Surgicogenomics in Parkinson's disease DBS

Genko Oyama, MD, PhD, FAAN

Department of Neurology,
Saitama Medical University, Saitama, Japan

50th ANNIVERSARY
Saitama Medical University

School for Device-Aided Therapies in Parkinson's Disease
Bangkok, Thailand | May 6-7, 2026

International Parkinson and Movement Disorder Society
Asian & Oceanian Section

Relevant Disclosures

Research Support

- JSPS KAKENHI Grant-in-Aid for Scientific Research C 24K10667
- JSPS KAKENHI Grant-in-Aid for Challenging Research (Pioneering) 25K21808
- Grant support from Medi-physics

Honoraria

- Honoraria from Medtronic Japan Co., Ltd., Boston Scientific Japan K.K., Abbott Japan Co., Ltd., Sumitomo Pharma Co., Ltd., Kyowa Kirin Co., Ltd., FP Pharmaceutical Corporation, Takeda Pharmaceutical Company Limited, Eisai Co., Ltd., EA Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Biogen Japan Ltd., Nihon Mediphysics Co., Ltd., Benesse Style Care Co., Ltd., Viatris Inc., Eli Lilly Japan K.K., Novartis Pharma K.K., Argenx Japan K.K., Alexion Pharma GK., UCB Japan Co. Ltd., and Teijin Pharma Ltd.

Consultation

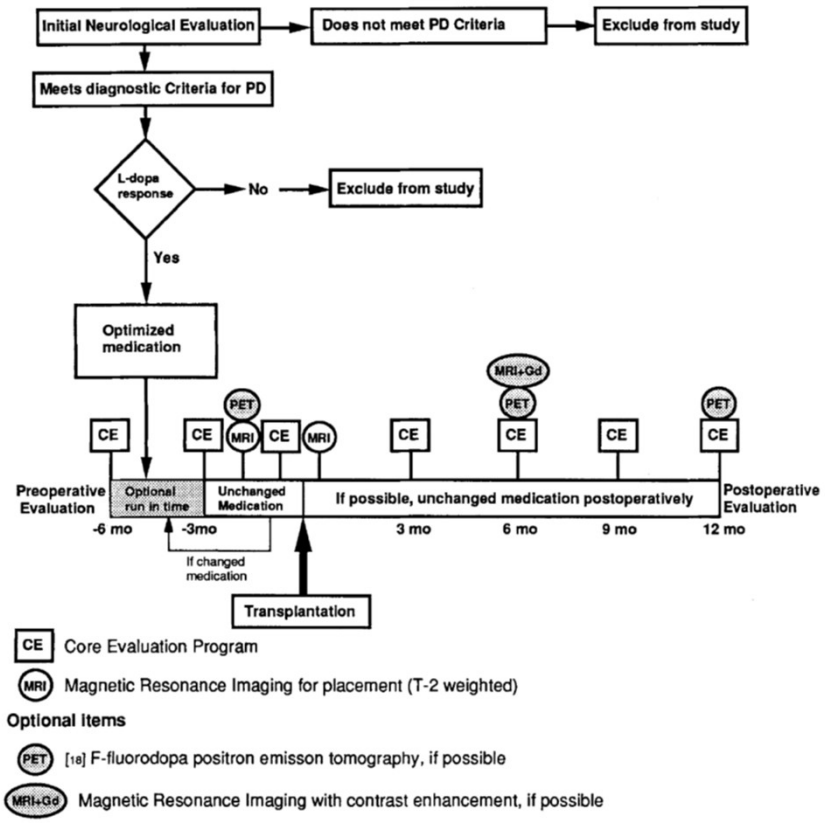
- Teijin Pharma Ltd., NysnoBio, and Lundbeck Japan K.K.

- Others
  None

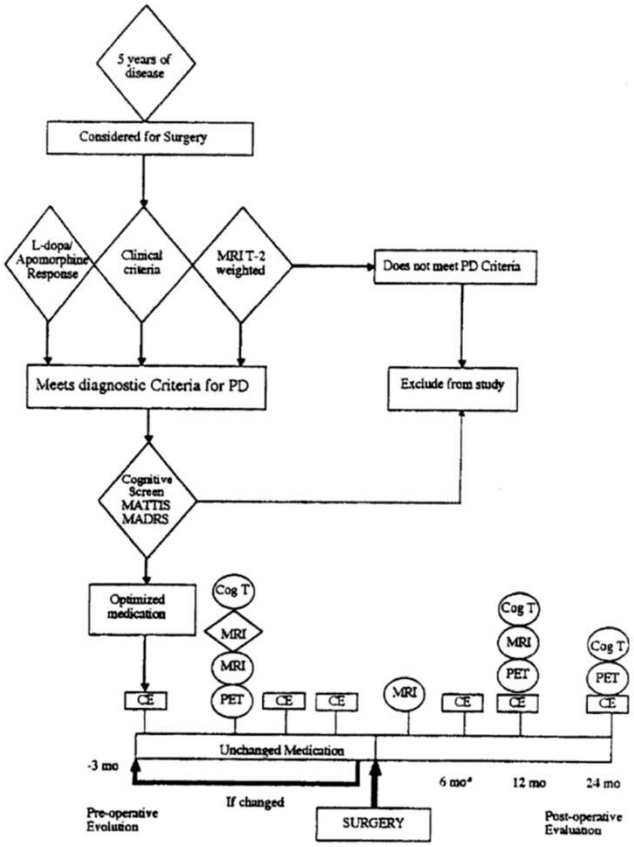
Historical Frameworks for DBS Candidacy Evaluation

