Supplementary Methods

PET/CT imaging and analysis methods

^{11}C-CFT and ^{18}F-FDG with ≥95% radiochemical purity were produced using an HM-12 cyclotron (Sumitomo Heavy Industries, Ltd., Kyoto, Japan). Brain PET/CT examinations were performed using a Siemens Discovery 16HR PET/CT (Siemens, Berlin, Germany). All patients fasted for at least 6 hours, and discontinued dopaminergic drugs for at least 12 hours prior to the scan. An ^{11}C-CFT PET scan lasting 10 min was started 60 min[1] following the intravenous injection of 370 MBq[2] of ^{11}C-CFT; and an ^{18}F-FDG PET scan of 10 min was started 60 min[3] after the intravenous injection of 3.7 MBq/Kg[4] of ^{18}F-FDG. All participants were asked to remain in a quiet, dark environment before the scan. We used a head rest to hold the patient's head motionless during the scanning process to prevent head movements from affecting the results. Two PET examinations were completed within one week. A CT scan of the brain was initially conducted using a fixed tube voltage of 120 kV (tube current 100 mA) for attenuation correction and anatomical localization, followed by a PET scan in the 3D mode. The attenuation of PET images was finally corrected using CT data, followed by iterative image reconstruction to obtain cross-sectional, coronal, sagittal CT, PET, and PET/CT images. Using the 3D ordered-subset expectation maximization (OSEM) algorithm (4 iterations, 24 subsets; Gaussian filter: 2 mm; zoom: 3; thickness: 3 mm; FOV: 585 mm*162 mm), PET images were reconstructed using the manufacturer's scatter, and random correction in addition to CT-based attenuation correction was performed. The reconstructed images measured 0.68×0.68×1.5 mm in voxel size and 400×400×148 in matrix size.

^{11}C-CFT PET/CT images were processed using a toolbox for spatial normalization of brain PET images (SNBPI; https://github.com/IHEP-Brain-Imaging/Spatial-Normalization-of-Brain-PET-Images; Chinese Academy of Sciences, Beijing, China)[5] running on MATLAB 2022a (MathWorks Inc., Natick, MA, USA). Using SNBPI based on the DARTEL method, each image was spatially normalized to the Montreal Neurological Institute brain space, resliced to 2-2-2 mm, and smoothed with an isotropic 3D Gaussian kernel (FWHM = 8-8-8 mm) using SPM12 statistical parametric mapping software (Wellcome Department of Imaging Neuroscience, London, UK). The regions of interest (ROIs) in the bilateral caudate and anterior and posterior putamen, as well as the occipital lobe, were extracted from the anatomical automatic labeling (AAL) atlas using SNBPI. In the AAL atlas, the putamen is automatically separated into two equally sized segments. The first half was identified as the anterior putamen, and the second as the posterior putamen. The mean standardized uptake value ratio (SUVR) was automatically generated for each ROI, using the following formula: (striatum-occipital)/occipital count, with the occipital lobe serving as a background reference. The average SUVR was determined using the values from both sides of the caudate and putamen[6].

^{18}F-FDG PET/CT images were quantitatively processed using CortexID Suite software (GE HealthCare, Chicago, IL, USA). This software extracts peak cortical activity from a preset selection of pixels on the brain surface using a 3D stereotactic surface projection method and automatic normalization of the brain anatomy by rotation correction and stereotactic transformation. This activity was compared with that of an age-matched database of healthy

controls using Z-score subtraction, yielding hypometabolic (Z-score) maps in eight standard directions. The ROI was automatically determined in 26 areas, including the bilateral lateral and medial prefrontal and temporal, sensorimotor, precuneus, inferior and superior parietal, anterior and posterior cingulate, lateral occipital, primary visual cortices, whole cerebellum, and pons regions. SUVRs were calculated, with whole-brain mean values serving as a reference[7]. Z-scores, which represent deviations from normal data, were calculated as follows: $Z = (SUVR_{subj} - SUVR_{normal}) / SD_{normal}$, where $SUVR_{subj}$ represents the mean SUVR of the study subject, $SUVR_{normal}$ represents the mean SUVR from the normal database, and SD_{normal} represents the standard deviation (SD) of the SUVR from the normal database[8-11].

The metabolism of the caudate, putamen and thalamus on ^{18}F-FDG PET/CT was analyzed using toolbox SNBPI running on MATLAB 2022a. Each image was spatially normalized to MNI space based on DARTEL algorithm and resliced to 2-2-2mm. Then utilizing SPM12 to smooth using an isotropic 3D Gaussian kernel (FWHM = 8-8-8 mm). The ROIs of the bilateral putamen, caudate and thalamus for each patient were retrieved from the AAL atlas. The whole brain was selected as the reference area to automatically calculate the SUVR. The mean SUVR value was automatically calculated for each ROI. In addition, 43 age-matched healthy individuals from the Physical Examination Center of the First Hospital of Jilin University were selected as the normal control group and their SUVRs for each ROI were calculated. The Z-scores were calculated using the Z-score formula described above.

