Transcranial sonography and functional imaging in glucocerebrosidase mutation Parkinson disease

MJ Barrett, MD1,* , J Hagenah, MD2, V Dhawan, PhD3, S Peng, PhD3, K Stanley, BS1, D Raymond, MS1, A Deik, MD1, SJ Gross, MD4,5, N Schreiber-Agus, PhD5, A Mirelman, PhD6,7, K Marder, MD, MPH8, LJ Ozelius, PhD9, D Eidelberg, MD3, SB Bressman, MD1,10, R Saunders-Pullman, MD, MPH1,10, and the LRRK2 Ashkenazi Jewish Consortium

1Department of Neurology, Beth Israel Medical Center, New York, NY, USA, 10003
2Department of Neurology, University of Lübeck, Lübeck, Germany
3Center for Neurosciences, The Feinstein Institute for Medical Research, Manhasset, NY, USA 11030
4Department of Obstetrics and Gynecology, North Bronx Healthcare Network, Albert Einstein College of Medicine, Bronx, NY, USA
5Human Genetics Laboratory at Jacobi Medical Center, North Bronx Healthcare Network, Bronx, NY, USA
6Movement Disorders Unit, Department of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
7Ben Gurion University, Beer Sheba, Israel
8Columbia University, Columbia University Medical Center, New York, NY, USA
9Department of Genetics, Mount Sinai School of Medicine, New York, NY, USA, 10029
10Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA, 10461

Abstract

Background—Heterozygous glucocerebrosidase (GBA) mutations are the leading genetic risk factor for Parkinson disease, yet imaging correlates, particularly transcranial sonography, have not been extensively described.

Methods—To determine whether GBA mutation heterozygotes with Parkinson disease demonstrate hyperechogenicity of the substantia nigra, transcranial sonography was performed in Ashkenazi Jewish Parkinson disease subjects, tested for the eight most common Gaucher disease mutations and the LRRK2 G2019S mutation, and in controls. [18F]-fluorodeoxyglucose or [18F]-fluorodopa positron emission tomography is also reported from a subset of Parkinson disease subjects with heterozygous GBA mutations.

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*Corresponding Author: Matthew J. Barrett, M.D., Beth Israel Medical Center, Department of Neurology, 10 Union Square East, Suite 5K, New York, NY 10003 Office: 212-844-8714 Fax: 212-844-8461, mabarrett@chpnet.org.

Conflicts of Interest: None of the authors have any financial disclosures that would represent a conflict of interest with the research presented in this manuscript.

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Results—Parkinson disease subjects with heterozygous GBA mutations (n=23) had a greater median maximal area of substantia nigral echogenicity compared to controls (n=34, aSNmax=0.30 vs. 0.18, p=0.007). There was no difference in median maximal area of nigral echogenicity between Parkinson disease groups defined by GBA and LRRK2 genotype: GBA heterozygotes; GBA homozygotes/compound heterozygotes (n=4, aSNmax=0.27); subjects without LRRK2 or GBA mutations (n=32, aSNmax=0.27); LRRK2 heterozygotes/homozygotes without GBA mutations (n=27, aSNmax=0.28); and GBA heterozygotes/LRRK2 heterozygotes (n=4, aSNmax=0.32, overall p=0.63). In secondary analyses among Parkinson disease subjects with GBA mutations, maximal area of nigral echogenicity did not differ based on GBA mutation severity or mutation number. [18F]-fluorodeoxyglucose (n=3) and [18F]-fluorodopa (n=2) positron emission tomography in Parkinson disease subjects with heterozygous GBA mutations was consistent with findings in idiopathic Parkinson disease.

Conclusions—Both transcranial sonography and positron emission tomography are abnormal in GBA mutation associated Parkinson disease, similar to other Parkinson disease subjects.

Keywords
Parkinson disease; parkinsonism; diffuse Lewy body disease; Transcranial sonography; PET; Glucocerebrosidase; GBA; Gaucher disease; LRRK2