- The Core Assessment Program for Intracerebral Transplantations (CAPIT)
- The Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease' (CAPSIT-PD)

<CAPSIT>

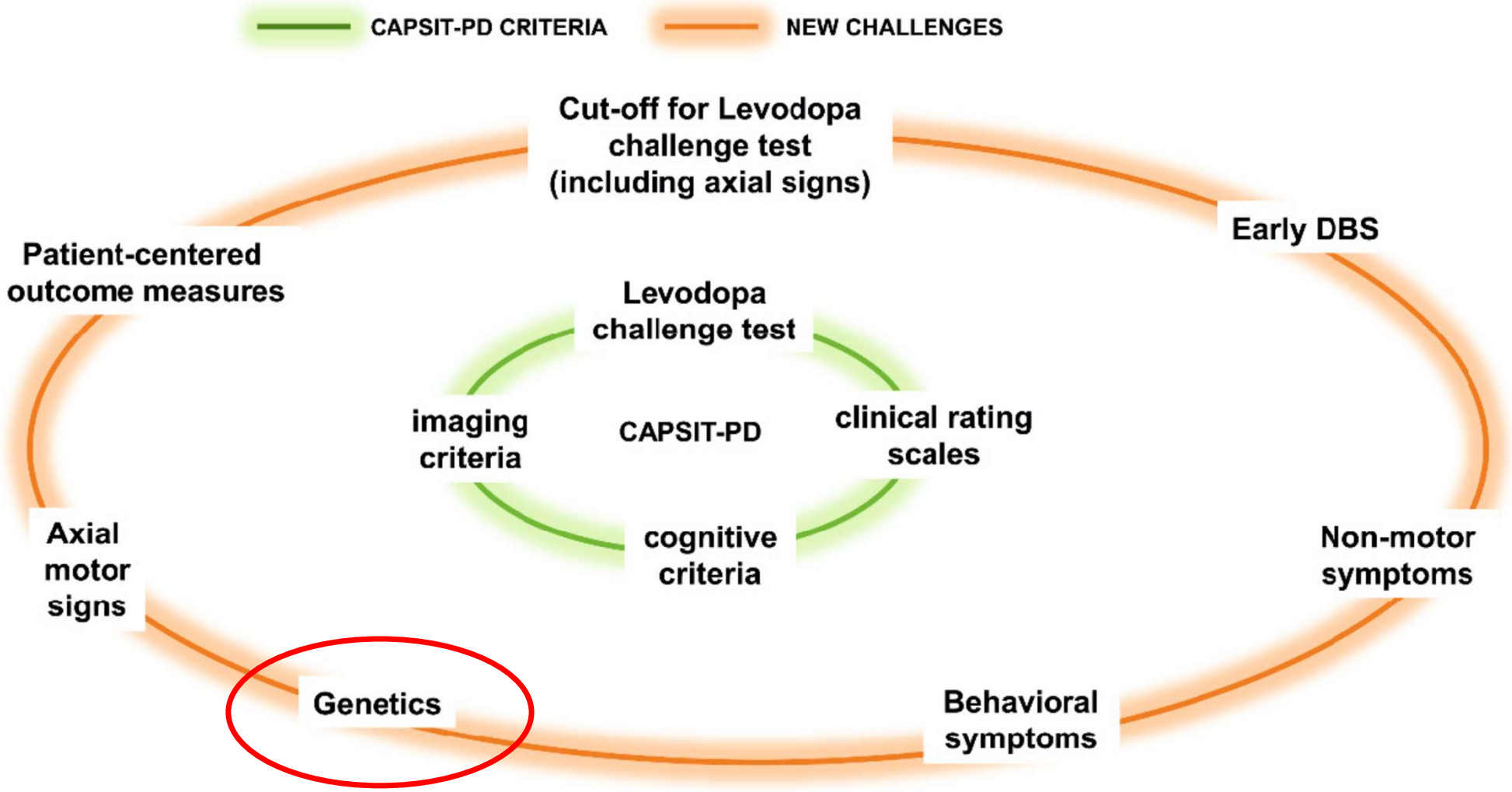


<CAPSIT-PD>



Langston JW, et al. Mov Disord 1992;7:2–13; Defer GL, et al. Mov Disord 1999;14:572–584

Time to revise selection criteria for precision medicine?



Atsui CA, et al. 2020 JCM

What is “Surgicogenomics”?

