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Imaging and Genetics in Parkinson's Disease: Assessment of the *GBA1* Mutation

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Introduction:

Recent discovery of specific genes associated with Parkinson's Disease (PD) has elucidated specific pathways that can help us better understand mechanisms of neurodegeneration. *GBA1*, the gene coding for the lysosomal enzyme glucocerebrosidase, is of particular interest, with some studies reporting an earlier age of onset and faster progression of motor and cognitive symptoms in *GBA1* mutation carriers compared to non-carriers [1–4]. The link between mutations in *GBA1* and PD was first observed in patients with Gaucher disease (GD), an autosomal recessive lysosomal storage disorder [1]. Over 300 *GBA1* mutations have been identified in patients with Gaucher disease and many of these are found in patients with PD. N370S is the most common *GBA1* mutation in the Ashkenazi Jewish population but is also frequently found in other populations. Interestingly, T369M and E326K are polymorphisms that do not cause GD but have been associated with an increased risk for PD [5, 6]. Despite these limited phenotypic differences in *GBA1* mutation carriers, the only way to distinguish between patients with and without the variant is through genetic testing [7]. Furthermore, phenotypic differences associated with specific *GBA1* variants have also been reported [4, 5, 8, 9].

Only recently have studies begun to distinguish differences in CSF biomarkers between different *GBA1* variants. There is evidence of significantly higher alpha-synuclein levels with E326K and T369M variants when compared to N370S variants and non-carriers [9].

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Author Contributions

SG: conception and design, statistical analysis, and writing of the manuscript. EY: conception and design, review, and critique of manuscript. GL: review of statistical analysis, and review and critique of manuscript. DE, SGH: conception and design, review of statistical analysis, and critique of manuscript.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

Ethical Standards

The data was retrieved from the PPMI, an online database that provides de-identified clinical data. That study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines after approval of the local ethics committees of the participating sites. For up-to-date information on the study, visit www.ppmiinfo.org.

However, there are no reported differences in CSF amyloid beta 1-42 and CSF Tau profiles [10].

Neuroimaging may provide insight into different disease presentations. While there are currently no neuroimaging studies that evaluate group differences between different *GBA1* variants, there is evidence suggesting cortical differences between *GBA1* carriers and non-carriers. A FDG-PET study in *GBA1*-PD patients showed hypometabolism in the parieto-occipital cortex [11]. Additional studies using Fluorodopa PET showed reduced cerebral blood flow to the parieto-occipital cortex in *GBA1*-PD patients when compared to PD non-carriers [12]. Diffusion imaging revealed white-matter alterations in similar regions are present in *GBA1*-PD patients when compared to non-carriers [13]. Morphometry showed that within a small sample size (n=10), *GBA1*-PD patients demonstrated faster cortical thinning in these regions when compared to non-carriers [14]. However, these studies do not distinguish among different *GBA1* variants.

In this study, we investigated the differential impact of selected *GBA1* variants on cortical thinning in Parkinson's disease.

Material & Methods

Study Cohort Selection

We selected subjects with available genetic and baseline T1-MRI data from the Parkinson's Progression Markers Initiative (PPMI) database. More information on genotyping can be found on the PPMI website (http://ppmi-info.org). For genotyping quality control, we used PLINK v.1.9 [15] to exclude samples with call rates less than 95%, heterozygous outliers with F cut-off between −0.15 and 0.15, genotypic and reported sex mismatches, duplicate and related subjects with pair-wise kinship coefficients exceeding 0.125. The subjects' genomic VCF was inspected for mean sequence depth (<30X), contamination rate (>2%) and single nucleotide variant count (<3 SD). We further corrected for population stratification by excluding non-European ancestry subjects with principal component analysis (PCA), comparing the first two PCA scores of the subjects to those in the International HapMap3 Project [16]. A graph comparing our subject population from the PPMI cohort to the HapMap3 population can be found in Online Resource 1.

PD subjects who possessed non-*GBA1* variants such as *LRRK2* or *PARKIN* were excluded. Our primary criterium was to select PD patients who possess a *GBA1* N370S, E326K, or T369M variant. Once the genetic cohort was established, we selected two sets of age and sex-matched subjects without any known PD-related mutation: one of PD non-mutation carriers (NC), and one of healthy controls (HC). We verified that HCs also possessed no known PD-related mutation. We also ensured that the MRI scanners of the NC and HC population overlapped with that of the *GBA1* mutation carriers cohort. Figure 1 provides a summary of the cohort selection process.

