Supplemental Material

	overall			male			female		
	WT	*GBA*	p	*WT*	*GBA*	p	*WT*	*GBA*	p
Age at examination	65.9 (±9.9) N=375	63.4 (±9.4) N=96	**0.025**	65.6 (±10.2) N=244	62.4 (±9.7) N=64	**0.025**	66.5 (±9.4) N=131	65.4 (±8.7) N=32	0.518
Age at onset	58.9 (±10.4) N=375	55.1 (±10.2) N=96	**0.002**	58.7 (±10.3) N=244	54.5 (±11.1) N=64	**0.005**	59.1 (±10.7) N=131	56.3 (±7.9) N=32	0.160
Disease duration	7.1 (±4.9) N=375	8.3 (±5.6) N=96	**0.041**	6.9 (±4.6) N=244	7.9 (±5.2) N=64	0.148	7.4 (±5.6) N=131	9.1 (±6.2) N=32	0.146
UPDRS III	25.9 (±11.4) N=350	26.6 (±11.7) N=92	0.744	26.8 (±11.4) N=228	25.9 (±11.5) N=61	0.523	24.3 (±11.2) N=122	28.0 (±12.2) N=31	0.164
MOCA	25.4 (±3.6) N=315	24.8 (±4.8) N=88	**0.039**	25.4 (±3.3) N=203	24.8 (±4.5) N=59	0.056	25.3 (±4.1) N=112	24.6 (±5.4) N=29	0.405
BDI II	8.8 (±7.0) N=274	10.2 (±7.3) N=73	0.201	8.2 (±6.0) N=169	11.6 (±7.9) N=49	**0.008**	9.9 (±8.3) N=105	7.4 (±5.0) N=24	0.211

Supplemental Table 1: Demographic data in patients with Parkinson´s disease (PD) with mutation in the *GBA* gene vs *wildtype* (*WT*) with stratification for sex. Analysis of variance with covariates sex (total cohort), disease duration and age at examination with significant p-values≤0.05 presented in bold letters. UPDRS III: Unified Parkinson`s Disease Rating Scale part III; MOCA: Montreal Cognitive Assessment; BDI II: Beck´s Depression Inventory.