Genomics × Surgery = Surgicogenomics

Generated by ChatGPT

- Surgicogenomics refers to the use of genetic information to predict, optimize, and personalize surgical outcomes.
- The term “surgicogenomics” have been introduced first in the bariatric surgery literature (Chu et al).
- Later, the concept was adapted to PD and DBS, where genetic background may influence postoperative motor, cognitive, and psychiatric outcome (Visangi et al).

Chu X, et al. JAMA Surgery. 2008; Visanji NP, et al. J Parkinsons Dis. 2022.

Genetic PD

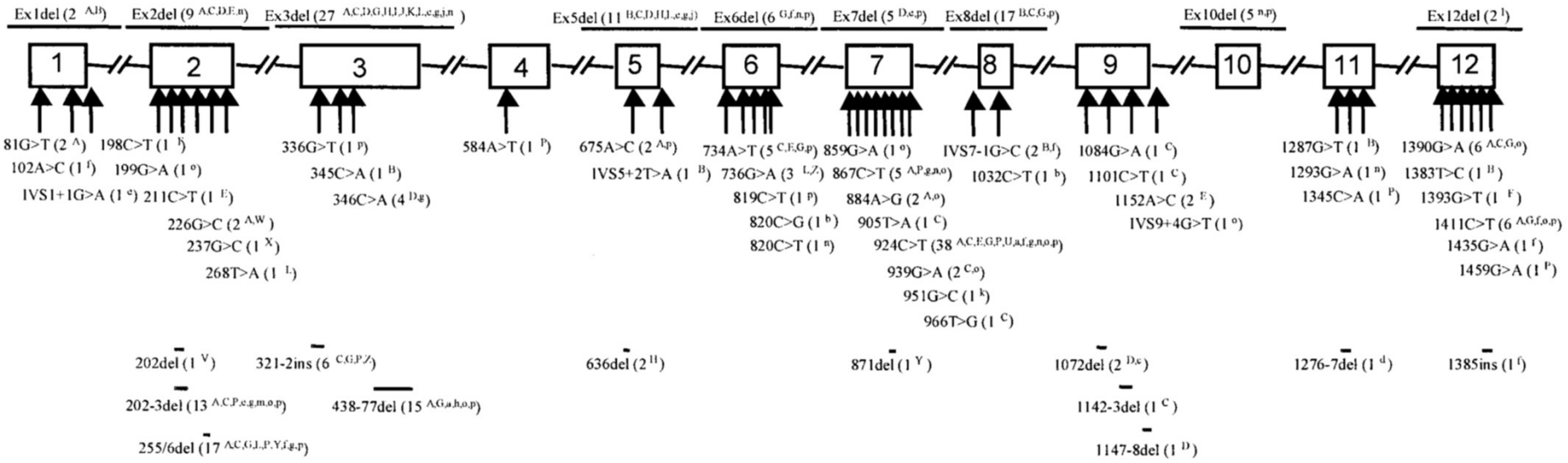
Gene (PARK#)	*Pathway*	*Clinical phenotype*
SNCA (PARK1/4)	α-synuclein aggregation, synaptic vesicle biology	Early-onset AD PD, dementia, LB pathology
PRKN (PARK2)	Mitophagy, ubiquitin ligase	Juvenile/early-onset PD, slow progression
UCHL1 (PARK5)	Ubiquitin–proteasome system	Rare AD PD, controversial
PINK1 (PARK6)	Mitochondrial damage sensing	Early-onset PD, gait and psychiatric features
DJ−1 (PARK7)	Oxidative stress response	Early-onset PD
LRRK2 (PARK8)	Kinase signaling, vesicle trafficking	Late-onset AD PD, variable penetrance
ATP13A2 (PARK9)	Lysosomal cation transport	Juvenile atypical parkinsonism
GIGYF2 (PARK11)	Insulin signalling, translation control	AD PD (controversial)
HTRA2 (PARK13)	Mitochondrial protease	PD risk modifier
PLA2G6 (PARK14)	Lipid metabolism, membrane remodeling	Early-onset PD with dystonia
FBXO7 (PARK15)	Proteostasis, mitophagy	Early-onset parkinsonism with pyramidal signs
VPS35 (PARK17)	Retromer trafficking	AD PD, classical motor phenotype
EIF4G1 (PARK18)	Translation initiation	AD PD (debated)
DNAJC6 (PARK19)	Clathrin-mediated endocytosis	Early-onset atypical PD
SYNJ1 (PARK20)	Phosphoinositide metabolism	Early-onset parkinsonism with seizures
DNAJC13 (PARK21)	Endosomal trafficking	AD PD (limited evidence)
CHCHD2 (PARK22)	Mitochondrial respiration	AD PD, late onset
VPS13C (PARK23)	Lysosome–mitochondria contact sites	Early-onset PD
PSAP (PARK24)	Saposin-mediated lysosomal function	PD risk/rare familial cases
PTPA (PARK25)	Phosphatase regulation	Rare familial PD
RAB32 (PARK26)	Vesicle trafficking, mitochondria	AD PD (emerging)
RAB39B (X-linked)	Synaptic vesicle trafficking	Early-onset PD with ID
TMEM230	Vesicle trafficking	AD PD (controversial)
LRP10	Endolysosomal transport	AD PD candidate
GBA1	Lysosomal glucocerebrosidase	PD with cognitive decline
POLG	mtDNA maintenance	Atypical parkinsonism

Chu X, et al. JAMA Surgery. 2008; Visanji NP, et al. J Parkinsons Dis. 2022.