Clinical Assessments and Biospecimen Sample Analysis downloaded from PPMI

We obtained demographic and clinical data from the PPMI database for all subjects. Additional data extracted for all subjects included Unified Parkinson's Disease Rating Scale

motor scores (UPDRS-III) to assess motor function [17] , Montreal Cognitive Assessment (MoCA) scores to assess cognitive performance [18], and Hoehn and Yahr (H&Y) scores to determine disease severity.

Along with the imaging data from the PPMI database, we also imported processed values for baseline serum NfL, CSF amyloid beta 1-42 ($A\beta_{1-42}$), CSF total tau (t-tau) and CSF tau protein phosphorylated at the threonine 181 position (p-tau) data for all available participants. More information about how data was collected and processed can be found on the PPMI website (http://ppmi-info.org).

Neuroimaging Analysis

We used FreeSurfer v6.0 program (http://surfer.nmr.mgh.harvard.edu/) to complete a standard cortical reconstruction of the T1-weighted MRI data retrieved from the PPMI repository. Information about scanner parameters can be found in Online Resource 2. We calculated the burden of PD on cortical thickness by comparing PD patients to HCs. For this, we included all patients, regardless of genotype. We used the Qdec v1.5 software under FreeSurfer to create a generalized linear fit model (GLM) correlating cortical thickness to group while accounting for age to observe group differences between the HCs and the PD group.

Statistical Analysis

Qdec statistical analysis was set to an FDR correction of 0.001.

We further explored the resulted ROIS by performing ANOVAs dividing the cohort into 4 sub-groups: N370S variants, E326K or T369M variants, NCs, and HCs, and including age as a covariate (Fig. 1). Demographic and clinical data were evaluated with a one-way ANOVA for the 4 sub-groups. CSF and serum markers were first tested between PD and HCs with a t-test. Subgroups were tested with ANOVAs. We adjusted p-values with an FDR correction for multiple comparisons. A p-value < 0.05 was considered statistically significant. ANOVAs and t-tests were analyzed in R v4.0.3 (https://www.R-project.org).

Results:

Forty-seven PD patients had the *GBA*1 variants of interest and imaging. After retrieving age and sex-matched NCs and HCs from the PPMI database, the total study cohort was comprised of 141 subjects. Summary of the demographic data and clinical assessment of the study cohort can be found in Table 1. The ANOVA showed no significant differences between groups in terms of age and age at diagnosis. However, while all subjects had MoCA within normal range, there was an effect of MoCA on sub-group, with the MoCA of the E326K and T369M variants being significantly lower than that of the HCs ($PD_{E326K\text{ or }T369M}$:$p = 0.013$, FDR corrected). For these measures, the PD sub-groups show no differences.

Differences in cortical thickness

Fig 2. summarizes these neuroimaging findings. Qdec analysis showed that average cortical thickness between PD and HCs significantly differed in clusters located in the postcentral (−52.3, −13.6, 30.4) and superior parietal regions (−31.3, −40.5, 46.9). Post-hoc ROI analysis showed that in the superior parietal cluster, the cortical thickness of all three PD groups was significantly less than HCs (PD_{NC}: p = 1.83E-07; $PD_{E326K\ or\ T369M}$: p= 1.13E-04; PD_{N370S}: p= 3.27E-02, FDR corrected). However, there were no significant differences within the PD group. In the postcentral cluster, the cortical thickness of non-carriers and variants were significantly less than HCs (PD_{NC}: p = 2.28E-10; $PD_{E326K\ or\ T369M}$: p= 5.61E-08; PD_{N370S}: p= 0.055, FDR corrected). Within PD group comparisons showed that the cortical thickness of NCs, E326K and T369M variants were significantly less than that of the N370S variants (PD_{NC}: p = .0061; $PD_{E326K\ or\ T369M}$: p = .016, FDR corrected)

Differences in serum and CSF markers

Fig. 3 summarizes these CSF markers findings. Serum NfL values were present in 79%, and CSF values in 91% of our study cohort (see Fig. 1). When looking at differences in serum NfL levels between the four groups, only N370S variants were significantly greater than that of the HCs (PD_{N370S}: p = 0.000405). Within PD group comparisons show that the NfL levels of N370S variants were significantly higher than NCs, E326K and T369M variants as well (PD_{NC}: p = 0.05; $PD_{E326K\ or\ T369M}$: p= 0.01). When looking at the CSF biomarkers ($A\beta_{1–42}$, t-tau, p-tau), there were no significant differences between the HCs and each of the PD groups. There were also no significant differences among the PD sub-groups.

