

Supplementary Table 1. Basic demographic characteristics of included subjects

Group	Group 1		Group 2	
	EOPD	Control	LOPD	Control
Number	1777	1652	2257	1279
Sequence Method	WES		WGS (except FPD who use WES)	
Age	49.81±7.18	62.03 ± 12.59	66.62± 7.04	62.32 ± 7.10
Age at Onset	43.81±5.75	-	61.74± 6.87	-
Sex (male/female)	987/789	795/857	1160/1097	613/666

WES, whole-exome sequencing; WGS, whole-genome sequencing.

Supplementary Table 2. Analysis of different *GBA1* variant types in cases and health controls.

Variants groups	Case	Control	OR	95%CI	P
All	301	53	4.38	3.26-5.89	<0.001
Severe	176	8	16.67	8.19-33.91	<0.001
Mild	34	4	6.22	2.21-17.55	<0.001
Risk	3	1	2.18	0.23-20.97	0.643
Unknown	88	40	1.61	1.11-2.35	0.016

Severe, known to cause GD type II or III; Mild, known to cause GD type I; Risk, variants that are associated with risk for PD but do not cause GD; Unknown, reported variants of unknown significance or unreported missense variants; GD, Gaucher disease; OR, odds ratio; CI, confidence interval; Chi-square test and Fisher exact test were used to analyze.

Supplementary Table 3. Analysis of single *GBA1* variant in cases and health controls.

Variant	Case	Control	OR	95%CI	P
p.L483P	95	4	17.65	6.48-48.05	<0.001
p.S310G	20	3	4.86	1.52-28.04	0.005
p.G241R	10	0	15.3	1.25-261.1	0.007
p.R202Q	22	21	0.76	0.417-1.384	0.439

OR, odds ratio; CI, confidence interval. Variants with the number of cases not less than ten were selected to analysis. Chi-square test and Fisher exact test were used to analyze. Haldane-Anscombe correction was used to calculate OR of p.G241R.

Supplementary Table 4. Demographic and clinical features in GBA1-EOPD vs. N-EOPD and GBA1-LOPD vs. N-LOPD

Clinical features	N-EOPD (N=1,592)	GBA1-EOPD (N=185)		L483P-EOPD (N=74)		N-LOPD (N=2,141)	GBA1-LOPD (N=116)		L483P-LOPD (N=21)	
		Values	p	Values	p		Values	p	Values	p
Age (years)	49.86±7.26	49.38±6.40	0.964	49.19±6.58	0.685	66.72±7.06	64.70±6.22	0.002	63.33±6.22	0.027
Age at onset (years)	43.81±5.82	43.82±5.15	0.957	43.51±5.35	0.689	61.84±6.88	59.86±6.34	0.002	58.57±6.30	0.027
Disease duration (years)	6.03±5.15	5.52±5.09	0.321	5.68±5.56	0.871	4.88±3.66	4.80±3.31	0.475	4.79±3.03	0.565
Sex (male)	873 (54.84%)	114 (61.62%)	0.77	48 (64.86%)	0.107	1,106 (51.66%)	54 (46.55%)	0.355	8 (38.10%)	0.261
Family history	195 (12.25%)	27 (14.59%)	0.378	9 (12.16%)	0.913	274 (12.80%)	21 (18.10%)	0.145	4 (19.05%)	0.487
UPDRS-I score	2.27±1.99	2.76±2.30	0.001	2.58±2.26	0.063	2.59±2.08	2.94±2.21	0.026	3.19±2.87	0.113
UPDRS-II score	11.32±6.65	11.68±6.84	0.023	11.69±6.20	0.051	12.31±6.39	12.94±6.41	0.022	13.57±7.05	0.107
UPDRS-III score	26.22±15.63	25.56±14.54	0.809	27.11±14.04	0.19	27.96±14.22	28.23±14.06	0.06	28.48±17.19	0.367
Tremor score	3.89±3.77	2.80±2.99	0.004	2.72±2.84	0.014	3.67±3.53	2.67±3.29	0.044	2.43±3.83	0.321
Rigidity score	5.38±4.15	5.87±4.52	0.225	6.59±4.45	0.036	5.57±4.15	6.03±4.15	0.012	6.14±4.29	0.425
Bradykinesia score	9.76±6.59	9.62±6.11	0.881	9.88±5.89	0.41	10.29±6.17	10.58±5.72	0.051	11.00±6.83	0.228
Postural instability score	3.74±3.10	3.60±2.75	0.347	3.92±2.82	0.023	4.48±2.94	4.79±3.01	0.023	4.57±3.39	0.394
Hoehn and Yahr Scale	1.89±0.77	2.13±0.75	<0.001	2.26±0.74	<0.001	2.04±0.75	2.12±0.77	0.027	1.81±0.70	0.346
Hoehn and Yahr stage			<0.001		<0.001			0.262		0.289
1-1.5	594 (37.32%)	52 (28.11%)		14 (18.92%)		567 (26.48%)	26 (22.42%)		8 (38.10%)	
2-2.5	648 (40.70%)	89 (48.11%)		37 (50.00%)		954 (44.56%)	59 (50.86%)		10 (47.62%)	
3-5	350 (21.98%)	44 (23.78%)		23 (31.08%)		620 (28.96%)	31 (26.72%)		3 (14.28%)	
Motor subtype										
TD	447 (28.06%)	32 (17.22%)		13 (17.57%)		503 (23.49%)	13 (11.21%)		3 (14.29%)	
Indeterminate	288 (18.11%)	30 (16.11%)	0.137	10 (13.51%)	0.512	353 (16.49%)	16 (13.79%)	0.321	5 (23.81%)	0.546
PIGD	857 (53.83%)	123 (66.67%)	<0.001	51 (68.92%)	0.003	1,285 (60.02%)	87 (75.00%)	0.022	13 (61.90%)	0.657