Genetic forms of Parkinson’s disease with reported DBS outcomes

PARK-PRKN (PARK2)

- PRKN is a gene on chromosome 6q25.2–q27/6q26 that encodes a 465-amino acid, ~51.6-kDa E3 ubiquitin ligase involved in mitochondrial quality control and mitophagy.
- Biallelic PRKN variants cause an autosomal recessive EOPD, typically with young onset, slow progression, good levodopa responsiveness, and frequent lower-limb dystonia/dyskinesia.



Hedrich K, et al. Movement Disorders. 2004; Kalinderi K, et al. Brain Sci. 2024

PARK-PRKN (PARK2)

- Patients with PRKN-associated PD generally show a favorable motor response to DBS, often with sustained benefit and reduction of motor fluctuations and medication burden.

Author + Year	Study design	N	Type of DBS	Follow-up	Main result
Romito et al., 2005	Case–control study	36	STN-DBS	21.6 ± 13.1 months	**Similar** clinical outcomes
Lohmann et al., 2008	Case–control study	54	STN-DBS	1–2 yrs	Levodopa doses were significantly lower in patients with 2 parkin mutations
Moro et al., 2008	Prospective observational study	80	STN-DBS	Short-term: 3–12 m Long-term: 3–6 yrs	In the long-term follow-up, **Similar** clinical outcomes
Johansen et al., 2011	Cross-sectional study	37	STN-DBS	5 yrs	**Similar** clinical outcomes postoperatively
Angeli et al., 2013	Case series	94	STN-DBS / GPi-DBS	1–5 yrs	**Similar** clinical outcomes postoperatively
Kim et al., 2014	Case–control study	9	STN-DBS	2–5 yrs	**Similar** clinical outcomes postoperatively

Case reprts: 4 cases

Modified from Kalinderi K, et al. Brain Sci. 2024

PARK-PINK1 (PARK6)

- PINK1 is located on chromosome 1p35–p36 and accounts for 2–4% of EOPD overall, with higher frequencies reported in Asian populations (4–9%).
- Phenotype is generally similar to PARK-PRKN, with good levodopa response and slow progression.
- STN-DBS may help, particularly for motor fluctuations, but outcomes are based on only a few case reports and may be complicated by gait problems, dyskinesia, and dystonia.

Author + Year	Study design	N	Type of DBS	Follow-up	Main result
Moro et al., 2008	Prospective observational study	80	STN-DBS	Short-term: 3–12 m Long-term: 3–6 yrs	**Similar** clinical outcomes
Borellini et al., 2017	Case report	1	GPi-DBS	Short-term: 1 + 2 m Long-term: >4 yrs	After a **transient benefit**, the patient was not responsive in the long term to medical therapy or stimulation, became unable to walk, and showed deterioration of dystonia
Balestrino et al., 2021	Case report	1	STN-DBS	3 yrs	Dyskinesias, freezing of gait, and a sub-continuous tremor emerged; however, motor fluctuations were well controlled and quality of life was better postoperatively

Modified from Kalinderi K, et al. Brain Sci. 2024

PARK-LRRK2 (PARK8)

- LRRK2 is a gene on chromosome 12q12, with G2019S being the most common pathogenic variant linked to both familial and sporadic PD.
- STN-DBS is generally effective in LRRK2-PD, especially in G2019S carriers, although DBS response may vary by mutation, with R1441G reported to have less favorable outcomes.