Introduction
Heterozygous glucocerebrosidase (GBA) mutations have emerged as the leading genetic risk factor for Parkinson disease (PD) [1–3]. In Asian [4, 5] and non-Jewish European populations [6–8], 4–9% of PD patients have heterozygous GBA mutations, while in the Ashkenazi Jewish population, up to 20% of PD patients are GBA heterozygotes [8]. Although many individual PD patients with heterozygous GBA mutations clinically resemble PD without identified mutations, carriers overall have an earlier age of onset and greater cognitive impairment [8–11]. Neuroimaging modalities have the potential to further clarify the phenotype and pathophysiology of PD associated with GBA mutations. Transcranial sonography (TCS) detects substantia nigral hyperechogenicity in 90% of patients with idiopathic PD [12]. The nigral hyperechogenicity likely reflects increased local iron content and microglial activation [13,14]. With the exception of parkinsonism associated with ATP13A2 mutations [15], TCS investigations in PINK1 [16], PRKN [17], SNCA [18], and LRRK2 associated PD [19], have revealed hyperechogenic substantia nigra. TCS in 3 Gaucher disease type 1 (GD1) patients with parkinsonism and 20 PD patients with heterozygous GBA mutations revealed hyperechogenic substantia nigra, suggesting that nigral hyperechogenicity is also a feature of GBA-associated PD [20,21]. The pathophysiological similarity of GBA-associated PD with idiopathic PD is also supported by functional imaging studies showing a presynaptic dopaminergic deficit in a small number of GBA homozygotes and heterozygotes [20,22]. Herein we evaluated TCS in a cohort with GBA-associated PD, including GBA heterozygotes with mild and severe mutations, GBA compound heterozygotes and homozygotes, and GBA/LRRK2 G2019S mutation carriers, and compared these with LRRK2 mutation carriers. We assessed whether GBA mutation severity and the number of mutant alleles is associated with the degree of hyperechogenicity in those with PD. We also extend the literature by reporting functional imaging with [18F]-fluorodeoxyglucose (FDG) and [18F]-fluorodopa (FDOPA) positron emission tomography (PET) in a subset.

Methods
Ashkenazi Jewish patients who met diagnostic criteria for PD were evaluated at the Movement Disorder Center at Beth Israel Medical Center and invited to participate in a...
genetic study of PD, including mutation screening and transcranial sonography [23,24]. Blood or saliva samples were obtained, DNA was extracted, and samples were screened for the \textit{LRRK2} G2019S mutation [24] and the eight most common Ashkenazi Jewish \textit{GBA} mutations (N370S, L444P, 84GG, IVS2+1G→A, V394L, del55bp, D409H, and R496H) as previously reported [20]. PD subjects were characterized as \textit{GBA} heterozygotes without \textit{LRRK2} mutations (PD-\textit{GBA} single), \textit{GBA} homozygotes or compound heterozygotes (PD-\textit{GBA} double), \textit{GBA} heterozygotes with \textit{LRRK2} mutations (PD-\textit{GBA}/\textit{LRRK2}), \textit{LRRK2} heterozygotes (PD-\textit{LRRK2} single), \textit{LRRK2} homozygotes (PD-\textit{LRRK2} double), and subjects without \textit{LRRK2} or \textit{GBA} mutations (PD-no mutation). Spouses and healthy laboratory controls (14 Ashkenazi Jewish, 16 non-Jewish) without neurological disease or a family history of PD were also recruited. The study procedures were approved by the institutional review board at Beth Israel Medical Center, and all subjects provided informed consent.

**Transcranial Sonography**

Experienced sonographers, blinded to the genetic status of the subjects, performed TCS on PD subjects and controls using the SONOS 5500 ultrasound system (Phillips) equipped with a 2.0–2.5 MHz sector transducer (S3 probe). The examination was performed bilaterally at the pre-auricular temporal bone window with a penetration depth of 14–15 cm. The images were adjusted for gain power, compression and time-gain compensation depending on the quality of the individual bone window. Images of the mesencephalic brainstem were digitally stored for later analysis. The area of hyperechogenicity in the ipsilateral SN was manually encircled by an independent investigator blinded to PD and gene status and measured using computer-based analysis (Scion Image Beta 4.02 Win software package). For statistical analysis, the larger aSN of each individual was selected (aSNmax), or in cases of an insufficient bone window on one side, the ipsilateral aSN of the analyzable side [25]. Analysis of TCS images included data from 30 non-PD controls, 52 new PD subjects and 35 PD subjects who were previously reported (22 PD-\textit{LRRK2}, 6 PD-no mutation, 3 PD-\textit{GBA}/\textit{LRRK2}, 1 PD-\textit{LRRK2} double [20], and 3 PD-\textit{GBA} double subjects [19]). Representative TCS images are included in Figure 1.