References

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Supplement Table 1 *GBA* variants identified in GBA-PD group.

Class of variant	Cases	Allele name (HGVS)	Chromosomal position	Nucleotide change	Exon	Variant type	RS (dbSNP)
severe	3	D448H	Chr1:155235727	c.1342G>C	10	Missense	rs1064651
severe	3	G241R	Chr1:155238174	c.721G>A	7	Missense	rs409652
severe	1	R170H	Chr1:155238596	c.509G>A	6	Missense	rs80356763
severe	1	R159W	Chr1:155238630	c.475C>T	6	Missense	rs439898
mild	3	L303I	Chr1:155237433	c.907C>A	8	Missense	rs1296507371
mild	3	L424P	Chr1:155235798	c.1271T>C	10	Missense	rs772548282
mild	1	R87Q	Chr1:155239933	c.260G>A	4	Missense	rs78769774
mild	1	N431S	Chr1:155235777	c.1292A>G	10	Missense	rs77738682
unknown	1	A229T	Chr1:155238210	c.685G>A	7	Missense	-
unknown	1	P240H	Chr1:155238176	c.719C>A	7	Missense	-
unknown	1	E293Nfs*11	Chr1:155237464	c.876del	8	Frameshift	-
unknown	1	R8G	Chr1:155241091	c.22A>G	2	Missense	-
unknown	1	H313R	Chr1:155237402	c.938A>G	8	Missense	-
unknown	2	Q182*	Chr1:155238561	c.544C>T	6	Stop gained	-
unknown	1	Q389H	Chr1:155236302	c.1167G>T	23	Missense	-
unknown	1	P178L	Chr1:155208363	c.533C>T	6	Missense	-

GBA-PD, glucocerebrosidase-related Parkinson disease; PD, Parkinson disease.

Supplement Table 2 p-value from the one-sample t-test for the analysis of ^{18}F-FDG Z-scores for the two groups.

Region of interest	p^1 Value	p^2 Value
Prefrontal Lateral	**<0.001***	**<0.001***
Prefrontal Medial	**0.002***	**<0.001***
Sensorimotor	0.224	**<0.001***
Anterior Cingulate	0.913	0.669
Posterior Cingulate	0.079	**0.002***
Precuneus	**<0.001***	**<0.001***
Parietal Superior	**<0.001***	**<0.001***
Parietal Inferior	**<0.001***	**<0.001***
Occipital Lateral	**<0.001***	0.525
Primary Visual	**0.010***	**<0.001***
Temporal Lateral	0.535	0.206
Temporal Mesial	0.528	0.080
Cerebellum Whole	0.219	0.565
Pons	0.612	0.764
Caudate	0.126	**0.015***
Putamen	**0.024***	**0.028***
Thalamus	**0.014***	**<0.001***

p^1 and p^2 values were calculated by one-sample t-test, which was used to assess the distribution of Z-score for different diseases relative to the normal subject database from CortexID Suite software and the hospital physical examination center (Z-score = 0). p^1, the p value for GBA-PD; p^2, the p value for NGBA-PD; GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; *, $p < 0.05$.

Supplement Table 3 Clinical data after 3-year follow-up of GBA-PD, NGBA-PD, and GBA-PD subgroups.

	GBA-PD[1]	GBA-PD[2]	NGBA-PD	p[1] Value	p[2] Value	Severe	Mild	Unknown
n	24	16	247	-	-	8	8	8
LEDD, mean (SD)	684.19 (429.01)	634.25 (389.84)	447.19 (265.29)	**<0.001[a]***	**0.004***	554.28 (232.63)	714.22 (506.87)	784.06 (511.83)
H-Y stage, mean (SD)	2.33 (0.75)	2.31 (0.68)	1.95 (0.82)	**0.007***	**0.027***	2.25 (0.85)	2.38 (0.52)	2.34 (0.92)
MDS-UPDRS-I, mean (SD)	14.79 (5.79)	14.81 (4.17)	11.76 (6.21)	**0.010***	**0.020***	14.88 (4.73)	14.75 (3.85)	14.75 (8.55)
MDS-UPDRS-II, mean (SD)	17.00 (6.72)	18.69 (6.15)	13.77 (6.69)	**<0.001***	**<0.001***	20.38 (7.44)	17.00 (4.38)	13.63 (6.93)
MDS-UPDRS-III, mean (SD)	44.42 (18.77)	47.19 (16.43)	34.40 (19.09)	**<0.001***	**<0.001***	53.88 (12.16)	40.50 (18.12)	38.88 (22.94)
Motor subtype, No. (%)								
PIGD	16 (52.00)	10 (62.50)	111 (40.94)	0.086	0.097	4 (50.00)	6 (75.00)	6 (75.00)
TD	7 (40.00)	4 (25.00)	106 (44.20)	0.361	0.149	2 (25.00)	2 (25.00)	2 (25.00)
Indeterminate	1 (8.00)	2 (12.50)	30 (14.86)	0.234	0.516	2 (25.00)	0	0
MoCA, mean (SD)	18.54 (4.41)	17.94 (4.73)	20.09 (5.19)	**<0.001***	**<0.001***	15.50 (5.29)	20.38 (2.50)	19.75 (3.69)
HAMD, mean (SD)	12.96 (6.00)	12.75 (5.87)	8.77 (5.52)	**<0.001***	**0.001***	15.63 (5.48)	9.88 (5.00)	13.38 (6.63)
HAMA, mean (SD)	13.00 (5.71)	12.81 (5.04)	9.93 (6.43)	**0.006***	**0.022***	14.63 (4.87)	11.00 (4.81)	13.38 (7.25)
PDSS-2, mean (SD)	16.17 (4.49)	16.81 (4.42)	11.55 (6.96)	**<0.001***	**<0.001***	18.25 (4.80)	15.38 (3.74)	14.88 (4.64)