Author + Year	Study design	N	Type of DBS	Follow-up	Main result
Schüpbach et al., 2007	Case–control study	69	STN-DBS	9–10 yrs	**G2019S patients: sustained beneficial effect** **T2031S patient: unfavorable outcomes**
Gómez-Esteban et al., 2008	Case series	45	STN-DBS	6 months	**R1441G carriers: worse response**
Johansen et al., 2011	Cross-sectional study	37	STN-DBS	5 yrs	**G2019S**: no significant postoperative difference
Angeli et al., 2013	Case series	94	STN-DBS	1–5 yrs	**G2019S**: no significant postoperative difference
Greenbaum et al., 2013	Case–control study	39	STN-DBS	6–12 months + 3 yrs	**G2019S**: no significant postoperative difference
Sayad et al., 2016	Case–control study	27	STN-DBS	2 yrs	**G2019S**: better surgical response
Weiss et al., 2016	Genetic association study of common SNPs versus DBS response	85	STN-DBS	2 yrs	rs1491923 LRRK2: did not predict motor symptom progression after STN-DBS
de Oliveira et al., 2019	Systematic review	19	STN-DBS	2–6 yrs	**R1441G carriers: worse DBS response**
Artusi et al., 2019	Systematic review and meta-analysis	33	STN-DBS	Mean follow-up 12 m	LRRK2 mutation carriers: sustained improvement in UPDRS-IV
Chen et al., 2019	Retrospective case–control study	57	STN-DBS	1 yr	**G2385R** mutation carriers: no significant difference in motor outcomes except for rigidity
Leaver et al., 2021	Retrospective cohort, case–control study	87	STN-DBS / GPi-DBS	2 yrs	**G2019S**: slightly slower rate of motor progression
Prendes Fernández et al., 2023	Case–control study	97	STN-DBS	1 yr	**G2019S**: no significant postoperative difference
Anis et al., 2024	Retrospective case–control study	103	STN-DBS / STN + GPi-DBS	Mean postoperative follow-up 7.0 ± 4.1 yrs	LRRK2: no significant differences in motor outcomes postoperatively

Modified from Kalinderi K, et al. Brain Sci. 2024

PARK-VPS35 (PARK17)

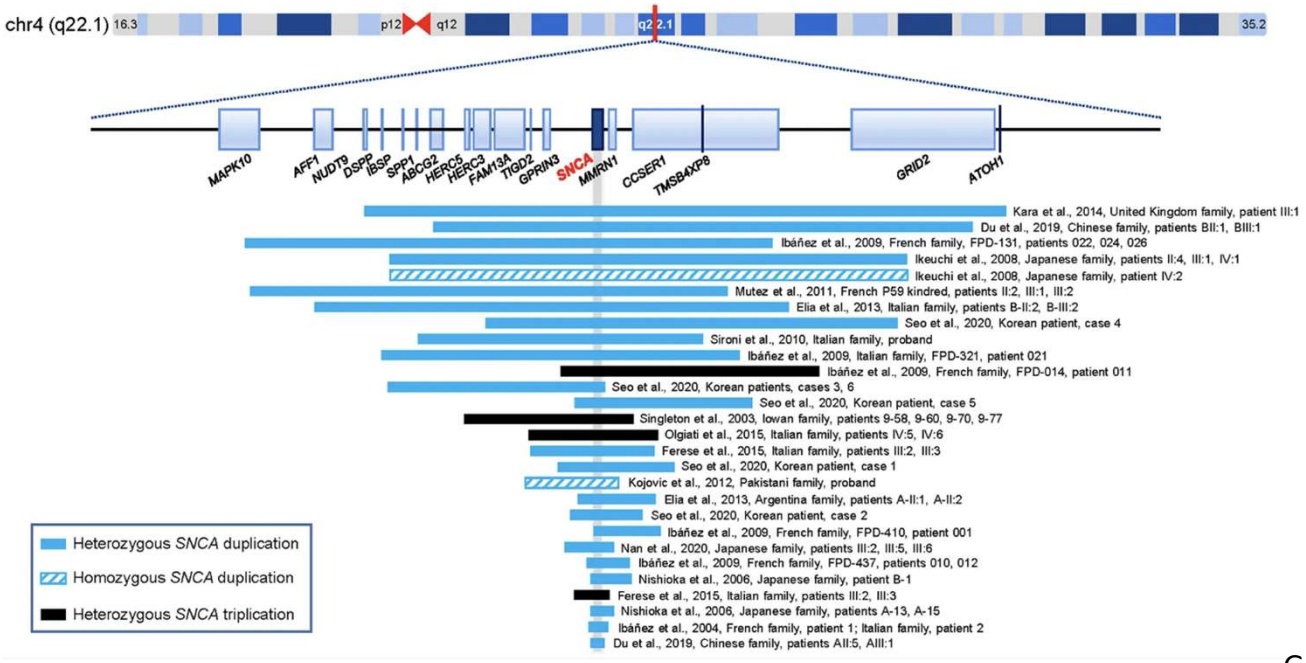
- VPS35 is located on chromosome 16 and is a cause of late-onset autosomal dominant PD.
- The D620N variant is the most common mutation.
- Clinical features are generally similar to idiopathic PD, including asymmetric onset, slow disease progression, and good levodopa responsiveness.
- Limited reports suggest that STN-DBS can provide good long-term benefit, with favorable outcomes reported for up to 8 years.

Author + Year	Study design	N	Type of DBS	Follow-up	Main result
Liu et al., 2019	Descriptive case series	2	STN-DBS	1 and 8 yrs	D620N mutation carriers showed good postoperative response
Wu et al., 2024	Descriptive case report	1	STN-DBS	5 yrs	Marked improvement in motor symptoms

Kalinderi K, et al. Brain Sci. 2024

PARK-SNCA (PARK1/4)

- SNCA is located on chromosome 4q21.3–q22 and encodes alpha-synuclein, a 140-amino-acid presynaptic protein.
- It was the first gene linked to genetic PD; missense mutations and gene multiplications cause autosomal dominant PD.
- SNCA duplication/triplication is often associated with early-onset, rapidly progressive PD and a higher risk of cognitive and psychiatric impairment.