Discussion

This study is, to date, the largest imaging study that characterizes *GBA1* variants in comparison to *GBA1* non-carrier PD and HCs.

Our findings confirm that there are cortical differences between the HCs and PD groups. Our main analysis found group differences in clusters in the postcentral and the superior parietal regions which co-localize with areas seen active in fMRI studies of motor tasks [19, 20]. These are common tasks that are deficient in PD patients [21–23]. Significant clusters in these regions also support previous findings, suggesting parietal cortical differences between *GBA1* carriers and HCs. [12, 13].

Our results also suggest that there are cortical differences within *GBA1* carriers in our cohort. Our neuroimaging findings show that for recently diagnosed PD patients, in the postcentral cluster, E326K and T369M variants and non-mutation carriers significantly differ from HCs, whereas there are no significant differences between carriers of the N370S variant and HCs. In fact, in the postcentral cluster, the different presentation of the average thickness of N370S variants is emphasized. Although the cortical thickness of all three PD groups is significantly different from HCs in the superior parietal cluster, the pattern of the average thickness of N370S variants is closer to that of HCs.

While neuroimaging analysis shows that N370S variants have a higher-than-average cortical thickness in affected regions when compared to NCs, E326K and T369M variants, biospecimen analysis might be perceived as contradictory results. Serum NfL levels of N370S variants were significantly higher than those of HCs, NCs, and E326K and T369M variants. Increased serum NfL levels have been shown to correlate with higher cortical atrophy. This increased cortical thickness with higher serum NfL levels suggests that reduced GCase, the enzyme coded for by *GBA1* gene, may contribute to neuroinflammation in *GBA1* N370S PD patients. This neuroinflammation could explain the increased values of cortical thickness that we saw in N370S variants [7, 24–27]. N370S is known to cause glucocerebrosidase deficiency while E326K and T369M variants are not considered Gaucher disease causing mutations [28].

A strength of this study is the homogeneity of the population studied. All participants had a Hoehn &Yahr score of 2 or lower, had been recently diagnosed, and results from the behavioral measures support the idea that none of the subjects had major cognitive impairments. The similarity of the CSF markers further emphasizes the homogeneity of our sample.

This study is limited by data available in the PPMI database, with neuroimaging data coming from multiple locations. However, when looking at the effect of scanner in the three regions of interest, scanner type did not have a significant effect. Our sample size is further limited by the number of *GBA1* carriers. Second, only 110 of the 141 subjects included have CSF data available. Moreover, the N370S variant group only had CSF data present for 9 out of 21 subjects. Nevertheless, the findings in this cohort confirms previous studies stating that there are no differences between these groups using CSF measures [10]. Due to the availability in the PPMI database, all subjects included in this study were of European ancestry. Future studies should aim to include samples of more diverse ancestral backgrounds.

In conclusion, our findings show that recently diagnosed PD patients with N370S variants differ from HCs, NCs, E326K and T369M variants. This is seen at the cortical level, where N370S variants displayed a cortical thickness more like that of the HCs. Despite this higher level of cortical thickness than other PD groups, N370S variants contrarily had significantly higher serum NfL levels, a measure of active cortical degeneration. Given these results, we speculate that trends seen in cortical thickness for these variants could be due to neuroinflammation. Our results demonstrate that there are different disease manifestations depending on the genotype of disease. Further research that investigates how serum NfL levels and cortical thickness changes longitudinally could further illuminate disease pathology in this subject population and thus help to determine whether imaging and serum NfL could be potential biomarkers for certain *GBA1* variants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmiinfo.org/data). For up-to-date information on the study, visit www.ppmiinfo.org.

