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

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A R T I C L E   I N F O

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A B S T R A C T

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 penetration 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, Akinetia Time; BRAIN, BRadykinesia Akinetia Incoordination; CRT, Choice Reaction Time; CRTACC, Choice Reaction Time – Accuracy; DPINACCC, Pattern Seperation - New Stimuli - Accuracy; DPCOACC, Pattern Seperation - 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; NWMT, Numeric Working Memory Reaction Time; NWMTINACC, Numeric Working Memory New Stimuli - Accuracy; NWMTORACC, Numeric Working Memory Original Stimuli – Accuracy; PD, Parkinson Disease; RBDdq, REM Sleep Behaviour Disorder Screening Questionnaire; TPMRT, Spatial Working Memory Reaction Time; SPMACC, 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.

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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; Cilia et al., 2016; Jesús et al., 2014; Hasan et al., 2019; Weil et al., 2016), moderate microsmia (Noyce et al., 2014; Hasan et al., 2019; Doty, 2007; Toffoli et al., 2021). The LRRK2 G2019S variant was genotyped with KBiosciences Competitive Allele scoring technology method previously described (Toffoli et al., 2021). The University of Exeter Sequencing Facility with a long read, nanopore technology method previously described (Toffoli et al., 2021). 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 “S” 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; Weil 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 was used for analysis was downloaded on the 3rd January 2023.

2. Material and methods

2.1. Recruitment of participants

Participants were recruited through RAPSODI (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 (predictrack.com) cohort. We hope to provide further insight into the phenotype-genotype correlation of GBA1 variants in the pathogenesis of PD.

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 REM Sleep Behaviour Disorder Questionnaire (RBDq) (Stajny-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 Snaith, 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 Snaith, 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 Aki(n)esia 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 “S” 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.

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 Allele-specific 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 and 9 of the GBA1 gene. We developed a targeted sequencing panel for GBA1 variants and validated our assay by Sanger sequencing of a subset of samples. The control variants were identified from 100 index cases and 100 controls from the PREDICT-PD study.

2.5. Statistical analysis

R version 4.2.2 (RRID:SCR_001905, http://www.r-project.org/) was used for all statistical analyses.
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 RBDseq. Linear regression was used to assess differences in KS30, AT30, SRT, CRT, VIGRT, SPMRT, NWMRT. The cognitive scores for accuracy (DPICOACC, DPICNACC, CRTACC, VIGACC, SPMOACC, SPMMACC, NWMOACC, NWMMACC) represent proportions of correct answers, so they were analysed with quasbinomial 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), RBDseq (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, VIGRT, SPMRT) 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 CRT (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, SPMMACC, NWMOACC, NWMMACC.

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

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*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 \textit{GBA1} variants carriers, as well as to explore phenotypic differences between individuals with \textit{GBA1}-positive and \textit{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 \textit{GBA1} variants compared to whole-genome short-read sequencing (Toffoli et al., 2021). Second, our study cohort encompasses a diverse range of \textit{GBA1} variants, in contrast to a larger study on prodromal parkinsonian features in \textit{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 \textit{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 \textit{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 \textit{GBA1}-positive PD patients compared to \textit{GBA1}-negative PD patients (constipation, anxiety and depression, RBD, working memory).

A previous study similarly showed a worse cognitive profile in 26 \textit{GBA1}-positive PD compared to 39 \textit{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 \textit{GBA1}-positive PD compared to 684 \textit{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 \textit{GBA1} variants and duration of disease <3.5 years (193 \textit{GBA1}-PD vs 1700 \textit{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 \textit{GBA1} positive and \textit{GBA1} negative PD patients.

Our findings support the notion that cognition is more affected in \textit{GBA1}-positive PD patients and suggest that olfaction is also worse in \textit{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 \textit{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 \textit{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 \textit{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 \textit{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 variant 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 future development of PD in GBA1 carriers.

Our studies use an online approach to assess participants. This enables us to reach a larger audience and facilitates participation. However, this process has limitations. First, there might be a selection bias toward more computer literate individuals, as participants that do not own a computer, or that do not know how to use one, are automatically excluded from the trial. Moreover, most of the assessment is 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 GBA1-negative controls among relatives (especially partners and spouses) of GBA1 carriers and PD and GD patients. This has the advantage of including controls that are exposed to similar environmental factors, but the disadvantage of creating a group that is inherently mismatched for sex.

Finally, in the context of the PREDICT-PD study, it is noteworthy that the sequencing was limited to exons 8 through 11 of GBA1. While this region encompasses the majority of GBA1 variants, certain variants may have escaped detection, potentially resulting in the misclassification of individuals as GBA1-negative.

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.

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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.
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Disclosures

Toffoli M Employee of NHS and UCL.
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Jesuthasan A Nothing to disclose.
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Loefflad N Employee of UCL.
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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 \times interquartile range of the hinge (whiskers).

KS30: Kinesia Score 30 Seconds, AT30: Akinesia Time 30 s.
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.

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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).

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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 “Aparticipant-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).
Appendix A. Supplementary data

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

References