Supplemental Material

	lowest tertile	mid tertile	highest tertile	p
Age at examination	O: 66.2 (±9.9), N= 157 M: 65.7 (±10.1), N= 103 F: 67.1 (±9.5), N= 54	O: 66.3 (±8.9), N=158 M: 66.3 (±8.9), N= 101 F: 66.2 (±9.0), N= 57	O: 63.8 (±10.5), N=156 M: 62.9 (±11.0), N= 104 F: 65.6 (±9.3), N= 52	O: **0.040** M: **0.035*** F: 0.693
Age at onset	O: 59.1 (±10.8), N=157 M: 58.8 (±10.2), N=103 F: 59.8 (±11.9), N=54	O: 58.6 (±9.3), N=158 M: 58.9 (±9.2), N=101 F: 58.1 (±9.4), N=57	O: 56.5 (±11.2), N=156 M: 55.9 (±12.0), N=104 F: 57.8 (±9.3), N=52	O: 0.067 M: 0.071 F: 0.565
Disease duration	O: 7.2 (±5.0), N=157 M: 7.0 (±4.5), N=103 F: 7.4 (±5.9), N=54	O: 7.6 (±4.9), N=158 M: 7.4 (±4.7), N=101 F: 8.0 (±5.4), N=57	O: 7.2 (±5.3), N=156 M: 7.0 (±5.0), N=104 F: 7.8 (±6.0), N=52	O: 0.703 M: 0.804 F: 0.825
UPDRS III	O: 26.0 (±10.5), N=149 M: 25.7 (±10.0), N=98 F: 26.7 (±11.5), N=51	O: 27.1 (±13.3), N=149 M: 28.9 (±13.8), N=95 F: 24.0 (±11.8), N=54	O: 25.0 (±10.3), N=144 M: 25.2 (±9.9), N=96 F: 24.5 (±11.2), N=48	O: 0.285 M: 0.056 F: 0.444
MOCA	O: 24.8 (±3.9), N=128 M: 24.6 (±3.7), N=87 F: 25.0 (±4.5), N=41	O: 25.1 (±4.1), N=140 M: 25.2 (±3.7), N=85 F: 25.0 (±4.7), N=55	O: 25.9 (±3.5), N=135 M: 26.1 (±3.2), N=90 F: 25.4 (±4.0), N=45	O: 0.055 M: **0.022°** F: 0.861
Prevalence of onset of cognitive impairment	O: 36/72 (50.0%) M: 27/47 (57.4%) F: 9/25 (36.0%)	O: 43/89 (48.3%) M: 26/51 (51.0%) F: 17/38 (44.7%)	O: 26/94 (27.7%) M: 16/64 (25.0%) F: 10/30 (33.3%)	O: **0.004** M: ≤**0.001** F: 0.599
BDI II	O: 9.5 (±6.7), N=116 M: 9.5 (±6.8), N=73 F: 9.5 (±6.5), N=43	O: 9.1 (±7.8), N=119 M: 8.9 (±6.4), N=75 F: 9.6 (±9.8), N=44	O: 8.7 (±6.8), N=112 M: 8.4 (±6.7), N=70 F: 9.1 (±7.0), N=42	O: 0.684 M: 0.621 F: 0.952
KL-VS haplotype	O: 23/139 (16.5%) M: 13/91 (14.3%) F: 10/48 (20.8%)	O: 28/139 (20.1%) M: 16/90 (17.8%) F: 12/49 (24.5%)	O: 36/119 (30.3%) M: 25/82 (30.5%) F: 11/37 (29.7%)	O: **0.024** M: **0.023** F: 0.640
beta-amyloid 1-42	O: 700.1 (±280.6), N= 146	O: 728.6 (±276.7), N=153	O: 738.7 (±250.6), N=150	O: 0.443

Supplemental Material

	M: 717.0 (±280.0), N= 98 F: 665.4 (±281.5), N= 48	M: 704.2 (±254.7), N= 96 F: 769.7 (±308.4), N= 57	M: 748.9 (±258.2), N= 100 F: 718.4(±236.1), N= 50	M: 0.476 F: 0.164
h-TAU	O: 245.0 (±135.1), N=146 M: 233.2 (±118.9), N=98 F: 269.0 (±162.1), N=48	O: 250.0 (±117.9), N=153 M: 228.0 (±99.9), N=96 F: 287.1 (±136.4), N=57	O: 255.8 (±139.7), N=150 M: 249.5 (±132.5), N=100 F: 268.3 (±153.7), N=50	O: 0.778 M: 0.412 F: 0.761
p-TAU	O: 41.9 (±17.7), N=142 M: 40.3 (±15.8), N=95 F: 45.0 (±20.8), N=47	O: 42.6 (±16.1), N=149 M: 39.6 (±14.8), N=94 F: 47.9 (±16.9), N=55	O: 42.1 (±17.2), N=149 M: 41.3 (±15.9), N=100 F: 43.8 (±19.7), N=49	O: 0.925 M: 0.736 F: 0.532
NfL	O: 939.1 (±600.2), N=132 M: 974.4 (±606.9), N=88 F: 868.3 (±587.0), N=44	O: 1050.6 (±1106.7), N=151 M: 1026.1 (±724.8), N=96 F: 1093.3 (±1573.2), N=55	O: 918.5 (±544.9), N=147 M: 932.7 (±522.1), N=100 F: 888.3 (±595.3), N=47	O: 0.313 M: 0.576 F: 0.503
alpha-synuclein	O: 589.8 (±315.0), N=149 M: 544.1 (±223.9), N=98 F: 677.6 (±429.4), N=51	O: 637.8 (±293.5), N=154 M: 556.9 (±233.5), N=97 F: 775.6 (±333.4), N=57	O: 614.5 (±287.5), N=141 M: 612.7 (±277.8), N=95 F: 618.3 (±309.8), N=46	O: 0.377 M: 0.123 F: 0.085