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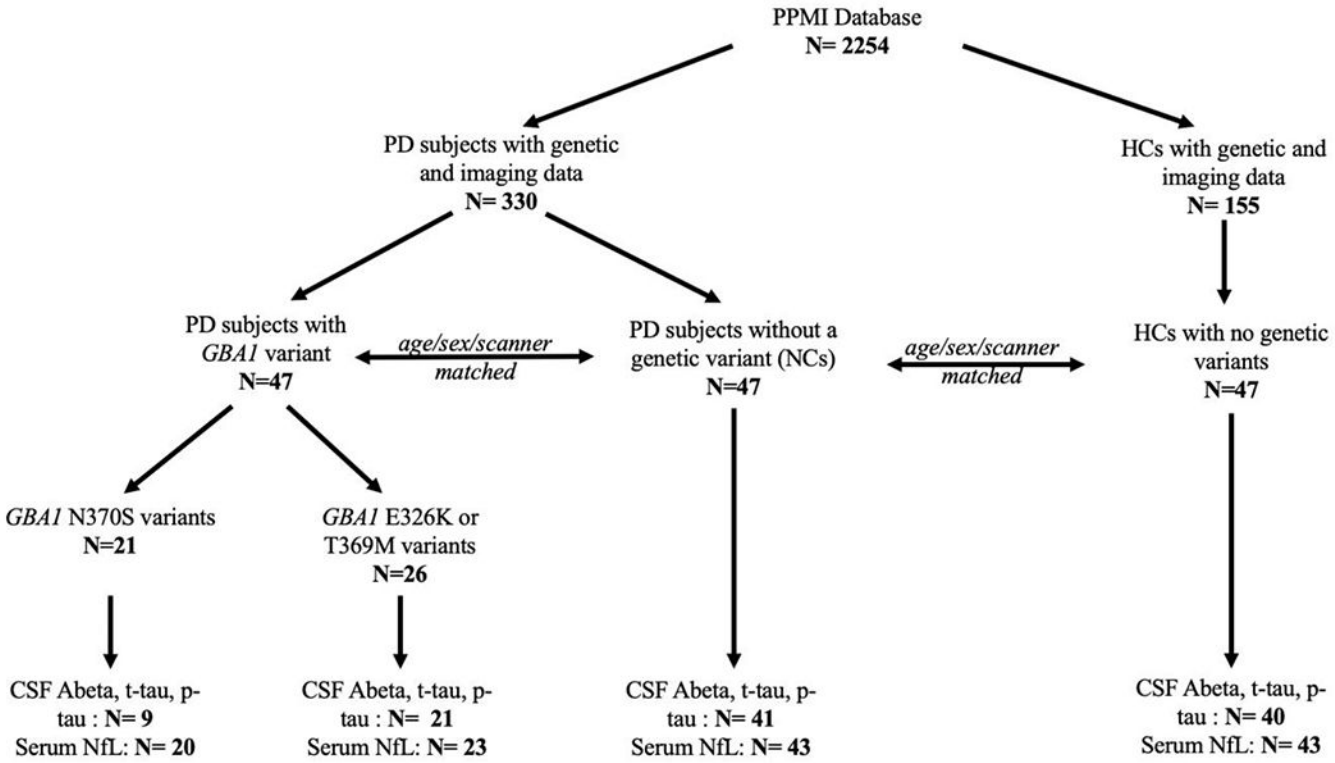

Fig. 1. Selection process for the study cohort

After determining PPMI subjects present with a *GBA1* variant of interest and imaging data, age and sex matched PD subjects without a genetic variant (NCs) and HCs with no genetic variant were retrieved from the database. Out of this study cohort, we retrieved available CSF and serum NfL data.

