Are GBA–Parkinson Disease patients' good candidates for Deep Brain Stimulation? A Longitudinal Multicentric study on a Large Italian Cohort

By Avenali M. et al

SUPPLEMENTARY DATA

SUPPLEMENTARY METHODS

Participating centers

This is a multicentric Italian study involving nine tertiary level Movement Disorder Centres across Italy, in the frame of the PARKNET network: IRCCS Mondino Foundation, Pavia; AOU Città della Salute e della Scienza, Torino; IRCCS Istituto delle Scienze Neurologiche, Bologna; IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan; IRCCS Humanitas Research Hospital, Milan; USL-IRCCS Reggio Emilia; IRCCS Besta Neurological Institute, Milan; Dipartimento di Scienze Neurologiche, Ospedale Santa Chiara, Trento, Italy; Antonio Perrino's Hospital, Brindisi.

Genetic analysis

All patients had genetic testing for *GBA* and other major PD-related genes performed before recruitment in the present study. However, it is worth noting that most patients underwent genetic testing recently (as part of the PARKNET project), and therefore after they received DBS implant. Analysis of the *GBA* gene (HGNC Approved Gene Symbol: *GBA1*) was performed mostly by an novel NGS-based method, which relies on the selective amplification of the whole *GBA* gene in one long PCR fragment (6kb) followed by Nextera sequencing and a customized bioinformatics pipeline aimed at masking the *GBAP1* pseudogene (1). In a minority of patients, the *GBA* gene was tested by conventional Sanger sequencing upon PCR-based amplification of the gene in three

overlapping fragments (2). Identified variants were all validated by conventional Sanger sequencing.

Variants were classified according to a classification initially developed for patients with Gaucher Disease (GD) and then widely adopted also in the context of PD (3,4), as follows: mild (causing GD type I), severe (causing GD type II or III), risk variant (variants that do not cause GD but have been associated with increased risk for PD), and unknown (variants not reported in GD patients). Carriers of variants unequivocally classified as benign or likely benign were considered as non-GBA-PD.

Pathogenic variants in 15 PD-related genes associated with autosomal dominant (*SNCA, LRRK2, VPS35, GBA1),* X-linked (*RAB39B*), and autosomal recessive PD (*PRKN*, *PINK1*, *PARK7*, *ATP13A2*, *PLA2G6*, *DNAJC6*, *SYNJ1*, *FBXO7*, *VPS13C*, *PTRHD1*) were searched for by means of NGS-based sequencing of a PD gene panel (which varies from center to center, but always includes this minimal set of genes) as well as MLPA analysis (SALSA Kit P51-P52, MRC Holland), as previously reported (5).

Variant Nomenclature

All variants were reported according to the up-to-date variant nomenclature guidelines (HGVS), indicating as amino acid number 1 the first residue (Met) of the signal sequence. Traditionally, amino acid numbering of *GBA* gene refers to the mature protein, excluding the 39-residue signal peptide. Nevertheless, we numbered *GBA* mutated amino acid residues including both the standard HSVG nomenclature and the traditional nomenclature (without parentheses and p. prefix).

Statistics

Statistical analysis was performed using “Stata” version v.13.0 (StataCorp, Texas). For numeric demographic variables (age, age at onset, age at DBS, year of education and disease duration)

differences between groups were analyzed using Student's t-test. For categorical variables (sex, and DBS target) difference between groups was tested with the Chi-square test.

We also performed an exploratory analysis to investigate the clinical characteristics of PD subjects who developed dementia at 5 years comparing the two PD groups. To this aim, we compared demographic and clinical data of 8 GBA-PD subjects with 15 non-GBA-PD subjects who developed a clinically defined dementia after 5 years from DBS surgery. Clinical comparison between groups was performed using Student's t-test (age, age at onset, age at DBS, year of education and disease duration) and Wilcoxon-Mann-Whitney test (clinical data) for numeric variables and Chi-square test for categorical variables. Logistic regression was used to test whether any preoperative features (age, age at onset, age at DBS, disease duration, sex, mutations severity) could predict the risk of cognitive deterioration after DBS.