Guo Y, et al. Frontiers in Aging Neuroscience. 2021

PARK-SNCA (PARK1/4)

Received: 29 April 2021 | Revised: 23 November 2021 | Accepted: 2 January 2022

DOI: 10.1002/brb3.2503

Brain and Behavior Open Access WILEY

ORIGINAL ARTICLE

Subthalamic deep brain stimulation in Parkinson's disease with *SNCA* mutations: Based on the follow-up to 10 years

Jinyoung Youn[1,2] | Genko Oyama[3] | Nobutaka Hattori[3] | Yasushi Shimo[3] | Tomi Kuusimäki[4,5] | Valtteri Kaasinen[4,5] | Angelo Antonini[6] | Dongyeop Kim[1,2] | Jung-Il Lee[7] | Kyung Rae Cho[8] | Jin Whan Cho[1,2]

Youn J, Oyama G, et al. Brain and Behavior. 2022

PARK-SNCA (PARK1/4)

- Multicenter retrospective study
- 4 SNCA-PD patients received bilateral STN-DBS
- Genotypes: 3 duplications, 1 missense mutation (p.A53E)
- Age at DBS: 44.3 ± 2.8 years
- Disease Duration: 5.5 ± 0.6 years
- Mean follow-up: 5.4 ± 3.7 years

SNCA duplication (n=3) (6.5 and 10 yrs)*	Missense mutation (n=1) (3.5 yrs)
● Good improvement in motor function ● Non-motor symptoms also stable *one patient died of breast cancer after 1.5 years	● Motor fluctuations improved ● worsening of axial symptoms ● decline in cognition (MMSE 28→18) ● Worsening of depression (BDI 11→30) ● Wheelchair-bound

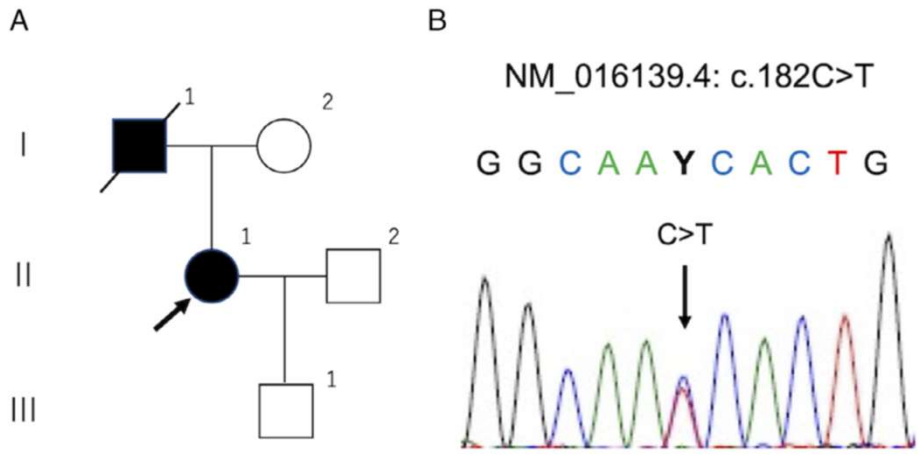
Youn J, Oyama G, et al. Brain and Behavior. 2022

PARK-CHCHD2 (PARK22)

Movement Disorders
CLINICAL PRACTICE
LETTERS: NEW OBSERVATIONS
Check for updates

Deep Brain Stimulation for a Patient with Familial Parkinson's Disease Harboring *CHCHD2* p.T61I

Hikaru Kamo, MD,[1] Genko Oyama, MD, PhD,[1,2,3,4,5,6,*] Kenya Nishioka, MD, PhD,[1] Manabu Funayama, PhD,[1,7] and Nobutaka Hattori, MD, PhD[1,2,3,4,5,6,7]



- Familial PD, symptom onset at 57, good levodopa responsiveness.
- Bilateral STN-DBS at 67 for wearing-off and dyskinesia.
- Excellent motor benefit without major complications.
- Benefit maintained for ~6 years; LEDD still reduced at 10 years
- Mild long-term cognitive decline observed
- Suggests DBS is effective for motor control in CHCHD2-PD, but cognitive outcome needs caution

Kamo H, Oyama G, et al.MDCP. 2022

GBA1

- GBA1 is located on chromosome 1q21 and encodes the lysosomal enzyme glucocerebrosidase, and biallelic GBA1 mutations cause Gaucher disease.
- GBA1 variants are among the most frequent genetic risk factors for PD, increasing risk by about 5–30 fold.
- In PD, GBA1 mutation carriers tend to show earlier onset, faster progression, and greater cognitive/neuropsychiatric burden.
- Given the intrinsic cognitive risk associated with GBA1 mutations, there has been concern that DBS could further worsen cognition in these patients.

