal analysis, Writing - original draft.
Chohan H Data Curation, Writing - review & editing.
Mullin S Study conception, Writing - review & editing.
Jesuthasan A Data Curation, Writing - review & editing.
Yalkic S Data Curation, Writing - review & editing.
Koletsi S Data Curation, Writing - review & editing.
Menozzi E Data Curation, Writing - review & editing.
Rahall S Data Curation, Writing - review & editing.
Limbachiya N Data Curation, Writing - review & editing.
Loefflad N Data Curation, Writing - review & editing.
Higgins A Data Curation, Writing - review & editing.
Bestwick J Data Curation, Writing - review & editing.
Lucas-Del-Pozo S Data Curation, Writing - review & editing.
Fierli F Data Curation, Writing - review & editing.
Farbos A Investigation.
Mezabrovschi R Data Curation, Writing - review & editing.
Lee-Yin C Data Curation, Writing - review & editing.
Schapira AHV Conceptualization, Writing - review & editing.

Disclosures

Toffoli M Employee of NHS and UCL.
Chohan H Employee of UCL.
Mullin S Employee of NHS.
Jesuthasan A Nothing to disclose.
Yalkic S Employee of UCL.
Koletsi S Employee of UCL.
Menozzi E was supported by a Royal Free Charity Fellowship.
Rahall S Nothing to disclose.
Limbachiya N Nothing to disclose.
Loefflad N Employee of UCL.
Higgins A Nothing to disclose.
Bestwick J Nothing to disclose.
Lucas-Del-Pozo S was supported by a UCL fellowship.
Fierli F Employee of UCL.
Farbos A Employee of University of Exeter.
Mezabrovschi R Employee of UCL.
Lee-Yin C Nothing to disclose.

Fig. 3. Tap-test data.
KS30 is reported as number of taps in 30 s, AT30 shows the mean dwell time on each key in milliseconds. Data are reported separately for dominant and non-dominant hands.
Data are reported as mean (central bar), 25th and 75th percentiles (hinges) and the smallest value at most 1.5 * interquartile range of the hinge (whiskers).
KS30: Kinesia Score 30 Seconds, AT30: Akinesia Time 30 s.
Schrag A Nothing to disclose.

Moreno-Martinez D received travel grants from Sanofi, Takeda and Amicus.

Hughes D received honoraria for speaking and consulting and travel arrangements from Sanofi and Takeda.

Noyce A grants from Parkinson’s UK, Barts Charity, Cure Parkinson’s, National Institute for Health and Care Research, Innovate UK, Virginia Keiley benefaction, Solvemed, the Medical College of Saint Bartholomew’s Hospital Trust, Alchemab, Aligning Science Across Parkinson’s Global Parkinson’s Genetics Program (ASAP-GP2) and the Michael J Fox Foundation. Prof Noyce reports consultancy and personal fees from AstraZeneca, AbbVie, Profile, Roche, Biogen, UCB, Bial, Charco Neurotech, uMedeo, Alchemab, Sosei Heptares and Britannia, outside the submitted work. Prof Noyce is an Associate Editor for the Journal of Parkinson’s Disease.

Colclough K Employee of NHS.

Jeffries AR Employee of University of Exeter.

Proukakis C Employee of NHS and UCL.

Schapira AHV Employee of NHS and UCL. Medical Research Council, Michael J. Fox Foundation (MJFF), Aligning Science Across Parkinson’s, and Cure Parkinson’s (research support); AvroBio, Auxilium, Coave, Destin, Enterin, Escape Bio, Genilac, and Sanofi (consulting fees); and Prada Foundation (speaking fees).

Ethical compliance statement

All participants gave informed consent to be included in the study. The work was approved by the London – Queen Square Research Ethics Committee (REC reference: 15/LO/1155).

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Ethical approval for the PREDICT-PD study was grant by Central London Research Ethics Committee 3 (reference number 10/H0716/85).

Acknowledgements

We would like to thank AH software for their support in designing and maintaining the RAPSDOI online portal.

We would like to thank Professor Keith Andrew Wesnes for his support with collecting and interpreting the CogTrack data.

Declaration of Competing Interest

The authors have no conflicts of interest or financial issues to declare in relation to this manuscript.

Data availability

Anonymised participant level data are reported as supplementary material in the file named “Participant-level data”.

All other data produced in the present study are available upon reasonable request to the authors.

The R code used for the analysis can be found on Zenodo (DOI: https://doi.org/10.5281/zenodo.8204348).

Fig. 4. Pattern separation test, differences between GBA1-positive and GBA1-negative PD. Data are reported as mean (central bar), 25th and 75th percentiles (hinges) and the smallest value at most 1.5 * interquartile range of the hinge (whiskers). DPICOACC: Percentage of correct answers recognising original pictures, DPICNACC: Percentage of correct answers recognising new pictures.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2023.106343.

References