SUPPLEMENTARY REFERENCES

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SUPPLEMENTARY TABLES

Supplementary Table 1 - Clinical motor and non-motor characteristic at baseline of the GBA-PD and non-GBA-PD groups

	non-GBA-PD *(n=292)*	GBA-PD *(n=73)*	p
H &Y at DBS	2.2±0.6	2.2±0.6	*ns*
LEDD (mg)	1045.6±402.9	1107.4±438.4	*ns*
MDS-UPDRS-III (OFF med)	42.8±15.3	42.2±16.9	*ns*
MDS-UPDRS-III (ON med)	18.9±10.2	17.8±10.3	*ns*
MDRS	138.9±5.0	138.9±4.7	*ns*
Dyskinesias (% yes)	230/291 (79.0%)	64/72 (88.9%)	*0.04*
On-off phenomenon (% yes)	145/290 (50.0%)	43/72 (59.7%)	*ns*
Wearing-off (% yes)	263/291 (90.4%)	69/72 (95.8%)	*ns*
Freezing of gait (% yes)	129/290 (44.5%)	32/71 (45.1%)	*ns*
Orthostatic hypotension (% yes)	17/271 (6.3%)	11/70 (15.7%)	*0.01*
ICD (% yes)	78/290 (26.9%)	16/72 (22.2%)	*ns*
Axial dystonia (% yes)	65/287 (22.7%)	16/71 (22.5%)	*ns*
REM Behaviour Disorders (% yes)	105/267 (39.3%)	29/72 (40.3%)	*ns*
MCI (% yes)	31/291 (10.7%)	5/72 (6.9%)	*ns*

Numeric variables are reported as means (± SD). Categorical variables are reported as absolute number and percentage of "yes". p-value: < 0.05 significance difference (GBA-PD vs non-GBA-PD). Group comparison was performed by Wilcoxon-Mann-Whitney test for numeric variables and chi-square test for categorical variables. ns=non-significant.

Supplementary Table 2 - GBA variants identified in the study

Cases	Allele name	Amino acid change	Nucleotide change	Class of variant	Exon
16	N370S	p.(Asn409Ser)	c.1226A>G	mild	9
1	R48W	p.(Arg87Trp)	c.259C>T	mild	3
5	E326K	p.(Glu365Lys)	c.1093G>A	risk	8
1#	T369M E326K	p.(Thr408Met) p.(Glu365Lys)	c.1223C>T c.1093G>A	risk	8 8
8	T369M	p.(Thr408Met)	c.1223C>T	risk	8

1	T369T	p.(Thr408=)	c.1224G>A	unknown	8
1	K(-27)R	p.(Lys13Arg)	c.38A>G	unknown	2
1	G202R	p.(Gly241Arg)	c.721G>A	severe	6
1	Y313X	p.(Tyr352Ter)	c.1056C>A	severe	8
2	D409H	p.(Asp448His)	c.1342G>C;	severe	9
15	L444P	p.(Leu483Pro)	c.1448 T>C;	severe	10
3	R47X	p.(Arg86Ter)	c.256C>T;	severe	3
1	R120W	p.(Arg159Trp)	c.475C>T	severe	5
1	R163X	p.(Arg202Ter)	c.604C>T	severe	6
1	N188S	p.(Asn227Ser)	c.681T>G	severe	6
1	H255Q	p.(His294Gln)	c.882T>G	severe	7
1	R257X	p.(Arg296Ter)	c.886C>T	severe	7
1	L444P E326K	p.(Leu483Pro) p.(Glu365Lys)	c.1448T>C c.1093G>A	severe	10 8
2	L444P A456P V460V	p.(Leu483Pro) p.(Ala495Pro) p.(Val499=)	c.1448 T>C; c.1483G>C; c.1497G>C;	complex (RecNcil)	10
1	H255Q D409H	p.(His294Gln) p.(Asp448His)	c.882T>G c.1342G>C	complex	7 9
1	M280T	p.(Met319Thr)	c.956T>C	unknown	7
1	S173T	p.(Ser212Thr)	c.634T>A	unknown	6
1	G325R	p.(Gly364Arg)	c.1090G>A	severe	8
1	-	-	c.115+1G>A	severe	intron 2
1	L385P	p.(Leu424Pro)	c.1271T>C	unknown	10
1	E388K	p.(Glu427Lys)	c.1279G>A	risk	9
1	M85V	p.(Met124Val)	c.370A>G	unknown	4
1	T86P	p.(Thr125Pro)	c.373A>C	unknown	4
1	-	-	c.762-4C>T	unknown	intron 6