GBA-PD[1], All patients with GBA-PD; GBA-PD[2], GBA-PD patients without carrying the unknown variant; p[1], GBA-PD[1] vs NGBA-PD; p[2], GBA-PD[2] vs NGBA-PD; [a] Adjusted for age, sex, and disease duration at baseline; The remaining p values are calculated by adjusting for age, sex, disease duration, years of education at baseline and LEDD; GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; H-Y, Hoehn and Yahr; EOPD, early onset PD; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; PIGD, postural instability/gait difficulty; TD, tremor dominant; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; SD, standard deviation. *, $p < 0.05$.

Supplement Table 4 Simple effects analysis of variables with interactive effects in linear mixed effects models in GBA-PD and NGBA-PD patients.

LEDD							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	279.63	52.01	280.76	**<0.001***	177.24, 382.01
	Baseline	Follow-up	-279.63	52.01	280.76	**<0.001***	-382.01, -177.24
NGBA-PD	Follow-up	Baseline	150.79	16.08	288.03	**<0.001***	119.15, 182.44
	Baseline	Follow-up	150.79	16.08	288.03	**<0.001***	-182.44, -119.15
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	107.46	53.15	466.03	0.044*	129.98, 342.60
	NGBA-PD	GBA-PD	-107.46	53.15	466.03	0.044*	-342.60, 129.98
Follow-up	GBA-PD	NGBA-PD	236.29	54.10	478.26	**<0.001***	3.02, 211.90
	NGBA-PD	GBA-PD	-236.29	54.10	478.26	**<0.001***	-211.90, -3.02
MDS-UPDRS-III							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	9.14	2.64	276.26	**<0.001***	3.95, 14.33
	Baseline	Follow-up	-9.14	2.64	276.26	**<0.001***	-14.33, 3.95
NGBA-PD	Follow-up	Baseline	2.92	0.83	280.15	**<0.001***	1.56, 4.79
	Baseline	Follow-up	-2.92	0.83	280.15	**<0.001***	-4.79, -1.56
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	3.84	3.90	375.43	0.325	-3.82, 11.50
	NGBA-PD	GBA-PD	-3.84	3.90	375.43	0.325	-11.50, -3.82
Follow-up	GBA-PD	NGBA-PD	9.80	3.94	386.21	**0.013***	2.06, 17.54
	NGBA-PD	GBA-PD	-9.80	3.94	386.21	**0.013***	-17.54, -2.06
H-Y Stage							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	0.45	0.14	276.04	**0.001***	0.18, 0.73
	Baseline	Follow-up	-0.45	0.14	276.04	**0.001***	-0.73, -0.18
NGBA-PD	Follow-up	Baseline	0.11	0.43	282.01	**0.011***	0.03, 0.20
	Baseline	Follow-up	-0.11	0.43	282.01	**0.011***	-0.20, -0.03
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	0.04	0.16	425.66	0.825	-0.28, 0.35
	NGBA-PD	GBA-PD	-0.04	0.16	425.66	0.825	-0.35, 0.28
Follow-up	GBA-PD	NGBA-PD	0.38	0.16	438.94	**0.023***	0.05, 0.70
	NGBA-PD	GBA-PD	-0.38	0.16	438.94	**0.023***	-0.70, 0.05
MoCA							

Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	-3.17	0.55	270.13	**<0.001***	-4.26, -2.08
	Baseline	Follow-up	3.17	0.55	270.13	**<0.001***	2.08, 4.26
NGBA-PD	Follow-up	Baseline	-1.85	0.17	272.49	**<0.001***	-2.19, -1.51
	Baseline	Follow-up	1.85	0.17	272.49	**<0.001***	1.51, 2.19
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	-0.08	1.07	339.11	0.937	-2.19, 2.02
	NGBA-PD	GBA-PD	0.08	1.07	339.11	0.937	-2.02, 2.19
Follow-up	GBA-PD	NGBA-PD	-1.41	1.08	346.32	0.192	-3.51, 0.71
	NGBA-PD	GBA-PD	1.41	1.08	346.32	0.192	0.71, 3.51
HAMD							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	3.34	0.94	269.15	**<0.001***	1.49, 5.19
	Baseline	Follow-up	-3.34	0.94	269.15	**<0.001***	-5.19, -1.49
NGBA-PD	Follow-up	Baseline	0.68	0.29	273.85	**0.021***	0.11, 1.25
	Baseline	Follow-up	-0.68	0.29	273.85	**0.021***	-1.25, -0.11
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	1.41	1.25	387.86	0.258	-1.04, 3.86
	NGBA-PD	GBA-PD	-1.41	1.25	387.86	0.258	-2.86, 1.04
Follow-up	GBA-PD	NGBA-PD	4.07	1.26	400.30	**0.001***	1.59, 3.86
	NGBA-PD	GBA-PD	-4.07	1.26	400.30	**0.001***	-3.86, -1.59
HAMA							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	2.94	1.05	269.85	**0.005***	0.88, 5.00
	Baseline	Follow-up	-2.94	1.05	269.85	**0.005***	-5.00, -0.88
NGBA-PD	Follow-up	Baseline	0.67	0.32	274.73	**0.035***	0.05, 1.32
	Baseline	Follow-up	-0.67	0.29	274.73	**0.035***	-1.32, -0.05
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	0.65	1.36	392.76	0.632	-2.02, 3.32
	NGBA-PD	GBA-PD	-0.65	1.36	392.76	0.632	-3.32, 2.02
Follow-up	GBA-PD	NGBA-PD	2.91	1.38	405.43	**0.035***	0.20, 5.61
	NGBA-PD	GBA-PD	-2.91	1.38	405.43	**0.035***	-5.61, -0.20

GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; SE, standard error; CI, confidence interval; *, $p < 0.05$.

Supplement Table 5 Comparison of annual progression rates in clinical scales between GBA-PD and NGBA-PD patients.

	GBA-PD	NGBA-PD	p Value	Severe	Mild	Unknow
n	24	247	-	8	8	8
LEDD, mean (SD)	83.60 (115.80)	51.85 (80.38)	0.078	89.03 (150.50)	81.50 (63.97)	80.30 (131.40)
H-Y stage, mean (SD)	0.11 (0.26)	0.03 (0.23)	0.064	0.01 (0.36)	0.15 (0.14)	0.17 (0.22)
MDS-UPDRS-I, mean (SD)	0.82 (0.67)	0.47 (1.45)	0.205	1.05 (0.72)	0.65 (0.78)	0.75 (0.48)
MDS-UPDRS-II, mean (SD)	0.69 (1.61)	0.32 (1.54)	0.160	0.81 (2.61)	0.46 (1.16)	0.80 (0.48)
MDS-UPDRS-III, mean (SD)	3.00 (1.75)	1.05 (4.50)	**0.029***	6.23 (2.11)	1.90 (0.77)	1.46 (1.16)
MoCA, mean (SD)	-0.97 (0.35)	-0.62 (0.93)	0.088	-1.05 (0.31)	-0.85 (0.15)	-0.99 (0.51)
HAMD, mean (SD)	1.01 (0.77)	0.23 (1.59)	**0.008***	1.29 (1.12)	0.97 (0.36)	0.79 (0.65)
HAMA, mean (SD)	0.85 (0.97)	0.23 (1.75)	0.052	0.83 (1.06)	0.88 (0.58)	0.83 (1.27)
PDSS-2, mean (SD)	1.26 (1.27)	0.61 (2.08)	0.112	1.29 (1.72)	0.71 (0.58)	1.78 (1.16)

p values were calculated by generalized linear model, adjusting for age, sex, years of education, and disease duration. GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; SE, standard error; CI, confidence interval; *, $p < 0.05$.

Supplement Table 6 Comparison of baseline data between patients who underwent PET/CT scans and those who did not.