**Positron Emission Tomography**

FDG PET had been performed in 3 subjects with heterozygous \textit{GBA} mutations using previously described methods [26]: 35 to 45 minutes after injection with 5–6.4 mCi of FDG, 35 PET slices parallel to the orbitomeatal line were acquired in 3D over 10 minutes. A measured attenuation correction and corrections for scatter and randoms were applied. For each subject, expression of the Parkinson disease-related metabolic covariance pattern (PDRP), as determined by network analysis of FDG PET in 20 PD patients and 20 age-matched healthy controls [27,28], was quantified using a fully automated voxel-based algorithm[27,29]. The results were Z-transformed and the mean control PDRP score was set to zero.

In addition to FDG PET, Fluorodopa (FDOPA) PET had been performed in 2 different subjects with heterozygous \textit{GBA} mutations using previously described methods [30]: 35 to 100 minutes after injection with 4.0 and 6.3 mCi of FDOPA, 35 PET slices parallel to the orbitomeatal line were acquired in 3D over 10 minutes. The striato-occipital ratio (SOR) was assessed by placing the regions of interest for the caudate, putamen, and the occipital cortex (0.6, 1.6, and 3.9 cm$^2$, respectively) on composite FDOPA PET slices. SOR values were obtained by dividing the difference between striatal and occipital activity by occipital activity. A dopaminergic deficit was defined as putamen SOR value 2 SD below the mean for 20 healthy controls (age: 51 ± 13 years) [31]. Additionally, putaminal FDOPA uptake
ratios were compared to the uptake for 20 early PD patients (mean age: 53 ± 9 years; disease duration: 2.6 ± 2.4 years) [31].

**Statistical Analysis**

Mann-Whitney and Fisher’s exact tests were used for bivariate comparisons of continuous and categorical variables, respectively. For comparison of all parkinsonian groups, Kruskal-Wallis and Fisher’s exact tests were used. (Stata 11, 2009. College Station, TX: StataCorp LP.)

**Results**

TCS was performed in 90 PD subjects: 23 PD-GBA single, 4 PD-GBA double, 32 PD-no mutation, 25 PD-LRRK2 single, 2 PD-LRRK2 double, and 4 PD-GBA/LRRK2. TCS was also performed in 34 non-PD controls. GBA mutations included 17 N370S, 2 R496H, 1 V394L, 2 L444P, and 1 84GG in the PD-GBA single group; 1 N370S/N370S, 2 N370S/R496H, and 1 N370S/84GG in the PD-GBA double group; and 3 N370S and 1 84GG in the PD-GBA/LRRK2 group. The mutations IVS2+1G, del55bp, and D409H were not encountered in our sample. Demographic characteristics and distribution of mutations are presented in Table 1. Because PD in LRRK2 homozygotes and LRRK2 heterozygotes does not differ [32], these groups were combined for analysis (PD-LRRK2). All other groups, including PD-GBA/LRRK2, were considered separately. There was no difference in the gender distribution (p=0.09) or the age at exam (p=0.22) between PD-GBA single and controls. Among the five parkinsonian groups, there were no differences in gender (p=0.71), age at symptom onset (p=0.49), or duration of disease at exam (p=0.45). The UPDRS III score at exam was lower in the LRRK2 mutation group compared to PD-GBA single (p=0.006), PD-GBA double (p=0.03), and PD-no mutation (p=0.005).

Seventy-six subjects had bilaterally adequate bone windows, and 10 had only one window (3 PD-GBA single, 2 PD-no mutation, 5 PD-LRRK2). One of the PD-GBA single subjects (N370S) did not have an adequate bone window and was not included in the analysis.

PD-GBA single were more echogenic than non-PD controls (p=0.007). There was no difference in aSNmax between the five parkinsonian groups (p=0.63) (Figure 2). The PD-GBA double subjects did not have a different aSNmax compared to the 23 PD-GBA single subjects (p=0.68). Nor did PD-GBA/LRRK2 differ from the PD-GBA single group (p=0.20). Further, when PD-GBA/LRRK2 and PD-GBA double were combined, echogenicity still did not differ from the heterozygous group (p=0.57).

A secondary analysis was performed to determine whether mutation severity, as previously defined, [33] was associated with the area of substantia nigra echogenicity. Among those with heterozygous GBA mutations, there was no difference in aSNmax between the 5 subjects with severe mutations (L444P, 84GG, or V394L) and the 22 subjects with mild mutations (p=0.21).