MMSE score	27.44±2.95	27.18±3.11	0.102	27.16±3.08	0.268	25.67±4.26	24.87±4.66	0.012	23.81±6.62	0.022
PDSS score	118.59±28.41	118.71±26.77	0.678	118.88±27.40	0.853	113.72±27.59	112.22±24.97	0.434	108.50±27.17	0.345
ESS score	6.66±5.87	7.47±6.50	0.063	7.96±6.87	0.074	8.45±6.46	7.95±6.23	0.769	6.71±6.16	0.412
EDS	320 (26.62%)	45 (31.03%)	0.144	20 (35.71%)	0.086	789 (38.68%)	42 (37.17%)	0.86	8 (38.10%)	0.724
RBDQ total score	12.87±15.21	18.86±19.73	<0.001	19.07±20.37	0.001	17.98±17.04	22.88±17.78	0.001	23.37±17.34	0.146
pRBD	318 (24.73%)	53 (35.57%)	0.001	18 (32.14%)	0.114	845 (37.04%)	64 (51.35%)	0.001	12 (57.14%)	0.036
HAMD score	5.65±5.57	6.23±6.03	0.123	6.09±6.72	0.419	5.91±5.48	6.56±5.21	0.24	6.25±6.35	0.873
Depression	365 (30.22%)	51 (34.69%)	0.17	17 (30.36%)	0.854	615 (30.49%)	46 (42.20%)	0.012	6 (30.00%)	0.874
HRS score	20.46±6.04	18.79±6.39	0.001	18.57±6.00	0.017	19.02±6.74	17.42±6.44	0.005	18.62±7.03	0.613
Olfactory dysfunction	403 (33.53%)	75 (48.39%)	<0.001	33 (51.56%)	0.02	927 (45.31%)	71 (62.83%)	<0.001	11 (52.38%)	0.396
PDQ39 score	27.98±25.08	29.05±26.30	0.194	26.54±24.08	0.993	30.39±26.01	31.87±24.66	0.237	25.43±23.15	0.532
Constipation	303 (25.85%)	56 (36.60%)	<0.001	21 (34.43%)	0.042	904 (45.70%)	55 (56.12%)	0.009	9 (45.00%)	0.731
Dyskinesia	241 (15.14%)	33 (17.83%)	0.174	16 (21.62%)	0.108	191 (8.92%)	15 (12.93%)	0.272	1 (4.76%)	0.212
Freezing gait	410 (25.75%)	50 (27.02%)	0.434	22 (29.73%)	0.076	492 (22.98%)	36 (31.03%)	0.11	5 (23.81%)	0.927
LEDD (mg)	428.05±305.19	429.92±219.49	0.476	446.87±218.21	0.369	388.97±273.34	453.76±247.17	0.035	520.88±308.31	0.019