	Underwent PET/CT			Non-underwent PET/CT			p^1 Value	p^2 Value
	All[1]	NGBA-PD[1]	GBA-PD[1]	All[2]	NGBA-PD[2]	GBA-PD[2]		
n	176	159	17	125	117	8	-	-
Age, mean (SD), year	59.86 (10.71)	60.31 (10.69)	55.59 (10.28)	58.79 (9.97)	59.15 (9.81)	53.63 (11.64)	0.354[a]	0.318[a]
Sex, male, No. (%)	75 (42.61)	68 (42.77)	7 (41.18)	57 (45.60)	53 (45.30)	4 (50.00)	0.582[b]	0.650[b]
Disease duration, mean (SD), year	3.62 (3.17)	3.53 (3.20)	4.48 (2.85)	3.92 (3.86)	3.99 (3.96)	2.81 (1.89)	0.412[c]	0.248[c]
Age at onset, mean (SD), year	56.24 (11.02)	56.78 (11.02)	51.12 (9.92)	54.88 (10.32)	55.15 (10.20)	50.81 (11.95)	0.276[d]	0.210[d]
EOPD, No. (%)	57 (32.39)	49 (30.82)	8 (47.06)	45 (36.00)	41 (35.04)	4 (50.00)	0.510[d]	0.461[d]
Years of education, mean (SD), year	10.52 (4.03)	10.42 (4.02)	11.94 (3.96)	9.62 (3.70)	9.49 (3.75)	11.63 (1.92)	**0.030*[e]**	**0.033*[e]**
LEDD, mean (SD), mg	297.69 (237.53)	287.22 (233.97)	395.59 (255.46)	327.26 (216.13)	319.83 (207.67)	435.94 (313.68)	0.289[e]	0.271[e]
H-Y stage, mean (SD),	1.80 (0.75)	1.81 (0.76)	1.88 (0.65)	1.88 (0.75)	1.88 (0.76)	1.81 (0.75)	0.672	0.703
MDS-UPDRS-I, mean (SD)	10.40 (6.30)	10.33 (6.41)	11.00 (5.32)	10.02 (6.16)	9.74 (5.98)	14.12 (7.70)	0.480	0.307
MDS-UPDRS-II, mean (SD)	12.82 (7.91)	12.81 (8.01)	12.94 (7.15)	12.86 (7.43)	12.50 (7.45)	18.13 (4.82)	0.745	0.455
MDS-UPDRS-III, mean (SD)	31.55 (17.96)	31.46 (18.10)	32.35 (17.06)	30.89 (19.71)	30.26 (19.57)	40.13 (20.82)	0.337	0.235
Motor subtype, No. (%)								
PIGD	78 (44.32)	70 (44.03)	8 (47.06)	48 (38.40)	43 (36.75)	5 (62.50)	0.287	0.200
TD	74 (42.05)	67 (42.14)	7 (41.18)	58 (46.40)	55 (47.01)	3 (37.50)	0.533	0.507
Indeterminate	24 (13.64)	22 (13.84)	2 (11.76)	19 (15.20)	19 (16.24)	0	0.542	0.406
MoCA, mean (SD)	22.03 (5.20)	22.03 (5.21)	22.06 (5.27)	21.47 (4.88)	21.50 (4.92)	21.00 (4.57)	0.531	0.563
HAMD, mean (SD)	8.29 (6.05)	8.13 (6.10)	9.82 (5.50)	8.14 (6.56)	8.09 (6.57)	8.88 (6.75)	0.804	0.932
HAMA, mean (SD)	9.24 (6.36)	9.20 (6.43)	9.65 (5.77)	9.44 (6.85)	9.37 6.77)	10.50 (8.42)	0.975	0.986
PDSS-2, mean (SD)	10.10 (6.12)	9.87 (6.24)	12.18 (4.49)	9.23 (5.27)	9.14 (5.31)	10.63 (4.72)	0.183	0.282

GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; EOPD, early onset PD; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; PIGD, postural instability/gait difficulty; TD, tremor dominant; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; SD, standard deviation. [a] Adjusted for sex, and disease duration; [b] Adjusted for age, and disease duration; [c] Adjusted for age, and sex; [d] Adjusted for sex; [e] Adjusted for age, sex, and disease duration. The remaining p values are calculated by adjusting for age, sex, disease duration, LEDD and years of education; The p^1 value is derived from a comparison of all patients who

underwent PET/CT with all patients who did not underwent PET/CT. The p^2 value was derived from a comparison between patients who underwent PET/CT and those who did not in the NGBA-PD study. No formal statistical comparison was performed within the GBA-PD subgroup because of the small number of patients. *, $p < 0.05$.

Supplement Table 7 Attrition analysis: comparison of baseline characteristics between patients included in and excluded from the longitudinal follow-up cohort.