#Phase not available

Supplementary Table 3 - Demographic and clinical parameters at baseline of the GBA-PD subgroups

	Mild (M) ***(n=17)***	**Risk (R)** ***(N=15)***	**Severe/complex (s)** ***(n=33)***	**p**
Age	58.6±10.7	62.2±8.5	58.8±8.7	*ns*
Age at Onset	43.1±10.5	44.9±7.5	44.4±7.5	*ns*
Age at DBS (years)	53.5±9.5	55.5±8.9	52.6±8.0	*ns*
Disease duration at DBS (years)	10.1±4.4	10.0±4	7.8±3.1	*ns*
Education (years)	11.3±3.6	10.9±3.9	11.9±3.8	*ns*
M/F (% M)	64.7%	66.7%	54.6%	*ns*
DBS target - STN vs GPi (%STN)	82.4%	100.0%	93.9%	*ns*
Family history for PD (% yes)	37.5%	26.7%	38.7%	*ns*
H &Y at DBS	2.26±0.6	2.3±0.7	2.2±0.5	*ns*
LEDD (mg)	1079.9±478.0	1218.5±517.9	1136.6±396.3	*ns*
MDS-UPDRS-III (OFF med)	45.3±21.8	39.5±15.6	41.9±16.4	*ns*
MDS-UPDRS-III (ON med)	23.9±13.5	17.3±9.2	15.9±7.6	*ns*
MDRS	137.5±6.9	139.9±2.5	138.7±4.7	*ns*
Dyskinesias (% yes)	15/17 (88.2%)	15/15 (100%)	27/32 (84.4%)	*ns*
On-off phenomenon (% yes)	9/17 (52.9%)	8/15 (53.3%)	22/32 (68.8%)	*ns*
Wearing-off (% yes)	16/17 (94.1%)	15/15 (100.0%)	31/32 (96.9%)	*ns*
Freezing of gait (% yes)	10/17 (58.8%)	5/14 (35.7%)	12/32 (37.5%)	*ns*
Orthostatic hypotension (% yes)	0/17 (0%)	3/15 (20.0%)	7/30 (23.3%)	*ns*
ICD (% yes)	2/17 (11.8%)	3/15 (20.0%)	9/32 (28.1%)	*ns*
Axial dystonia (% yes)	3/17 (17.7%)	3/15 (20.0%)	6/31 (19.4%)	*ns*
REM Behaviour Disorders (% yes)	5/17 (29.4%)	6/15 (40.0%)	13/32 (40.6%)	*ns*
MCI (% yes)	1/17 (5.9%)	2/15 (13.3%)	2/32 (6.3%)	*ns*

Numeric variables are reported as means (± SD). Categorical variables are reported as absolute number and percentage of "yes". p-value: < 0.05 significance difference. Group comparison performed with Kruskal-Wallis followed by post-hoc analysis with Dunn's Pairwise Comparison test for independent samples and chi-square test for categorical variables. OFF med: OFF meditation; ON med: ON medication; ICD: impulsive-compulsive disorders; MCI: mild cognitive impairment. ns=non-significant.