Supplemental Table 2A: Demographic data and levels of neurodegenerative proteins (in pg/ml) in patients with Parkinson´s disease (**PD total cohort**) with stratification for lowest, mid and highest tertile of CSF-alpha-Klotho-levels and with stratification for sex. Analysis of variance (ANOVA) with significant p-values≤0.05 presented in bold letters. UPDRS III: Unified Parkinson`s Disease Rating Scale part III; MOCA: Montreal Cognitive Assessment; BDI II: Beck´s Depression Inventory. Post-hoc-Tests with adapted p-values according to Bonferroni: § 1 vs. 2; ° 1 vs. 3; * 2 vs. 3; p ≤0.001: §§§/°°°/***; 0.001<p≤0.01: §§/°°/**; 0.01<p≤0.05: §/°/*. For comparison of the prevalence of onset of cognitive impairment (MoCA≤25) during study and the prevalence of *KL-VS*-variant, chi-squared test was applied.

Supplemental Material

	lowest tertile	mid tertile	highest tertile	p
Age at examination	O: 67.3 (±9.9), N= 125 M: 67.1 (±10.1), N= 83 F: 67.8 (±9.7), N= 42	O: 66.3 (±8.9), N=125 M: 66.3 (±9.0), N= 78 F: 66.2 (±9.0), N= 47	O: 64.2 (±10.6), N=125 M: 63.5 (±11.0), N= 83 F: 65.7 (±9.6), N= 42	O: **0.043°** M: 0.058 F: 0.559
Age at onset	O: 60.4 (±10.9), N=125 M: 60.2 (±10.2), N=83 F: 60.7 (±12.2), N=42	O: 59.0 (±9.4), N=125 M: 59.0 (±9.1), N=78 F: 59.0 (±9.9), N=47	O: 57.3 (±10.8), N=125 M: 57.1 (±11.3), N=83 F: 57.7 (±9.8), N=42	O: 0.064 M: 0.139 F: 0.452
Disease duration	O: 7.0 (±5.0), N=125 M: 7.0 (±4.4), N=83 F: 7.1 (±6.1), N=42	O: 7.3 (±4.7), N=125 M: 7.4 (±4.9), N=78 F: 7.2 (±4.4), N=47	O: 6.9 (±5.2), N=125 M: 6.4 (±4.4), N=83 F: 7.9 (±6.3), N=42	O: 0.824 M: 0.433 F: 0.770
UPDRS III	O: 25.9 (±10.4), N=118 M: 25.9 (±9.8), N=79 F: 26.0 (±11.8), N=39	O: 26.6 (±13.2), N=118 M: 29.1 (±13.9), N=73 F: 22.5 (±11.0), N=45	O: 25.1 (±10.3), N=114 M: 25.4 (±10.1), N=76 F: 24.7 (±10.8), N=38	O: 0.635 M: 0.098 F: 0.349
MOCA	O: 25.2 (±3.4), N=97 M: 25.3 (±2.8), N=67 F: 24.8 (±4.4), N=30	O: 25.3 (±3.8), N=110 M: 25.1 (±3.7), N=65 F: 25.8 (±4.0), N=45	O: 25.6 (±3.6), N=108 M: 25.9 (±3.3), N=71 F: 25.1 (±4.0), N=37	O: 0.654 M: 0.323 F: 0.592
Prevalence of onset of cognitive impairment	O: 25/55 (45.5%) M: 20/38 (52.6%) F: 5/17 (29.4%)	O: 36/74 (48.6%) M: 21/40 (52.5%) F: 15/34 (44.1%)	O: 18/69 (26.1%) M: 11/46 (23.9%) F: 7/23 (30.4%)	O: **0.014** M: **0.008** F: 0.453
BDI II	O: 9.1 (±6.0), N=90 M: 8.2 (±5.7), N=57 F: 10.6 (±6.3), N=33	O: 9.1 (±8.2), N=96 M: 8.4 (±6.4), N=57 F: 10.0 (±10.3), N=39	O: 8.3 (±6.7), N=88 M: 7.9 (±6.1), N=55 F: 8.9 (±7.6), N=33	O: 0.673 M: 0.884 F: 0.717
KL-VS haplotype	O: 20/109 (18.3%) M: 11/73 (15.1%) F: 9/36 (25.0%)	O: 23/106 (21.7%) M: 14/67 (20.9%) F: 9/39 (23.1%)	O: 28/95 (29.5%) M: 18/64 (28.1%) F: 10/31 (32.3%)	O: 0.158 M: 0.174 F: 0.669
beta-amyloid 1-42	O: 709.8 (±291.6), N= 116	O: 720.4 (±256.1), N=120	O: 730.1 (±260.3), N=120	O: 0.847