Values are expressed as mean ± standard deviation, or number (%).

PD, Parkinson's disease; EOPD, early-onset PD; LOPD, late-onset PD; N-EOPD, EOPD patients without *GBA1* variants; GBA1-EOPD, EOPD patients with *GBA1* variants; L483P-EOPD, EOPD patients with p.L483P variant; N-LOPD, LOPD patients without *GBA1* variants; GBA1-LOPD, LOPD patients with *GBA1* variants; L483P-LOPD, LOPD patients with p.L483P variant. UPDRS, Unified Parkinson's disease Rating Scale; TD, tremor-dominant; PIGD, postural instability and gait difficulty; MMSE, Mini-Mental State Examination; PDSS, Parkinson's Disease Sleep Scale; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; RBDQ, Rapid-eye-movement Sleep Behavior Disorder Questionnaire; pRBD, probable rapid-eye-movement sleep behavior disorder; HAMD, Hamilton Depression Scale; HRS, Hyposmia Rating Scale; PDQ-39, Parkinson Disease Quality of Life Questionnaire-39 item version, LEDD, levodopa equivalent daily dose. The scores of UPDRS items 20 and 21 added up to the tremor score. The score for item 22 was the rigidity score. The scores for items 23 to 26 added up to the bradykinesia score. The scores for items 27 to 30 added up to the postural instability score. Disease motor subtype was classified as tremor-dominant (TD) phenotype when the ratio of tremor score and postural instability and gait difficulty (PIGD) score was no less than 1.5, while patients with a ratio of no more than 1.0 were defined to PIGD phenotype and rest of patients belonged to the indeterminate phenotype.

Supplementary Table 5. Comparison of clinical features between patients with different *GBA1* variant types

Clinical features	Severe-PD (N=176)	Mild-PD (N=34)	P
Age (years)	53.74±9.21	57.77±9.85	0.044
Age at onset (years)	48.41±8.68	51.32±10.02	0.046
Disease duration (years)	5.33±4.68	6.43±4.96	0.12
Sex (male)	92 (52.27%)	18 (52.94%)	0.71
Family history	31 (17.61%)	3 (8.82%)	0.21
UPDRS-I score	2.80±2.38	2.91±2.01	0.91
UPDRS-II score	12.20±6.59	13.38±8.65	0.97
UPDRS-III score	27.55±14.58	28.12±17.62	0.58
Tremor score	2.87±3.29	2.59±3.58	0.59
Rigidity score	6.47±4.51	5.88±4.60	0.23
Bradykinesia score	10.25±6.05	11.24±6.94	0.82
Postural instability score	4.02±2.86	4.74±3.93	0.62
Hoehn and Yahr Scale	2.18±0.76	2.31±0.90	0.95
Hoehn and Yahr stage			0.98
1-1.5	73 (41.48%)	13 (38.24%)	
2-2.5	76 (43.18%)	13 (38.24%)	
3-5	27 (15.34%)	8 (23.52%)	
Motor subtype			
TD	28 (15.91%)	2 (5.88%)	
Indeterminate	29 (16.48%)	6 (17.65%)	
PIGD	119 (67.61%)	26 (76.47%)	
MMSE score	26.04±4.28	26.47±3.35	0.15
PDSS score	114.22±25.08	116.46±26.64	0.34
ESS score	7.54±6.61	7.69±6.76	0.94
EDS	53 (35.33%)	8 (30.77%)	0.45
RBDQ total score	21.66±19.93	18.52±17.93	0.20
pRBD	69 (44.66%)	11 (37.93%)	0.20
HAMD score	6.69±6.06	6.93±5.09	0.99
Depression	60 (40.54%)	13 (46.43%)	0.67
HRS score	18.28±6.39	18.64±6.31	0.65
Olfactory dysfunction	83 (52.53%)	16 (57.14%)	0.78
PDQ39 score	30.72±26.28	33.32±26.67	0.90
Constipation	64 (43.54%)	9 (37.5%)	0.23
Dyskinesia	34 (19.32%)	4 (11.76%)	0.20
Freezing gait	52 (29.55%)	11 (32.35%)	0.93
LEDD (mg)	462.22±239.82	359.17±186.23	0.017