Supplementary Table 4 - Clinical motor and non-motor parameters at T1 of the non-GBA-PD and GBA-PD groups

	non-GBA-PD ***(n=292)***		**GBA-PD** ***(n=73)***		**p between**
		p T1 vs T0		***pT1 VS T0***	
MDS-UPDRS-III (OFF Med)	28.5±9.7	*0.0001*	33.6±15.2	*0.009*	*0.03*
MDS-UPDRS-III (ON Med)	17.5±9.1	*ns*	18.9±10.1	*ns*	*ns*
LEDD (MG)	697.1±352.6	*0.0001*	685.0±309.6	*0.0001*	*ns*
H &Y	2.15±0.5	*ns*	2.16±0.5	*ns*	*ns*
MDRS	137.7±7.2	*ns*	136.1±6.1	*0.008*	*ns*
Dyskinesias (% yes)	118/281 (42.0%)	*0.001*	36/68 (52.9%)	*0.001*	*ns*
On-off phenomenon (% yes)	29/281 (10.3%)	*0.001*	7/67 (10.5%)	*0.001*	*ns*
Wearing-off (% yes)	138/280 (49.3%)	*0.001*	31/67 (46.3%)	*0.001*	*ns*
Freezing of gait (% yes)	80/277 (28.9%)	*0.001*	22/67 (32.8%)	*ns*	*ns*
Orthostatic hypotension (% yes)	11/256 (4.3%)	*ns*	12/67 (17.9%)	*ns*	*0.001*
ICD (% yes)	24/278 (8.6%)	*0.001*	5/66 (7.6%)	*0.001*	*ns*
Dementia (% yes)	5/278 (1.8%)	-	3/67 (4.5%)	-	*ns*
Depression (% yes)	81/276 (29.4%)	-	16/67 (23.9%)	-	*ns*
Hallucinations (% yes)	10/264 (3.8%)	-	4/67 (6.0%)	-	*ns*
Inability to walk (% yes)	2/277 (0.7%)	-	1/67 (1.5%)	-	*ns*
Recurrent falls (% yes)	28/267 (10.5%)	-	7/67 (10.5%)	-	*ns*
Urinary Incontinence (%yes)	17/260 (6.5%)	-	6/67 (9.0%)	-	*ns*

Numeric variables are reported as means (± SD). Categorical variables are reported as absolute number and percentage of "yes". p-value: < 0.05 significance difference. Between group comparison (GBA-PD vs non-GBA-PD) and within group comparison (T0 vs T1) performed with Wilcoxon-Mann-Whitney test for numeric variables and chi-square test for categorical variables. ns=non-significant.

Supplementary Table 5 - Clinical motor and non-motor parameters at T1 of the GBA-PD subgroups