Supplemental Material

	M: 724.6 (±291.1), N= 79 F: 678.3 (±294.0), N= 37	M: 699.7 (±232.2), N= 73 F: 752.5 (±289.1), N= 47	M: 733.8 (±261.8), N= 80 F: 722.7 (±260.6), N= 40	M: 0.714 F: 0.489
h-TAU	O: 254.0 (±146.6), N=116 M: 240.3 (±128.4), N=79 F: 283.2 (±177.9), N=37	O: 245.6 (±109.3), N=120 M: 218.6 (±74.1), N=73 F: 287.5 (±139.1), N=47	O: 252.7 (±133.2), N=120 M: 238.1 (±110.2), N=80 F: 282.0 (±168.0), N=40	O: 0.866 M: 0.396 F: 0.986
p-TAU	O: 42.7 (±17.7), N=112 M: 41.0 (±14.7), N=76 F: 46.4 (±22.6), N=36	O: 42.6 (±14.8), N=118 M: 38.5 (±11.4), N=72 F: 48.9 (±17.3), N=46	O: 42.6 (±18.5), N=119 M: 41.3 (±16.8), N=80 F: 45.4 (±21.5), N=39	O: 0.998 M: 0.438 F: 0.704
NfL	O: 983.2 (±696.1), N=104 M: 1055.0 (±765.5), N=71 F: 828.5 (±491.7), N=33	O: 1027.6 (±1149.9), N=118 M: 946.4 (±548.6), N=73 F: 1159.2 (±1730.6), N=45	O: 947.4 (±568.0), N=118 M: 951.3 (±538.8), N=81 F: 939.0 (±635.1), N=37	O: 0.768 M: 0.494 F: 0.445
Alpha-synuclein	O: 607.2 (±329.4), N=120 M: 555.4 (±237.3), N=80 F: 710.8 (±447.9), N=40	O: 658.8 (±293.1), N=121 M: 561.3 (±213.6), N=74 F: 812.4 (±335.0), N=47	O: 627.7 (±299.5), N=115 M: 619.4 (±293.5), N=76 F: 644.1 (±314.0), N=39	O: 0.425 M: 0.219 F: 0.106

Supplemental Table 2B: Demographic data and levels of neurodegenerative proteins (in pg/ml) in patients with Parkinson´s disease (**PD *WT***) with stratification for lowest, mid and highest tertile of CSF-alpha-Klotho-levels and with stratification for sex. Analysis of variance (ANOVA) with significant p-values≤0.05 presented in bold letters. UPDRS III: Unified Parkinson`s Disease Rating Scale part III; MOCA: Montreal Cognitive Assessment; BDI II: Beck´s Depression Inventory. Post-hoc-Tests with adapted p-values according to Bonferroni: § 1 vs. 2; ° 1 vs. 3; * 2 vs. 3; p ≤0.001: §§§/°°°/***; 0.001<p≤0.01: §§/°°/**; 0.01<p≤0.05: §/°/*. For comparison of the prevalence of onset of cognitive impairment (MoCA≤25) during study and the prevalence of *KL-VS*-variant, chi-squared test was applied.

