

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

1. Cuconato G, Palmieri I, Monfrini E, Percetti M, Morelli M, Zapparoli E, Di Fonzo A, et al. A newly implemented NGS-based methods to detect GBA variants in patients with Parkinson disease. *Eur J Hum Genet.* 2023;31(Suppl 1):P10.065.D.
2. Stone DL, Tayebi N, Orvisky E, Stubblefield B, Madike V, Sidransky E. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. *Hum Mutat.* 2000 Feb;15(2):181–8.
3. Parlar SC, Grenn FP, Kim JJ, Blauwendraat C, Gan-Or Z. Classification of GBA1 Variants in Parkinson's Disease: The GBA1-PD Browser. *Mov Disord.* 2023 Mar;38(3):489–95.
4. Petrucci S, Ginevrino M, Trezzi I, Monfrini E, Ricciardi L, Albanese A, et al. GBA-Related Parkinson's Disease: Dissection of Genotype–Phenotype Correlates in a Large Italian Cohort. *Mov Disord.* 2020;35(11):2106–11.
5. Di Fonzo AB, Percetti M, Monfrini E, Palmieri I, Albanese A, Avenali M, et al. Harmonizing genetic testing for Parkinson's disease: results of the PARKNET multicentric study. *Mov Disord.* 2023;in press.

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 (\pm 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	p.(Thr408Met)	c.1223C>T	risk	8
	E326K	p.(Glu365Lys)	c.1093G>A		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	p.(Leu483Pro)	c.1448T>C	severe	10
	E326K	p.(Glu365Lys)	c.1093G>A		8
2	L444P	p.(Leu483Pro)	c.1448 T>C;	complex (RecNcil)	10
	A456P	p.(Ala495Pro)	c.1483G>C;		
	V460V	p.(Val499=)	c.1497G>C;		
1	H255Q	p.(His294Gln)	c.882T>G	complex	7
	D409H	p.(Asp448His)	c.1342G>C		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 (\pm 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 medication; 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
		<i>p T1 vs T0</i>		<i>pT1 VS T0</i>	
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 (\pm 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)		<i>P</i> <i>Between</i>
		<i>p</i> T1 vs T0		<i>p</i> T1 vs T0		<i>p</i> 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	<i>ns</i>
MDS-UPDRS-III (ON MED/ON STIM)	23.6±15	<i>ns</i>	19.2±9.7	<i>ns</i>	15.9±7.4	<i>ns</i>	<i>ns</i>
LEDD (MG)	695.1±433.1	0.007	623.3±218.3	0.0005	686.0±288.8	0.0001	<i>ns</i>
H & Y	2.34±0.6	<i>ns</i>	2.1±0.6	<i>ns</i>	2.03±0.325	<i>ns</i>	<i>ns</i>
MDRS	134.1±7.4	<i>ns</i>	137.8±4.9	<i>ns</i>	136.5±4.7	<i>ns</i>	<i>ns</i>
Dyskinesias (% yes)	9/16 (56.3%)	0.03	6/14 (42.9%)	0.002	18/30 (60.0%)	0.04	<i>ns</i>
On-off phenomenon (% yes)	2/16 (12.5%)	0.01	1/14 (7.1%)	0.001	4/29 (13.8%)	0.0001	<i>ns</i>
Wearing-off (% yes)	7/16 (43.8%)	0.002	6/14 (42.9%)	0.0001	13/29 (44.8%)	0.001	<i>ns</i>
Freezing of gait (% yes)	6/16 (37.5%)	<i>ns</i>	7/14 (50.0%)	<i>ns</i>	5/29 (17.2%)	<i>ns</i>	0.03 (R vs S)
Orthostatic hypotension (% yes)	4/16 (25.0%)	0.02	3/14 (21.43%)	<i>ns</i>	4/29 (13.8%)	<i>ns</i>	<i>ns</i>
ICD (% yes)	1/16 (6.3%)	<i>ns</i>	0/14 (0%)	<i>ns</i>	3/28 (10.7%)	<i>ns</i>	<i>ns</i>
Dementia (% yes)	2/16 (12.5%)	-	0/14 (0%)	-	1/29 (3.5%)	-	<i>ns</i>
Depression (% yes)	3/16 (18.8%)	-	3/14 (21.4%)	-	10/29 (34.5%)	-	<i>ns</i>
Hallucinations (% yes)	2/16 (12.5%)	-	1/14 (7.1%)	-	1/29 (3.5%)	-	<i>ns</i>
Inability to walk (% yes)	0/16 (0%)	-	0/14 (0%)	-	1/29 (3.5%)	-	<i>ns</i>
Recurrent falls (% yes)	2/16 (12.5%)	-	2/14 (14.3%)	-	2/29 (6.9%)	-	<i>ns</i>
Urinary Incontinence (% yes)	2/16 (12.5%)	-	2/14 (14.3%)	-	1/29 (3.5%)	-	<i>ns</i>

Numeric variables are reported as means (\pm 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

	<i>non-GBA-PD</i>			<i>GBA-PD</i>			
<i>N. AT 3-YEAR (T3)</i>	<i>180</i>			<i>50</i>			
<i>N. AT 5-YEAR (T5)</i>	<i>141</i>			<i>32</i>			
		<i>p</i> <i>vs T0</i>	<i>p</i> <i>vs T1</i>		<i>p</i> <i>vs T0</i>	<i>p</i> <i>vs T1</i>	<i>p</i> <i>between</i>
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 (\pm 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

Fondazione Santa Lucia IRCCS, Roma, Italy: M. Bozzali, L. Battistini, C. Caltagirone, A. Costa, F.R. Fusco, E. Giardina, M. Iosa, G. Koch, N. Mercuri, A. Peppe, F. Pontieri, G. Sancesario, A. Termine.

Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Milano, Italy: R. Cilia, F. De Giorgi, G. Devigili, R. Eleopra, A. Elia, B. Garavaglia, G. Giaccone, M. Grisoli, F. Moda, B. Reggiori, L.M. Romito, I. Tramacere, S. Piacentini.

Fondazione IRCCS Istituto Neurologico C. Mondino, Pavia, Italy: M. Avenali, R. Bergamaschi, R. Calabrese, S. Cerri, G. Cosentino, G. Cuconato, R. De Icco, S. Figini, C. Galandra, A. Imarisio, P.F. Mitrotti, C. Pacchetti, I. Palmieri, M. Picascia, A. Pichiecchio, A. Pisani, C. Tassorelli, E.M. Valente, F. Valentino, R. Zangaglia.

Fondazione Don Carlo Gnocchi, Milano, Italy: C. Agliardi, F. Baglio, A. Caronni, F. Guerini, R. Mancuso, A. Mannini, M. Meloni, F. Saibene, S. Sorbi, F. Vannetti,

IRCCS Istituto Auxologico Italiano, Milano, Italy: A. Ciammola, L. Maderna, B. Poletti, A. Ratti, V. Silani, N. Ticozzi, F. Triulzi, F. Verde, G. Zebellin.

IRCCS Ospedale San Raffaele, Milano, Italy: F. Agosta, S. Amadio, V. Broccoli, R. Cardamone, M. Filippi, S. Galantucci, L. Gianolli, M. Morelli, E. Sarasso, J. Sassone, M.R. Terreni, M. A. Volontè

Istituti Clinici Scientifici Maugeri, Pavia, Italy: R. Bellazzi, E. Brigonzi, M. Buonocore, R. Campini, F. Cossa, E. Federici, M. Gennuso, E. Losavio, A. Losurdo, G. Maggioni, A. Malovini, C. Morasso, M. Nolano, E. Parati, C. Pistarini, D.M. Rossi, M. Terzaghi, V. Tibollo.

Ospedale Policlinico San Martino, Genova, Italy: L. Avanzino, G. Bonanno, L. Boni, C. Campi, E. Capello, G. Ferrara, G. Lagravinese, P. Mandich, R. Marchese, F. Massa S. Morbelli, F. Nobili, E. Pelosin, L. Roccatagliata.

IRCCS Neuromed - Istituto Neurologico Mediterraneo, Pozzilli (IS), Italy: A. Arcella, G. Battaglia, D. Belvisi, A. Berardelli, D. Centonze, Ferese, S. Gambardella, A. Gialluisi, F. Giangaspero, C. Limatola, N. Modugno, P. Pantano, L. Pavone, S. Puglisi Allegra.

IRCCS - Centro Neurolesi Bonino Pulejo, Messina, Italy: C. Anfuso, L. Bonanno, V. Cimino F. Corallo, G. Di Lorenzo, S. Marino, E. Mazzon

IRCCS San Raffaele, Roma, Italy: S. Bonassi, F. Brancati, M.F. De Pandis, B. Picconi, P.M. Rossini, F. Stocchi, L. Vacca.

IRCCS Humanitas Research Hospital, Rozzano (MI), Italy: A. Albanese, L. Antunovic, R. Gatti, S. Lalli, E. Lauranzano, M. Matteoli, R. Minerì, E. Paraboschi, E. Perdixi, L. Politi, D. Pozzi, G. Savini.

Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy: A.R. Bentivoglio, F. Bove, P. Calabresi, C. Colosimo, G. Di Lazzaro, E. Di Stasio, D. Di Giuda, M. Genuardi, M.R. Lomonaco, C. Piano, M.G. Vita.

Ospedale San Camillo IRCCS, Venezia, Italy: G. Arcara, R. Barresi, V. Camparini, P. Cudia, G. Ferrazzi, K. Koutsikos, N. Manzo, F. Pellizzari.

IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy: A. Arighi, F. Blandini, F. Cogiamanian, M. Castellani, F. Colucci, M. Cribiù, A. Di Fonzo, G. Franco, E. Frattini, C. Losa, F. Mameli, E. Monfrini, E. Scola, I. Trezzi.

IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy: M.G. Bacalini, L. Baldelli, G. Calandra-Buonaura, I. Cani, V. Carelli, M. Contin, P. Cortelli, P. Ghedini, G. Giannini, G. Lopane, R. Minardi, F. Nonino, R. Pantieri, P. Parchi, F. Provini, C. Tonon, L. Sambati.