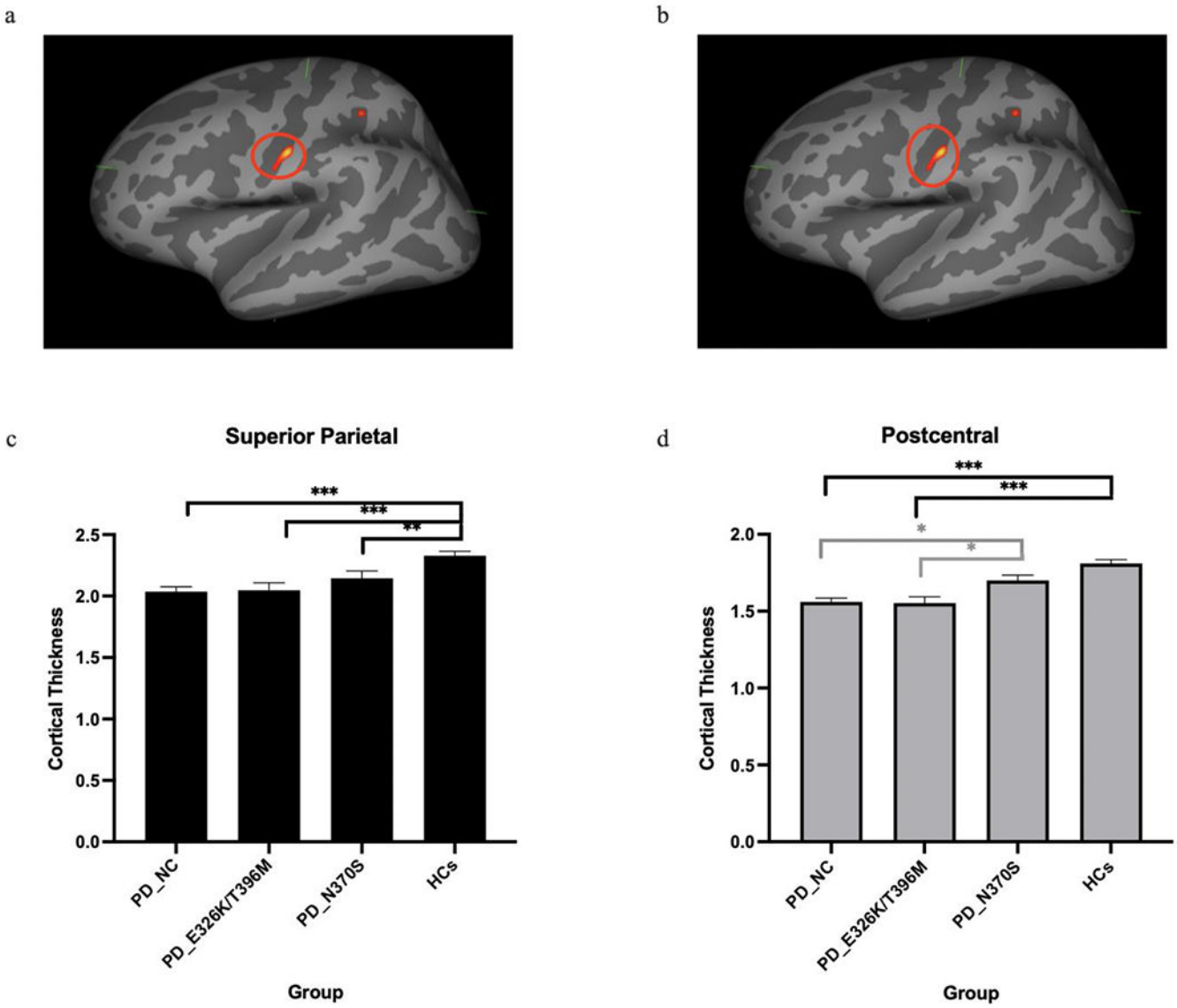

Fig. 2. Cortical differences of PD groups compared to HC

***p<0.001 **0.001<p<0.01 *0.01<p<0.05. Significant differences in cortical thickness between all PD patients and HC were found in the (a) superior parietal cluster (−31.4, −40.7, 47.3), and (b) postcentral cluster (−53.3, −13.4, 31.0). Cortical thickness of all three PD groups significantly differs from HCs in superior parietal cluster (c). The E326K variant, T369M variant, and NC significantly differ from HCs in the post centralcluster (d). Moreover, NC, E326K, and T369M variants significantly differ from N370S variant in postcentral cluster (d). Black lines represent differences between HCs and PD sub-groups, while gray lines represent differences within the PD sub-groups.