	Followed patients			Non-followed patients			p^1 Value	p^2 Value
	All[1]	NGBA-PD[1]	GBA-PD[1]	All[2]	NGBA-PD[2]	GBA-PD[2]		
n	271	247	24	30	29	1	-	-
Age, mean (SD), year	59.23 (10.47)	59.67 (10.37)	54.67 (10.65)	61.10 (9.82)	61.07 (9.97)	62	0.343[a]	0.478[a]
Sex, male, No. (%)	115 (42.44)	115 (46.56)	10 (41.67)	17 (56.67)	16 (55.17)	1	0.128[b]	0.184[b]
Disease duration, mean (SD), year	3.73 (3.51)	3.71 (3.58)	3.94 (2.72)	3.83 (3.15)	3.83 (3.20)	4	0.861[c]	0.856[c]
Age at onset, mean (SD), year	55.49 (10.85)	55.96 (10.79)	50.73 (10.48)	57.27 (9.75)	57.24 (9.92)	58	0.392[d]	0.534[d]
EOPD, No. (%)	12 (35.06)	83 (33.60)	12 (50.00)	7 (23.33)	7 (24.14)	2	0.201[d]	0.296[d]
Years of education, mean (SD), year	10.30 (3.83)	10.15 (3.83)	11.83 (2.47)	9.53 (3.88)	9.45 (3.92)	12	0.271[e]	0.288[e]
LEDD, mean (SD), mg	301.28 (233.62)	291.64 (227.87)	400.52 (272.16)	388.46 (164.83)	381.16 (162.74)	600	0.054[e]	**0.042[e]***
H-Y stage, mean (SD),	1.85 (0.74)	1.85 (0.75)	1.90 (0.66)	1.72 (0.70)	1.74 (0.70)	1	0.057	0.107
MDS-UPDRS-I, mean (SD)	10.46 (6.42)	10.31 (6.42)	12.08 (6.31)	8.70 (3.64)	8.66 (3.70)	10	0.081	0.111
MDS-UPDRS-II, mean (SD)	12.92 (8.00)	12.77 (8.09)	14.46 (6.96)	12.07 (4.11)	11.86 (4.02)	18	0.162	0.179
MDS-UPDRS-III, mean (SD)	31.61 (19.40)	31.23 (19.49)	35.42 (18.44)	28.27 (9.66)	28.52 (9.73)	21	0.119	0.209
Motor subtype, No. (%)								
PIGD	113 (41.70)	100 (40.49)	13 (54.17)	12 (40.00)	12 (41.38)	0	0.605	0.788
TD	116 (42.80)	107 (43.32)	9 (37.50)	17 (56.67)	16 (55.17)	1	0.127	0.198
Indeterminate	42 (15.50)	40 (16.19)	2 (8.33)	1 (3.33)	1 (3.45)	0	0.148	0.150
MoCA, mean (SD)	21.94 (5.03)	21.96 (5.04)	21.71 (5.09)	20.50 (5.29)	20.45 (5.38)	22	0.672	0.555
HAMD, mean (SD)	8.22 (6.16)	8.08 (6.18)	9.67 (5.88)	8.30 (7.20)	8.38 (7.31)	6	0.816	0.674
HAMA, mean (SD)	9.31 (6.44)	9.23 (6.44)	10.13 (6.62)	9.40 (7.62)	9.55 (7.71)	5	0.890	0.755
PDSS-2, mean (SD)	9.91 (5.94)	9.71 (6.04)	11.96 (4.40)	8.17 (3.86)	8.28 (3.88)	5	0.110	0.236

GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; EOPD, early onset PD; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; PIGD, postural instability/gait difficulty; TD, tremor dominant; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; SD, standard deviation. [a] Adjusted for sex, and disease duration; [b] Adjusted for age, and disease duration; [c] Adjusted for age, and sex; [d] Adjusted for sex; [e] Adjusted for age, sex, and disease duration. The remaining p values are calculated by adjusting for age, sex, disease duration, LEDD and years of education; The p^1 value is derived from a comparison of all patients who participated in the follow-up with all patients who did not participate in the follow-up. The p^2 value

was derived from a comparison between patients who participated in the follow-up and those who did not in the NGBA-PD study. No formal statistical comparison was performed within the GBA-PD subgroup because only one patient was not followed up. *, $p < 0.05$.

Supplement Table 8 Baseline demographic and clinical scale data for patients with GBA-PD （without patients carrying the unknown variant）and NGBA-PD.

	GBA-PD	NGBA-PD	p Value
n	16	276	-
Age, mean (SD), year	55.12 (12.04)	59.82 (10.32)	0.080[a]
Sex, male, No. (%)	7 (43.75)	121 (43.84)	0.950[b]
Disease duration, mean (SD), year	3.59 (2.62)	3.73 (3.54)	0.991[c]
Age at onset, mean (SD), year	51.53 (11.19)	56.09 (10.69)	0.097[d]
EOPD, No. (%)	7 (43.75)	90 (32.61)	0.357[d]
Years of education, mean (SD), year	11.50 (4.00)	10.00 (3.81)	0.167[e]
LEDD, mean (SD), mg	373.91 (277.84)	301.04 (223.39)	0.104[e]
H-Y stage, mean (SD),	2.00 (0.73)	1.82 (0.74)	0.082
MDS-UPDRS-I, mean (SD)	12.31 (4.13)	10.08 (6.23)	0.077
MDS-UPDRS-II, mean (SD)	16.56 (5.40)	12.67 (7.76)	**0.008***
MDS-UPDRS-III, mean (SD)	36.81 (16.53)	31.07 (18.73)	**0.044***
Motor subtype, No. (%)			
PIGD	10 (62.50)	113 (40.94)	**0.049***
TD	4 (25.00)	122 (44.20)	0.096
Indeterminate	2 (12.50)	41 (14.86)	0.701
MoCA, mean (SD)	20.63 (5.04)	21.80 (5.09)	**0.004***
HAMD, mean (SD)	9.44 (5.61)	8.11 (6.29)	0.287
HAMA, mean (SD)	10.25 (4.84)	9.27 (6.57)	0.405
PDSS-2, mean (SD)	14.00 (3.12)	9.56 (5.87)	**0.001***

GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; EOPD, early onset PD; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; PIGD, postural instability/gait difficulty; TD, tremor dominant; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; SD, standard deviation. [a] Adjusted for sex, and disease duration; [b] Adjusted for age, and disease duration; [c] Adjusted for age, and sex; [d] Adjusted for sex; [e] Adjusted for age, sex, and disease duration. The remaining *p* values are calculated by adjusting for age, sex, disease duration, LEDD and Years of education; *, $p < 0.05$.

Supplement Table 9 Comparison of ^{11}C-CFT SUVR, and ^{18}F-FDG Z-score between GBA-PD （without patients carrying the unknown variant） and NGBA-PD.

Region of interest	GBA-PD, mean (SD)	NGBA-PD, mean (SD)	p Value	q Value
n	17	159	-	-
^{11}C-CFT SUVR				
Caudate	1.24 (0.43)	1.50 (0.46)	**0.023***	**0.038***
Anterior Putamen	1.58 (0.40)	1.96 (0.53)	**0.025***	**0.038***
Posterior Putamen	1.39 (0.24)	1.65 (0.43)	0.077	0.077
^{18}F-FDG Z-score				
Prefrontal Lateral	-1.86 (1.95)	-1.38 (1.78)	0.287	0.813
Prefrontal Medial	-0.86 (1.32)	-0.58 (1.65)	0.473	0.823
Sensorimotor	-0.57 (2.18)	-0.86 (2.11)	0.580	0.823
Anterior Cingulate	0.34 (1.62)	-0.05 (1.47)	0.512	0.823
Posterior Cingulate	-0.56 (1.25)	-0.38 (1.50)	0.546	0.823
Precuneus	-2.14 (1.46)	-0.51 (1.48)	**<0.001***	**<0.001***
Parietal Superior	-2.70 (1.32)	-1.37 (1.88)	**0.026***	0.204
Parietal Inferior	-3.80 (1.64)	-2.63 (2.03)	0.066	0.281
Occipital Lateral	-1.80 (1.70)	-0.12 (2.46)	**0.036***	0.204
Primary Visual	0.98 (1.82)	1.24 (1.98)	0.533	0.823
Temporal Lateral	-0.03 (0.82)	-0.14 (1.43)	0.898	0.961
Temporal Mesial	1.00 (2.93)	-0.14 (1.43)	0.426	0.823
Cerebellum Whole	-0.64 (2.25)	0.17 (1.49)	0.126	0.428
Pons	0.17 (2.17)	0.04 (1.68)	0.948	0.988
Caudate	0.66 (1.40)	1.05 (5.39)	0.736	0.953
Putamen	1.95 (1.71)	1.78 (10.15)	0.904	0.961
Thalamus	1.46 (1.48)	0.92 (2.84)	0.785	0.953

p values were calculated by generalized linear model, adjusting for age, levodopa equivalent daily dose (LEDD), sex, and disease duration. The q value is obtained by applying the false discovery rate (FDR) correction to the p-values derived from the analysis of the generalised linear model. SD, standard deviation; GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; SUVR, standardized uptake value ratio; *, $p < 0.05$.

eTable 10 Longitudinal progression of clinical outcomes in GBA-PD (without unknown variants) and NGBA-PD over 3 years: linear mixed-effects model analysis.

	NGBA-PD		GBA-PD		β (time*group)	95% CI	p value
	Baseline	Follow-up	Baseline	Follow-up			
n	276	247	16	16			
LEDD, mean (SE)	299.75 (12.78)	452.06 (16.68)	387.19 (53.29)	647.69 (66.52)	108.19	-17.05, 233.43	0.090
H-Y stage, mean (SE)	1.84 (0.04)	1.91 (0.05)	2.13 (0.17)	2.37 (0.19)	0.17	-0.18, 0.51	0.347
MDS-UPDRS-I, mean (SE)	10.11 (0.36)	11.46 (0.36)	12.87 (1.49)	15.13 (1.46)	0.92	-1.23, 3.07	0.400
MDS-UPDRS-II, mean (SE)	12.76 (0.44)	13.42 (0.36)	17.86 (1.80)	19.40 (1.47)	0.87	-1.47, 3.22	0.463
MDS-UPDRS-III, mean (SE)	30.78 (1.07)	33.91 (1.09)	39.90 (4.39)	50.09 (4.40)	7.05	0.36, 13.74	**0.039***
MoCA, mean (SE)	21.94 (0.25)	20.08 (0.26)	19.02 (1.01)	16.33 (1.07)	-0.84	-2.23, 0.55	0.237
HAMD, mean (SE)	8.09 (0.38)	8.75 (0.34)	9.90 (1.56)	13.19 (1.39)	2.63	0.25, 5.01	**0.030***
HAMA, mean (SE)	9.28 (0.39)	9.88 (0.39)	10.78 (1.61)	13.19 (1.57)	1.82	-0.81, 4.44	0.174
PDSS-2, mean (SE)	9.55 (0.35)	11.44 (0.42)	14.36 (1.43)	17.16 (1.67)	0.90	-2.20, 4.01	0.567
Motor subtype							
PIGD, No. (%)	113 (40.94)	111 (44.94)	10 (62.50)	10 (62.50)	-	-	-
TD, No. (%)	122 (44.20)	106 (42.91)	4 (25.00)	4 (25.00)	-	-	-
Indeterminate, No. (%)	41 (14.86)	30 (12.15)	2 (12.50)	2 (12.50)	-	-	-