The characteristics of the PD-GBA single subjects who underwent FDG and FDOPA PET scans are summarized in Table 2. In the three subjects who had FDG PET, findings were consistent with idiopathic PD. PDRP z-scores were above the range for healthy controls (−1.09 to 0.88) and fell within 2 SD of the mean for PD controls (mean±SD=1.55±0.74). In the two subjects with FDOPA PET, there were bilateral reductions in FDOPA uptake. Both putaminal SOR values were below the range for healthy controls (1.30 to 1.97) and within 2 SD of the mean for PD controls (mean±SD=0.67±0.15) (Supplementary Figure 1). TCS aSNmax was enlarged in both subjects with FDOPA PET (aSNmax=0.22, 0.33) and in two of the three subjects with FDG PET (aSNmax=0.33, 0.23, 0.05).
Discussion

Our data support that GBA mutation carriers with PD have greater substantia nigra echogenicity than non-PD controls and do not differ from PD subjects without GBA mutations [20,21]. This further strengthens the idea that Lewy body disorders, including GBA-associated PD, idiopathic PD, and LRRK2-associated PD, demonstrate nigral hyperechogenicity. While cases with non-G2019S LRRK2 mutations less consistently show midbrain Lewy body pathology, the majority of neuropathology studies in LRRK2 G2019S mutation-associated PD demonstrated prominent dopaminergic cell loss in the substantia nigra pars compacta and locus coeruleus and midbrain Lewy body deposition typical for PD. In these cases cortical Lewy bodies were variably present. (reviewed by [34]) Almost all reported autopsy cases of GBA-associated PD show nigral cell loss and Lewy body pathology, although the distribution of Lewy body pathology may be more likely to be cortical. While the more frequent neocortical pathology in those with PD and GBA mutations compared to non-mutation PD controls is concordant with a clinical phenotype more similar to dementia with Lewy bodies, [10,35,36] the shared Lewy body pathology and nigral hyperechogenicity among GBA-associated PD, LRRK2 G2019S-associated PD, and idiopathic PD suggest a shared pathophysiological mechanism. Therefore, agents specifically targeting the mechanism of LRRK2- or GBA-associated PD may provide benefit for those with idiopathic PD.

The pathogenic etiology of GBA-associated PD is not yet defined. Proposed mechanisms include reduced α-synuclein degradation secondary to impairment of the ubiquitin-proteasome system by mutant protein; lysosomal dysfunction leading to either or both reduced α-synuclein degradation and impaired autophagy and mitophagy; and alteration in lipid metabolism and lipid membrane composition ultimately resulting in α-synuclein aggregation (reviewed by [37]). These mechanisms, however, may not be exclusive and other factors likely also contribute to the development of parkinsonism in GBA mutation carriers. The finding of nigral hyperechogenicity among our PD subjects with GBA mutations is consistent with the proposed mechanisms, as they may be associated with oxidative stress and apoptosis and, thus, iron deposition.

TCS in PD and non-PD subjects with PRKN mutations and in non-PD subjects with PINK1 mutations suggests a possible gene dosage effect with homozygotes having larger areas of echogenicity than heterozygotes [16,17,38]. The loss of function mechanisms postulated for both PRKN and PINK1 mutations support this difference. GBA mutations have been hypothesized to contribute to PD via both loss of function and gain-of-toxic-function mechanisms [37]. Among GBA mutation carriers with PD in our study, nigral hyperechogenicity does not appear to be dependent on the number of GBA mutations. This is not consistent with a gene dosage effect, and is a finding similar to LRRK2 PD [19].

GBA mutations can be divided into mild and severe mutations based on their propensity to cause neuronopathic Gaucher disease phenotypes (Type 2 and 3) [33]. Compared to mild GBA mutations, severe mutations are associated with an increased risk of developing PD and an earlier age of PD onset [39]. In a secondary analysis we did not detect a difference in nigral echogenicity between PD subjects with severe mutations compared to those with mild mutations, although the small sample size may have limited our ability to detect a difference between these two subgroups.

One limitation to our study is that the GBA genotype of most of our controls was unknown. As the carrier frequency in the Ashkenazim is approximately 6% and is less than 1% in the non-Jewish population [40], we expect that very few, if any, of our controls were carriers. However, if they were, this would bias our results toward finding no difference between
parkinsonian patients and non-PD controls. Similar to PRKN and PINK1 mutation carriers without PD, LRRK2 mutation carriers without parkinsonism have also been shown to have hyperechogenic SN compared to controls, suggesting that TCS may be a risk marker in these genetic etiologies of parkinsonism [16,17,19]. Finally, whereas Brockmann et al. noted interrupted raphe in PD-GBA heterozygotes [21], we did not systematically evaluate the raphe in our scans, and cannot comment in our population.