Values are expressed as mean ± standard deviation, or number (%).

PD, Parkinson's disease; Severe-PD, patients with severe variants; Mild-PD, patients with mild variants; UPDRS, Unified Parkinson's disease Rating Scale; TD, tremor-dominant; PIGD, postural instability and gait difficulty;

MMSE, Mini-Mental State Examination; PDSS, Parkinson's Disease Sleep Scale; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; RBDQ, Rapid-eye-movement Sleep Behavior Disorder Questionnaire; pRBD, probable rapid-eye-movement sleep behavior disorder; HAMD, Hamilton Depression Scale; HRS, Hyposmia Rating Scale; PDQ-39, Parkinson Disease Quality of Life Questionnaire-39 item version, LEDD, levodopa equivalent daily dose. The scores of UPDRS items 20 and 21 added up to the tremor score. The score for item 22 was the rigidity score. The scores for items 23 to 26 added up to the bradykinesia score. The scores for items 27 to 30 added up to the postural instability score. Disease motor subtype was classified as tremor-dominant (TD) phenotype when the ratio of tremor score and postural instability and gait difficulty (PIGD) score was no less than 1.5, while patients with a ratio of no more than 1.0 were defined to PIGD phenotype and rest of patients belonged to the indeterminate phenotype.

Supplementary Table 6. Primers used in the present study

Name	Primers for PCR
<i>GBAI</i> Exon2	F: 5'-TGTGGGCCTTGTCCCTAATGA-3' R: 5'-GGTTTCAAAATTCCTCACCCCT-3'
<i>GBAI</i> Exon4	F: 5'-AACCATTACACCCCTCACCC-3' R: 5'-GGCAGGTATATCATTTGAGGTCA-3'
<i>GBAI</i> Exon6	F: 5'-CCAAGCTCAAGGTAGGCATTC-3' R: 5'-AGAACAGCCTGGCGAAAC-3'
<i>GBAI</i> Exon7	F: 5'-GTTTCGCCAGGCTGTTCT-3' R: 5'-CTGGGTTTGCATGAGTGAGC-3'
<i>GBAI</i> Exon8	F: 5'-GGGGTGGTGGTTCATGTATG-3' R: 5'-TGTGCAGACCTGTGAAGGAA-3'
<i>GBAI</i> Exon9	F: 5'-GTCACCCAACCTCCAGGATT-3' R: 5'-GAACACCTTCCTGCTCCCT-3'
<i>GBAI</i> Exon10&Exon11	F: 5'-GACTGGAACCTTGCCCTGA-3' R: 5'-TGCTGTGCCCTCTTTAGTCA-3'
Primers for Nested PCR	
<i>GBAI</i> Exon1-Exon5	F: 5'-CCTAAAGTTGTCACCCATAC-3' R: 5'-AGCAGACCTACCCTACAGTTT-3'
<i>GBAI</i> Exon1	F: 5'-CTGTGTCATGTGACGCTCCT-3' R: 5'-CAGTGCCAGGATTCCAGAAG-3'
<i>GBAI</i> Exon3	F: 5'-ATGTGTCCATTCTCCATGTC-3' R: 5'-GGTGATCACTGACACCATTT-3'
<i>GBAI</i> Exon5	F: 5'-GCAAGTGATAAGCAGAGTCC-3' R: 5'-AGCAGACCTACCCTACAGTTT-3'