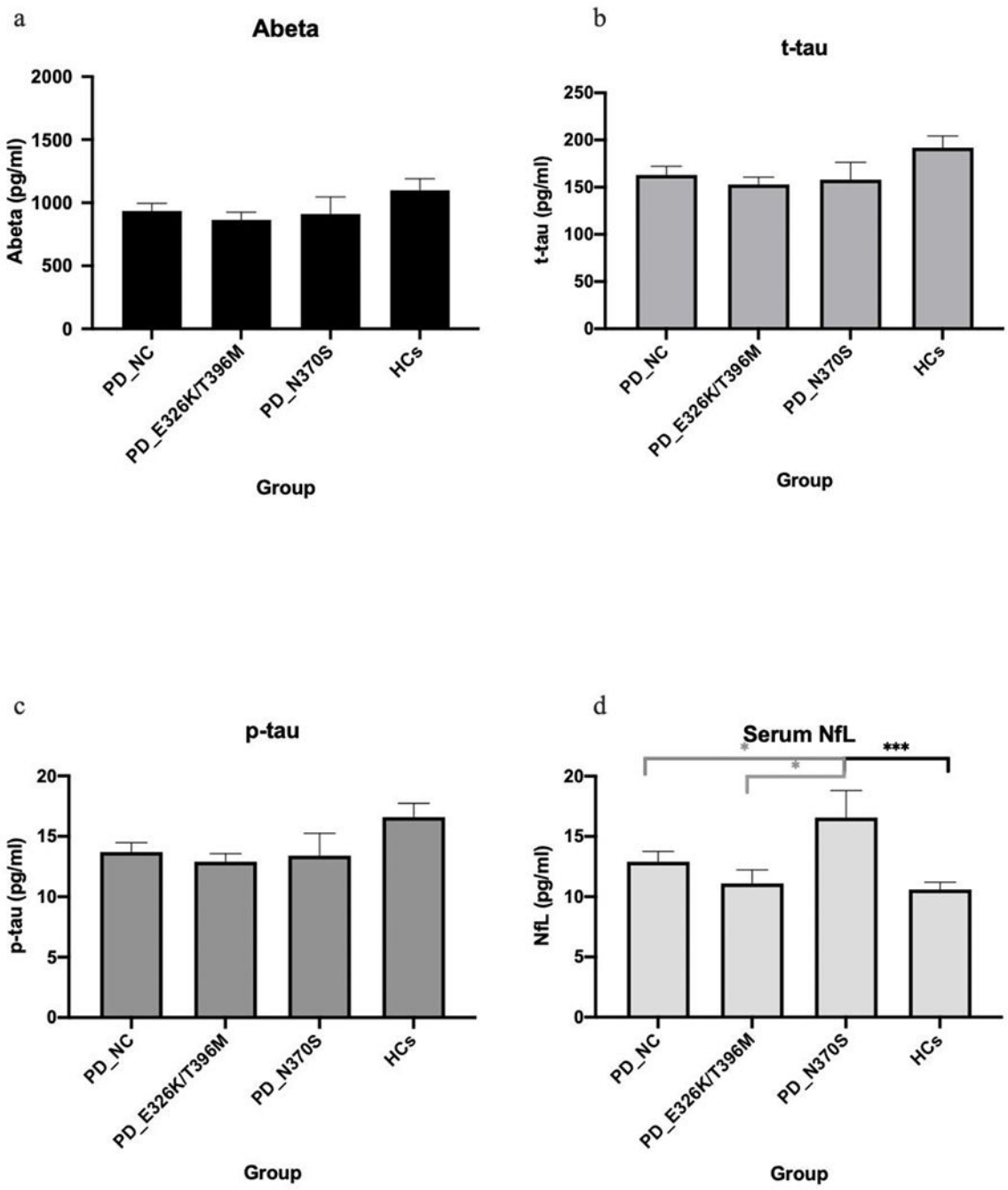

Fig. 3. CSF and serum marker comparison of PD groups to HC

***p<0.001 **0.001<p<0.01 *0.01<p<0.05. There were no significant differences between PD cohort and HCs in terms of CSF Abeta levels (a), CSF t-tau levels (b), and CSF p-tau levels (c). N370S variant showed to have significantly higher levels of serum NfL levels when compared to the NCs, E326K and T369M variants, and HCs (d). Black lines represent differences between HCs and PD sub-groups, while gray lines represent differences within the PD sub-groups.