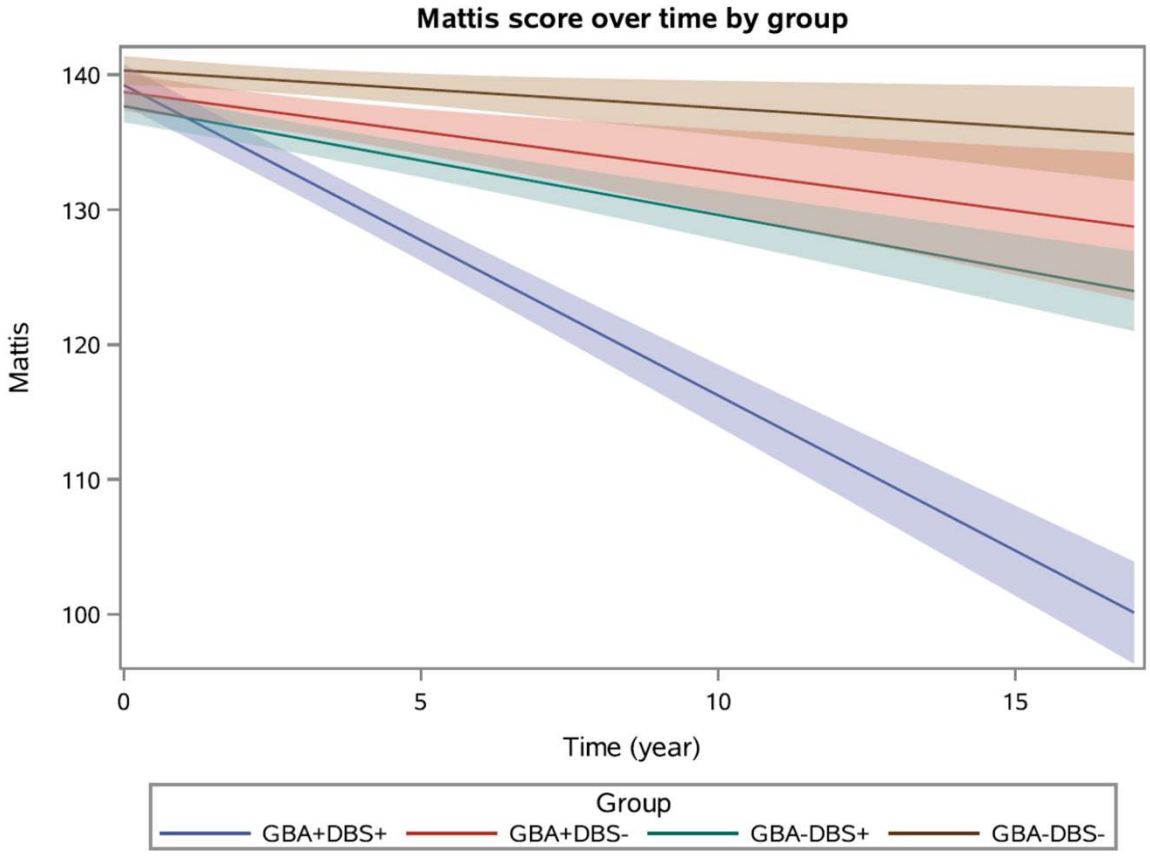
Ra˘cki V, et al. Genes. 2026

GBA1

Author + Year	Study design	N	Type of DBS	Follow-up	Main result
Weiss et al., 2012	Case series	9	STN-DBS	6–10 yrs	GBA carriers showed **increased axial motor impairment, decline in therapeutic efficacy**, and **cognitive decline**
Angeli et al., 2013	Case series	94	STN-DBS / GPi-DBS / Vim-DBS	1–5 yrs	GBA carriers showed steeper **cognitive decline**
Lythe et al., 2017	Case–control	34	STN-DBS / GPi-DBS	7.5 yrs	GBA carriers had more **severe cognitive impairme**nt, more severe non-motor symptoms, and lower quality of life
Mangone et al., 2020	Retrospective	208	STN-DBS	1 yr	GBA carriers showed earlier **cognitive decline**
Pal et al., 2022	Case–control	366	STN-DBS	3–5 yrs	GBA carriers showed more rapid **cognitive decline**
Almelegy et al., 2024	Cross-sectional	66	STN-DBS	1 yr	GBA1+ DBS+ PD patients showed more severe **cognitive dysfunction**
Avenali et al., 2024	Retrospective	365	STN-DBS	1–5 yrs	GBA carriers showed significant **motor improvement** and **reduction in fluctuations**, dyskinesias, and **impulsive-compulsive disorders**, but a **faster rate of cognitive decline**
Asimakidou et al., 2024	Meta-analysis	380	STN-DBS		GBA carriers were more prone to postoperative **cognitive decline** and low quality of life

GBA1

- 12 datasets, n=366
- UPDRS improvement and LEDD reduction did not differ by GBA status.
- Cognitive outcomes were worse in GBA carriers who underwent DBS.