	Mild (M) ***(n=17)***		**Risk (R)** ***(n=15)***		**Severe/complex (S)** ***(n=33)***		***P*** ***Between***
		p T1 vs T0		***p T1 vs T0***		***p T1 vs T0***	
MDS-UPDRS-III (*OFF MED/ON STIM*)	39.8±23.1	*0.001*	30.4±13.3	*0.03*	32.2±12.8	*0.005*	*ns*
MDS-UPDRS-III (*ON MED/ON STIM*)	23.6±15	*ns*	19.2±9.7	*ns*	15.9±7.4	*ns*	*ns*
LEDD (MG)	695.1±433.1	*0.007*	623.3±218.3	*0.0005*	686.0±288.8	*0.0001*	*ns*
H &Y	2.34±0.6	*ns*	2.1±0.6	*ns*	2.03±0.325	*ns*	*ns*
MDRS	134.1±7.4	*ns*	137.8±4.9	*ns*	136.5±4.7	*ns*	*ns*
Dyskinesias (% yes)	9/16 (56.3%)	*0.03*	6/14 (42.9%)	*0.002*	18/30 (60.0%)	*0.04*	*ns*
On-off phenomenon (% yes)	2/16 (12.5%)	*0.01*	1/14 (7.1%)	*0.001*	4/29 (13.8%)	*0.0001*	*ns*
Wearing-off (% yes)	7/16 (43.8%)	*0.002*	6/14 (42.9%)	*0.0001*	13/29 (44.8%)	*0.001*	*ns*
Freezing of gait (% yes)	6/16 (37.5%)	*ns*	7/14 (50.0%)	*ns*	5/29 (17.2%)	*ns*	*0.03 (R vs S)*
Orthostatic hypotension (% yes)	4/16 (25.0%)	*0.02*	3/14 (21.43%)	*ns*	4/29 (13.8%)	*ns*	*ns*
ICD (% yes)	1/16 (6.3%)	*ns*	0/14 (0%)	*ns*	3/28 (10.7%)	*ns*	*ns*
Dementia (% yes)	2/16 (12.5%)	-	0/14 (0%)	-	1/29 (3.5%)	-	*ns*
Depression (% yes)	3/16 (18.8%)	-	3/14 (21.4%)	-	10/29 (34.5%)	-	*ns*
Hallucinations (% yes)	2/16 (12.5%)	-	1/14 (7.1%)	-	1/29 (3.5%)	-	*ns*
Inability to walk (%yes)	0/16 (0%)	-	0/14 (0%)	-	1/29 (3.5%)	-	*ns*
Recurrent falls (% yes)	2/16 (12.5%)	-	2/14 (14.3%)	-	2/29 (6.9%)	-	*ns*
Urinary Incontinence (% yes)	2/16 (12.5%)	-	2/14 (14.3%)	-	1/29 (3.5%)	-	*ns*

Numeric variables are reported as means (± SD). Categorical variables are reported as absolute number and percentage of "yes". p-value: < 0.05 significance difference. Between group comparison at T1 (mild vs risk vs severe/complex) performed with Kruskal-Wallis followed by post-hoc analysis with Dunn's Pairwise comparison test for independent samples and chi-square test for categorical variables. Within group comparison (T0 vs T1) performed with Wilcoxon-Mann-Whitney test for numeric variables and chi-square test for categorical variables. ICD=impulsive compulsive disorders; ns=non-significant.

Supplementary Table 6 - Clinical motor and non-motor parameters at T3 and T5 of the GBA-PD and non-GBA-PD groups