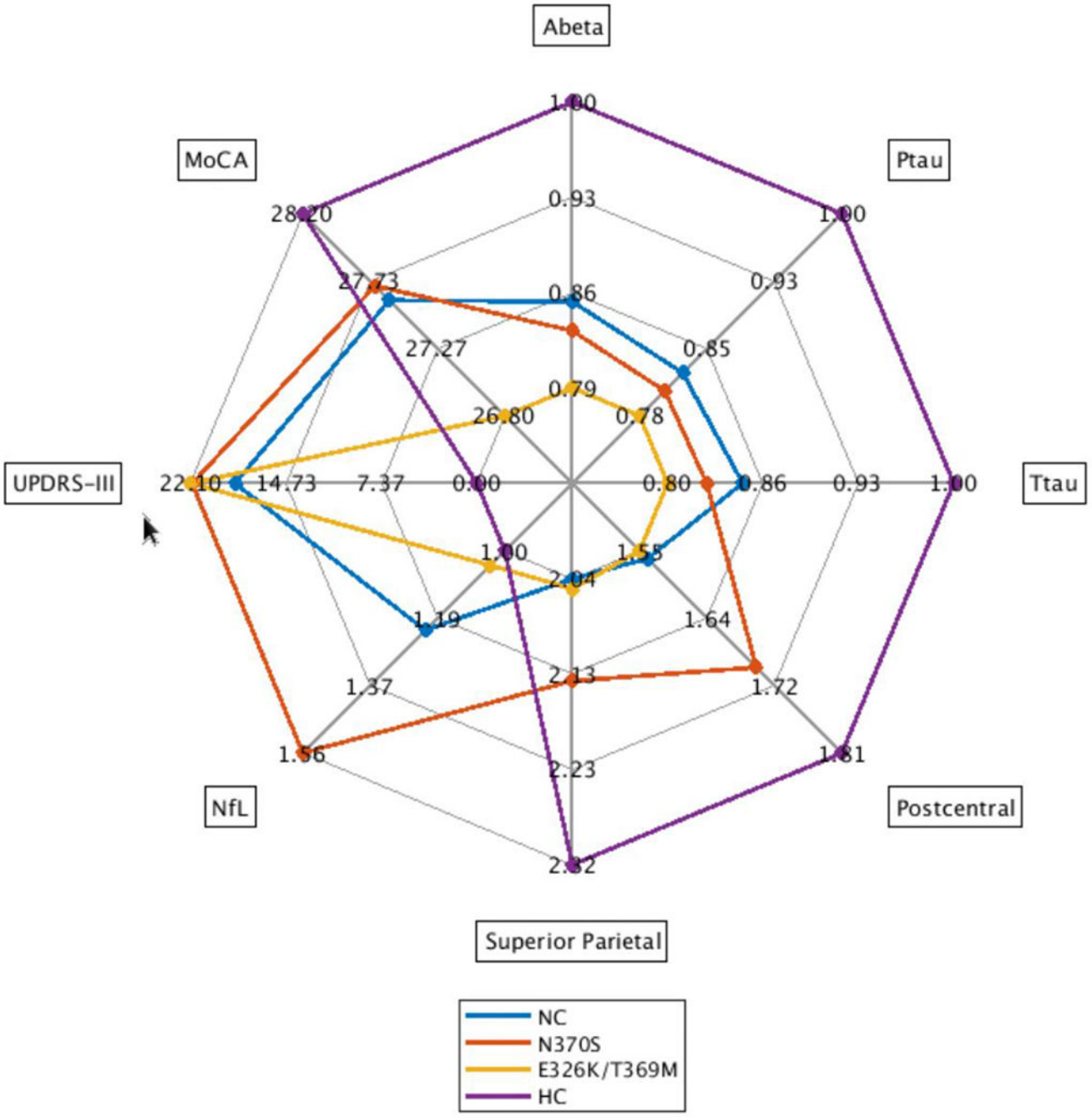

Fig. 4. Correlations between imaging, biofluid, and behavioral findings.

The spider plot shows how the reported measures correlate between the four groups. Scores for CSF and Serum markers are reported as percentage of the control. A max score of 30 is possible for the MoCA, a max score of 132 is possible for the UPDRS-III.

Table I.

Demographic and clinical assessment summary.

Measures are reported as mean ± SD unless otherwise stated. ANOVA was used to calculate significance between the four sub-groups. NC: Non-carriers of GBA gene variants.

	PD_{NC} n= 47	**$PD_{E326K\ or\ T369M}$ n= 26**	**PD_{N370S} n= 21**	**HC n= 47**
GBA1 Genotype	NC	E326K (69%) T369M (31%)	N370S (100%)	NC
Male, n(%)	27 (57)	14 (54)	13 (62)	27 (57)
Age, y	60.2 ± 8.37	57.3 ± 8.70°	64.1 ± 9.35	60.1 ± 8.67
Disease Duration, y	0.523 ± .492	0.558 ± .576	1.97 ± 2.05†	
Education (yrs)	14.4 ± 2.97*†	17.0 ± 2.24	17.2 ± 3.32	16.9 ± 2.55
H&Y	1.49 ± .505	1.62 ± .496	1.71 ± .463	
UPDRS-III	18.7 ± 8.47	22.1 ± 10.2	24.0 ± 9.33	
MoCA	27.6 ± 2.11	26.8 ± 2.68*	27.8 ± 1.34	28.2 ± 1.14