Supplemental Material

	lowest terile	mid tertile	highest tertile	P
Age at examination	O: 60.8 (±8.7), N=32 M: 59.9 (±8.7), N= 21 F: 62.3 (±9.0), N= 11	O: 67.7 (±7.9), N=32 M: 66.7 (±8.2), N= 22 F: 70.0 (±7.1), N= 10	O: 61.7 (±10.3), N=32 M: 60.5 (±11.0), N= 21 F: 64.2 (±8.7), N= 11	O: **0.005§§*** M: **0.038** F: 0.109
Age at onset	O: 53.4 (±8.8), N=32 M: 53.0 (±.8.9), N=21 F: 54.1 (±9.1), N=11	O: 58.6 (±8.5), N=32 M: 59.0 (±9.0), N=22 F: 57.7 (±7.7), N=10	O: 53.4 (±12.1), N=32 M: 51.5 (±13.9), N=21 F: 57.2 (±7.1), N=11	O: 0.062 M: 0.063 F: 0.535
Disease duration	O: 7.4 (±4.6), N=32 M: 6.9 (±3.9), N=21 F: 8.2 (±5.7), N=11	O: 9.1 (±6.1), N=32 M: 7.7 (±4.9), N=22 F: 12.3 (±7.6), N=10	O: 8.3 (±5.9), N=32 M: 9.0 (±6.5), N=21 F: 7.0 (±4.5), N=11	O: 0.454 M: 0.446 F: 0.130
UPDRS III	O: 25.3 (±10.1), N=32 M: 23.4 (±9.4), N=21 F: 28.8 (±10.9), N=11	O: 30.3 (±13.9), N=30 M: 29.8 (±14.7), N=20 F: 31.4 (±12.7), N=10	O: 24.3 (±10.4), N=30 M: 24.6 (±9.2), N=20 F: 23.6 (±13.1), N=10	O: 0.098 M: 0.173 F: 0.360
MOCA	O: 24.3 (±4.8), N=31 M: 23.7 (±4.7), N=21 F: 25.6 (±5.0), N=10	O: 23.5 (±5.4), N=29 M: 24.2 (±5.0), N=19 F: 22.2 (±6.3), N=10	O: 26.6 (±3.3), N=28 M: 26.8 (±2.9), N=19 F: 26.1 (±4.1), N=9	O: **0.035*** M: 0.056 F: 0.221
Prevalence of onset of cognitive impairment	O:12/18 (66.7%) M: 9/11 (81.8%) F: 3/7 (42.9%)	O: 6/14 (42.9%) M: 3/9 (33.3%) F: 3/5 (60.0%)	O: 8/25 (32.0%) M: 5/18 (27.8%) F: 3/7 (42.9%)	O: 0.077 M: **0.013** F: 0.805
BDI II	O: 10.4 (±8.2), N=26 M: 12.5 (±8.4), N=17 F: 6.3 (±6.1), N=9	O: 10.0 (±6.7), N=23 M: 11.6 (±7.0), N=17 F: 5.7 (±2.7), N=6	O: 10.2 (±7.2), N=24 M: 10.5 (±8.5), N=15 F: 9.7 (±4.6), N=9	O: 0.987 M: 0.781 F: 0.235
KL-VS haplotype	O: 1/31 (3.2%) M: 1/20 (5.0%) F: 0/11 (0 %)	O: 6/31 (19.4%) M: 3/21 (14.3%) F: 3/10 (30.0%)	O: 9/25 (36.0%) M: 7/18 (38.9%) F: 2/7 (28.6%)	O: **0.007** M: **0.023** F: 0.139
Prevalence of	O:4/32(12.5%)/15/32(46.9%)/13/32(40.6%)	O:8/32(25.0%)/16/32(50.0%)/8/32(25.0%)	O:8/32(25.0%)/17/32(53.1%)/7/32(21.9%)	O: 0.414