	non-GBA-PD			***GBA-PD***			
N. AT 3-YEAR (T3)	*180*			*50*			
N. AT 5-YEAR (T5)	*141*			*32*			
		p vs T0	***p vs T1***		***p vs T0***	***p vs T1***	***p between***
MDS-UPDRS-III (*OFF MED / ON STIM*)							
3-year (T3)	35.7±11.6	*0.001*	*0.001*	33.0±10.7	*0.02*	*ns*	*ns*
5-year (T5)	35.7±12	*0.007*	*0.003*	33.6±10.1	*0.04*	*ns*	*ns*
MDS-UPDRS-III (*ON MED / ON STIM*)							
3-year (T3)	21.5±9.9	*0.001*	*0.001*	21.6±9.7	*0.001*	*0.005*	*ns*
5-year (T5)	23.6±10.6	*0.001*	*0.001*	23.5±10.5	*0.001*	*0.001*	*ns*
LEDD (mg)							
3-year (T3)	763.8±381	*0.001*	*0.01*	705.6±328.3	*0.001*	*ns*	*ns*
5-year (T5)	817±391	*0.001*	*0.002*	751±330.1	*0.001*	*ns*	*ns*
H &Y							
3-year (T3)	2.35±0.6	*0.001*	*0.001*	2.39±0.6	*ns*	*0.003*	*ns*
5-year (T5)	2.6±0.6	*0.001*	*0.001*	2.55±0.6	*0.001*	*0.001*	*ns*
MDRS							
3-year (T3)	134.9±8.2	*0.001*	*0.001*	131.2±7.3	*0.001*	*0.001*	*0.02*
5-year (T5)	133.4±8.1	*0.001*	*0.001*	124.7±12.3	*0.001*	*0.001*	*0.002*
Dyskinesias (% yes)							
3-year (T3)	97/179 (54.2%)	*0.001*	*0.01*	30/50 (60.0%)	*0.001*	*ns*	*ns*
5-year (T5)	75/141 (53.2%)	*0.001*	*0.03*	20/32 (62.5%)	*0.001*	*ns*	*ns*
ON-OFF phenomenon (% yes)							
3-year (T3)	28/179 (15.6%)	*0.001*	*ns*	13/50 (26.0%)	*0.001*	*ns*	*ns*
5-year (T5)	30/141 (21.3%)	*0.001*	*0.003*	13/32 (40.6%)	*0.03*	*0.003*	*0.02*
Wearing-off (% yes)							
3-year (T3)	110/179(61.5%)	*0.001*	*0.01*	33/50 (66.0%)	*0.001*	*0.02*	*ns*
5-year (T5)	95/141 (67.4%)	*0.001*	*0.001*	19/32 (59.4%)	*0.001*	*ns*	*ns*
Freezing of gait (% yes)							
3-year (T3)	87/178 (48.9%)	*ns*	*0.001*	21/50 (42.0%)	*ns*	*ns*	*ns*
5-year (T5)	82/136 (60.3%)	*0.004*	*0.001*	20/32 (62.5%)	*ns*	*0.008*	*ns*
Orthostatic hypotension (% yes)							
3-year (T3)	8/173 (4.6%)	*ns*	*ns*	9/50 (18.0%)	*ns*	*ns*	*0.002*
5-year (T5)	8/114 (7.0%)	*ns*	*ns*	8/32 (25.0%)	*ns*	*ns*	*0.004*
ICD (% yes)							
3-year (T3)	16/178 (9.0%)	*0.001*	*ns*	5/50 (10.0%)	*0.001*	*ns*	*ns*
5-year (T5)	15/131 (11.5%)	*0.001*	*ns*	4/32 (12.5%)	*0.001*	*ns*	*ns*
Dementia (% yes)							
3-year (T3)	16/177 (9.0%)	-	*0.001*	8/50 (16.0%)	-	*ns*	*ns*

5-year (T5)	15/140 (10.7%)	-	*0.001*	8/32 (25.0%)	-	*0.01*	*0.03*
Depression (% yes)							
3-year (T3)	65/177 (36.7%)	-	*ns*	15/50 (30.0%)	-	*ns*	*ns*
5-year (T5)	54/130 (41.5%)	-	*0.01*	12/32 (37.5%)	-	*ns*	*ns*
Hallucinations (% yes)							
3-year (T3)	7/178 (3.9%)	-	*ns*	6/49 (12.2%)	-	*ns*	*0.03*
5-year (T5)	9/123 (7.3%)	-	*ns*	5/32 (15.6%)	-	*ns*	*ns*
Inability to walk (% yes)							
3-year (T3)	4/178 (2.3%)	-	*ns*	2/50 (4.0%)	-	*ns*	*ns*
5-year (T5)	5/128 (3.9%)	-	*ns*	1/32 (3.1%)	-	*ns*	*ns*
Recurrent falls (% yes)							
3-year (T3)	41/178 (23.0%)	-	*0.001*	12/50 (24.0%)	-	*ns*	*ns*
5-year (T5)	48/131 (36.6%)	-	*0.001*	7/32 (21.9%)	-	*ns*	*ns*
Urinary Incontinence (% yes)							
3-year (T3)	17/176 (9.7%)	-	*ns*	6/50 (12.0%)	-	*ns*	*ns*
5-year (T5)	15/115 (13.0%)	-	*ns*	7/32 (21.9%)	-	*ns*	*ns*

Numeric variables are reported as means (± SD). Categorical variables are reported as absolute number and percentage of "yes". p-value: < 0.05 significance difference. Generalised linear mixed-effects model with groups as independent variable and age, sex,years of education and disease duration as covariates. ICD=impulsive compulsive disorders; ns=non-significant.

APPENDIX 1 – MEMBERS OF THE PARKNET STUDY GROUP

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