Because there are few reports of functional imaging studies in PD subjects with GBA mutations we also reported PET imaging in a subset of those who had TCS. Overall our findings are consistent with those in idiopathic PD. In a study of five heterozygous GBA mutation carriers with parkinsonism and three asymptomatic carriers, FDG PET demonstrated supplemental motor area hypometabolism in all, while only GBA heterozygotes with parkinsonism showed parieto-occipital hypometabolism [22]. The latter finding is consistent with the greater cognitive impairment reported in parkinsonian GBA heterozygotes. Further, [11C] CFT and [11C] raclopride PET did not reveal dopaminergic dysfunction in the asymptomatic carriers [22]. In our prior study of GD1 subjects with parkinsonism, FDG PET revealed hypermetabolic lentiform nuclei and areas of cortical hypometabolism (parieto-occipital, temporal, and anteromedial frontal) [20]. FDOPA PET showed reduced striatal uptake bilaterally [20]. Here we extend this data and demonstrate that PD patients with heterozygous GBA mutations have hypermetabolic lentiform nuclei on FDG PET and reduced striatal FDOPA uptake bilaterally. While our primary analysis was the comparison of PDRP, heterozygous GBA mutation carriers also had regions of cortical hypometabolism on FDG-PET, specifically in the parietal and temporal, parietal and anteromedial frontal, and parieto-occipital and temporal regions.

Two of three subjects with FDG PET consistent with PD and both subjects with reduced FDOPA uptake showed nigral hyperechogenicity. This is similar to a previous study among PRKN mutation carriers that found that those with abnormal FDOPA PET, regardless of PD status, also demonstrated nigral hyperechogenicity on TCS [38]. In order to address whether TCS nigral hyperechogenicity and functional imaging abnormalities are associated with GBA mutations independent of PD, further imaging studies of asymptomatic GBA carriers are warranted.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

The research presented in this manuscript was supported by the Empire State Clinical Research Training Program, the Marcled Foundation, and NIH-NINDS NS073836. LRRK2 and control ultrasound work was supported in part by the Michael J. Fox Foundation. MJB was also supported in part by the CTSA Grant UL1RR025750, a component of the NIH, and roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR or NIH. This study was not industry sponsored.

The authors thank all patients and family members who graciously participated in this study; and Akhila Iyer and Jeannie Soto-Valencia for assistance in data collection and recruitment. The LRRK2 Ashkenazi Jewish Consortium includes Karen Marder, Lorraine Clark, Itsik Pe’er, Helen Mejia, Brian Rakitin, Ming-Xin Tang, Roy Alcalay, Tsivyatko Dorovski, Martha Orbe Reilly, Llency Rosado, Elan Louis, Lucien Cote, Cheryl Waters, Blair Ford, Steven Frucht, Stanley Fahn, Oren Levy, and Ernest Roos at Columbia University; Nir Giladi, Avi Orr-Urtreger, Anat Mirelman, Tanya Gurevich, Elissa Ash, Avner Thaler, Shiran Levi, Anat Bar Shiria, Mali Gana Weiss, Noa Bregman, Meir Kestenbaum, Talma Hendler, Hedva Lehrman, Einat Even Sapir, Maayan Zelis, Kira Yasinsovsky, Anat Shkedy, Arella Hillel, Merav Kedmi, Ziv Gan-Or, Hila Kobo at Tel Aviv University; Susan Bressman, Rachel Saunders-Pullman, Deborah Raymond, Vicki Shanker, Mark Groves, Christina Palmese, Naomi Lubarr, Jeannie Soto-Valencia, Akhila Iyer, Matthew Barrett, Jose Cabassa, Andres Deik, and Ann Hunt at Beth Israel Medical Center; Laurie Ozelius at Mount Sinai School of Medicine; Gary Heiman at Rutgers University; in collaboration...
with Ken Marek at the Institute for Neurodegenerative Disease; and in collaboration with Caroline Tanner at the Parkinson’s Institute.