Supplemental Material

GBA-variants	M:2/21(9.5%)/9/21(42.9%)/10/21(47.6%) F: 2/11(18.2%)/6/11(54.5%)/3/11(27.3%)	M:6/22(27.3%)/12/22(54.5%)/4/22(18.2%) F:2/10(20.0%)/4/10(40.0%)/4/10(40.0%)	M:4/21(19.0%)/12/21(57.1%)/5/21(23.8%) F: 4/11(36.4%)/5/11(45.5%)/2/11(18.2%)	M: 0.216 F: 0.734
beta-amyloid 1-42	O: 691.2 (±268.0), N= 31 M: 716.3 (±283.1), N= 20 F: 645.5 (±244.1), N= 11	O: 722.6 (±328.1), N=31 M: 691.8 (±286.8), N= 22 F: 797.7 (±423.0), N= 9	O: 782.8 (±210.9), N=31 M: 809.3 (±239.8), N= 20 F: 734.6 (±141.9), N= 11	O: 0.410 M: 0.349 F: 0.487
h-TAU	O: 200.7 (±73.8), N=31 M: 192.0 (±69.9), N=20 F: 216.4 (±81.4), N=11	O: 280.2 (±141.2), N=31 M: 271.4 (±148.3), N=22 F: 301.6 (±127.8), N=9	O: 265.4 (±163.0), N=31 M: 295.2 (±195.6), N=20 F: 211.4 (±45.2), N=11	O: **0.045** M: 0.076 F: 0.057
p-TAU	O: 37.6 (±18.0), N=31 M: 36.2 (±20.4), N=20 F: 40.3 (±13.2), N=11	O: 44.4 (±20.2) N=29 M: 44.8 (±22.1), N=21 F: 43.4 (±15.2), N=8	O: 39.9 (±10.8), N=31 M: 41.4 (±12.2), N=20 F: 37.4 (±7.3), N=11	O: 0.284 M: 0.339 F: 0.564
NfL	O: 956.8 (±647.7), N=29 M: 938.0 (±534.5), N=18 F: 987.5 (±829.0), N=11	O: 985.9 (±711.7), N=31 M: 1062.4 (±815.2), N=22 F: 799.0 (±315.3), N=9	O: 800.1 (±419.5), N=30 M: 853.3 (±448.5), N=19 F: 708.0 (±365.6), N=11	O: 0.444 M: 0.570 F: 0.509
alpha-synuclein	O: 488.6 (±248.6), N=29 M: 462.4 (±158.3), N=19 F: 538.3 (±371.5), N=10	O: 590.3 (±274.6), N=32 M: 572.3 (±285.5), N=22 F: 630.1 (±259.1), N=10	O: 552.7 (±219.2), N=27 M: 585.9 (±207.7), N=19 F: 473.7 (±239.6), N=8	O: 0.284 M: 0.188 F**:** 0.545

Supplemental Table 2C: Demographic data and levels of neurodegenerative proteins (in pg/ml) in patients with Parkinson´s disease (**PD *GBA1***) with stratification for lowest, mid and highest tertile of CSF-alpha-Klotho-levels and with stratification for sex. Analysis of variance (ANOVA) with significant p-values≤0.05 presented in bold letters. UPDRS III: Unified Parkinson`s Disease Rating Scale part III; MOCA: Montreal Cognitive Assessment; BDI II: Beck´s Depression Inventory. Post-hoc-Tests with adapted p-values according to Bonferroni: § 1 vs. 2; ° 1 vs. 3; * 2 vs. 3; p

Supplemental Material

≤0.001: §§§/°°°/***; 0.001<p≤0.01: §§/°°/**; 0.01<p≤0.05: §/°/*. For comparison of the prevalence of onset of cognitive impairment (MoCA≤25) during study and the prevalence of *KL*-*VS*-variant, chi-squared test was applied.