The mean (SE) refers to the marginal estimate of the mean and standard error (SE) obtained through linear mixed-effects model analysis. GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; EOPD, early onset PD; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; PIGD, postural instability/gait difficulty; TD, tremor dominant; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; CI, confidence interval; *, $p < 0.05$.

Supplement Table 11 Simple effects analysis of variables with interactive effects in linear mixed effects models in GBA-PD (without unknown variants) and NGBA-PD patients.

MDS-UPDRS-III							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	10.38	3.28	265.96	**0.002***	3.92, 16.83
	Baseline	Follow-up	-10.38	3.28	265.96	**0.002***	-16.83, 3.92
NGBA-PD	Follow-up	Baseline	3.18	0.83	272.18	**<0.001***	1.55, 4.81
	Baseline	Follow-up	-3.18	0.83	272.18	**<0.001***	-4.81, -1.55
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	5.81	4.78	366.87	0.224	-3.58, 15.20
	NGBA-PD	GBA-PD	-5.81	4.78	366.87	0.224	-15.20, -3.58
Follow-up	GBA-PD	NGBA-PD	13.01	4.78	368.32	**0.007***	3.61, 22.41
	NGBA-PD	GBA-PD	-13.01	4.78	368.32	**0.007***	-22.41, -3.61
HAMD							
Group	(I) Time	(J) Time	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
GBA-PD	Follow-up	Baseline	3.31	1.17	258.09	**0.005***	1.02, 5.61
	Baseline	Follow-up	-3.31	1.17	258.09	**0.005***	-5.61, -1.02
NGBA-PD	Follow-up	Baseline	0.68	0.30	265.53	**0.022***	0.10, 1.26
	Baseline	Follow-up	-0.68	0.30	265.53	**0.022***	-1.26, -0.10
Time	(I) Group	(J) Group	Mean value difference (I-J)	SE	Degree of freedom	p value	95% CI
Baseline	GBA-PD	NGBA-PD	1.33	1.53	378.35	0.387	-1.69, 4.34
	NGBA-PD	GBA-PD	-1.33	1.53	378.35	0.387	-4.34, 1.69
Follow-up	GBA-PD	NGBA-PD	3.96	1.54	380.02	**0.010***	0.94, 6.98
	NGBA-PD	GBA-PD	-3.96	1.54	380.02	**0.010***	-6.98, -0.94

GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; SE, standard error; CI, confidence interval; *, $p < 0.05$.

Supplement Table 12 Comparison of annual progression rates in clinical sc alesbetween GBA-PD (without unknown variants) and NGBA-PD patients.

	GBA-PD	NGBA-PD	p Value
n	16	247	-
LEDD, mean (SD)	85.26 (111.78)	51.85 (80.38)	0.126
H-Y stage, mean (SD)	0.08 (0.28)	0.03 (0.23)	0.332
MDS-UPDRS-I, mean (SD)	0.85 (0.75)	0.47 (1.45)	0.255
MDS-UPDRS-II, mean (SD)	0.64 (1.96)	0.32 (1.54)	0.325
MDS-UPDRS-III, mean (SD)	3.46 (1.62)	1.05 (4.50)	**0.028***
MoCA, mean (SD)	-0.95 (0.26)	-0.62 (0.93)	0.156
HAMD, mean (SD)	1.13 (0.82)	0.23 (1.59)	**0.013***
HAMA, mean (SD)	0.86 (0.83)	0.23 (1.75)	0.087
PDSS-2, mean (SD)	1.00 (1.28)	0.61 (2.08)	0.385

p values were calculated by generalized linear model, adjusting for age, sex, years of education, and disease duration. GBA-PD, glucocerebrosidase-related Parkinson disease; NGBA-PD, non-glucocerebrosidase-related Parkinson disease; PD, Parkinson disease; LEDD, levodopa equivalent daily dose; H-Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; SE, standard error; CI, confidence interval; *, $p < 0.05$.