References


Figure 1. Representative transcranial sonography images for control and PD subjects
Transcranial sonography images of midbrain through the preauricular bone window. The ipsilateral echogenic substantia nigral area is encircled with a yellow line for a control subject (A), a PD subject with a heterozygous GBA mutation without a LRRK2 mutation (B), a PD subject with a LRRK2 mutation without a GBA mutation (C), and a PD subject without a GBA or LRRK2 mutation (D).
Figure 2. aSNmax of PD subjects by GBA/LRRK2 status and controls
Bracket limits represent the 25th and 75th percentiles of the range of aSNmax values for each group. Abbreviations: asnmax = area of maximal substantia nigral echogenicity; PD-GBA single = GBA heterozygotes without LRRK2 mutations; PD-no mutation = subjects without LRRK2 or GBA mutations; PD-LRRK2 = LRRK2 heterozygotes and homozygotes without GBA mutations.
Table 1
TCS of Parkinson’s disease patients by *GBA* and *LRRK2* mutation status and non-PD controls

<table>
<thead>
<tr>
<th></th>
<th>PD-GBA single (n=23)</th>
<th>PD-GBA double (n=4)**</th>
<th>PD-no mutation (n=32)*</th>
<th>PD-LRRK2 single (n=25)*</th>
<th>PD-LRRK2 double (n=2)*</th>
<th>PD-GBA/LRRK2 PD (n=4)*</th>
<th>Controls (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>39.1</td>
<td>25.0</td>
<td>43.8</td>
<td>40.0</td>
<td>50.0</td>
<td>75</td>
<td>62.8</td>
</tr>
<tr>
<td>Age at onset</td>
<td>54 (48, 62)</td>
<td>51 (44.5, 59)</td>
<td>58.5 (52, 64)</td>
<td>60 (48, 70)</td>
<td>53.5 (48, 59)</td>
<td>55.5 (43, 63.5)</td>
<td>-</td>
</tr>
<tr>
<td>Duration of disease, y</td>
<td>9.0 (4.0, 13.9)</td>
<td>7.7 (5.0, 9.2)</td>
<td>6.9 (3.1, 9.0)</td>
<td>8.5 (4.5, 10.5)</td>
<td>10.9 (7.2, 14.7)</td>
<td>8.9 (3.8, 21.9)</td>
<td>-</td>
</tr>
<tr>
<td>UPDRS III score</td>
<td>19 (14, 25)</td>
<td>32 (22, 35)</td>
<td>19 (13, 24)</td>
<td>12 (6, 20)</td>
<td>13 (12, 14)</td>
<td>18 (16, 19)</td>
<td>-</td>
</tr>
<tr>
<td>Age at exam, y</td>
<td>65.0 (59.0, 68.2)</td>
<td>60.2 (50.2, 67.6)</td>
<td>64.8 (60.5, 73.8)</td>
<td>68.2 (60.6, 74.5)</td>
<td>64.4 (62.7, 66.2)</td>
<td>65.3 (64.3, 68.0)</td>
<td>60 (51, 68)</td>
</tr>
<tr>
<td>aSNmax, cm²</td>
<td>0.3 (0.20, .32)</td>
<td>0.27 (0.17, 0.31)</td>
<td>0.27 (0.24, 0.33)</td>
<td>0.28 (0.24,0.33)</td>
<td>0.23 (0.14, 0.32)</td>
<td>0.32 (0.29, 0.49)</td>
<td>0.18 (0.11,0.27)</td>
</tr>
</tbody>
</table>

Data are presented as medians with interquartile ranges.

** PD-LRRK2 single subjects; 6 PD-no mutation subjects; 1 PD-LRRK2 double; and 3 PD-GBA/LRRK2 subjects were previously reported.(19)

* Three PD-GBA double subjects were previously reported.(20)
Table 2

Characteristics of PD-GBA single subjects with brain PET imaging.

<table>
<thead>
<tr>
<th>Subject</th>
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<th>4</th>
<th>5</th>
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<tr>
<td>Age at PET, y</td>
<td>39</td>
<td>59</td>
<td>69</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Duration of PD, y</td>
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<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>UPDRS Part I Mentation Score</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>GBA mutation</td>
<td>N370S</td>
<td>L444P</td>
<td>N370S</td>
<td>N370S</td>
<td>V394L</td>
</tr>
<tr>
<td>TCS (aSNmax)</td>
<td>.22</td>
<td>.33</td>
<td>.23</td>
<td>0.05</td>
<td>0.34</td>
</tr>
<tr>
<td>FDOPA PET putamen</td>
<td>71% below control</td>
<td>56% below control</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FDG PET PDRP z-score</td>
<td>-</td>
<td>-</td>
<td>1.98</td>
<td>2.59</td>
<td>1.61</td>
</tr>
<tr>
<td>FDG PET cortical hypometabolism</td>
<td>-</td>
<td>-</td>
<td>Parietal, temporal</td>
<td>Parietal, anteromedial frontal</td>
<td>Parieto-occipital, temporal</td>
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