Pal G, et al. Annals of Neurol. 2022.

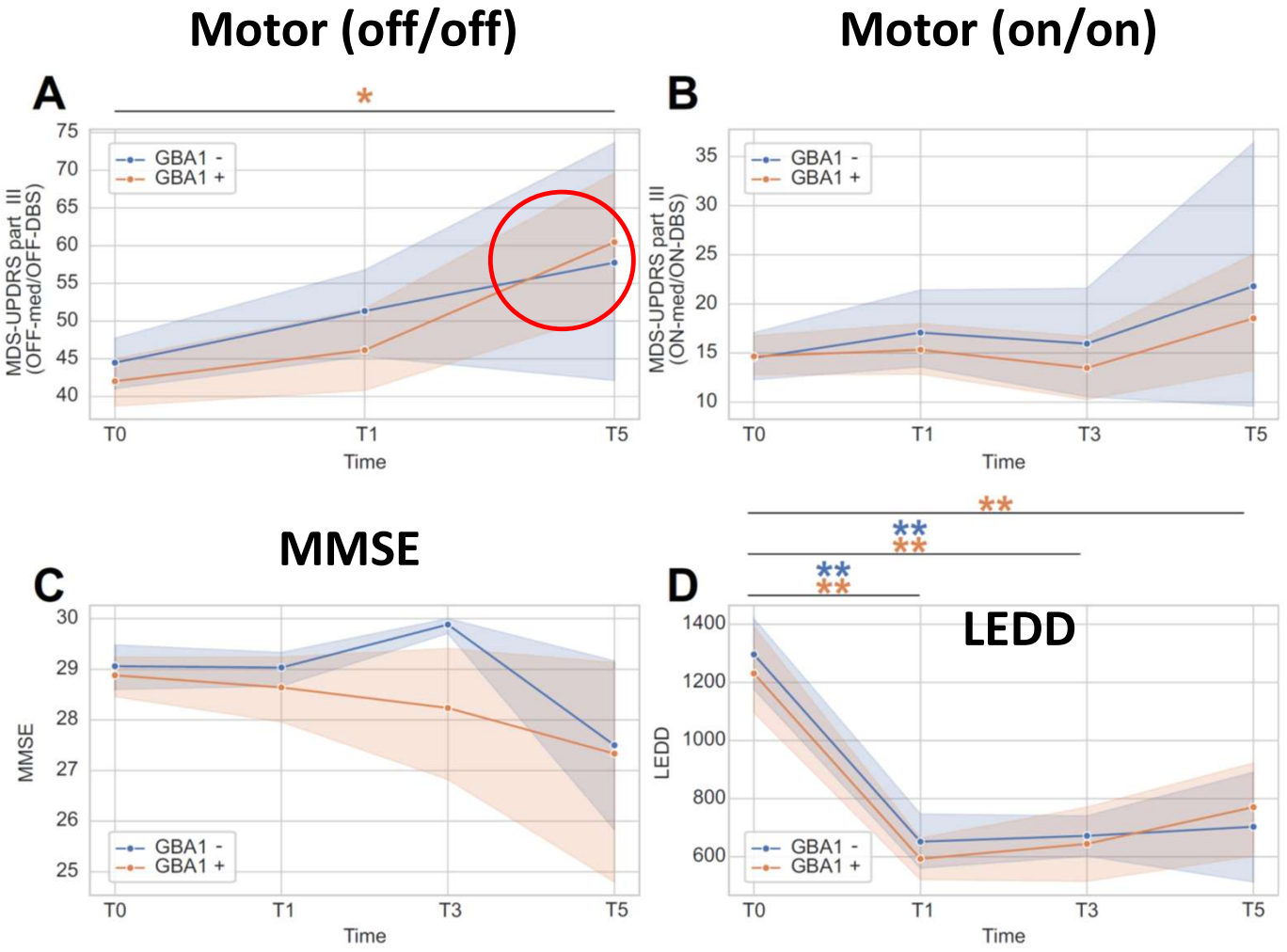
GBA1

Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Motor and Cognitive Outcome After Subthalamic Nucleus Deep Brain Stimulation in Patients with Parkinson's Disease Harboring *GBA1* Variant

Hikaru Kamo, MD, PhD,[1,2] Genko Oyama, MD, PhD,[1,3,*] Mai Shimizu, MD,[1] Haruka Takeshige-Amano, MD, PhD,[1] Takashi Ogawa, MD, PhD,[4] Wataru Sako, MD, PhD,[1] Noriko Nishikawa, MD, PhD,[1] Taku Hatano, MD, PhD,[1] Yuanzhe Li, PhD,[1] Hiroyo Yoshino, PhD,[1] Manabu Funayama, PhD,[1] Masanobu Ito, MD, PhD,[5] Hirokazu Iwamura, MD, PhD,[5] Atsushi Umemura, MD, PhD,[6] and Nobutaka Hattori, MD, PhD[1,*]

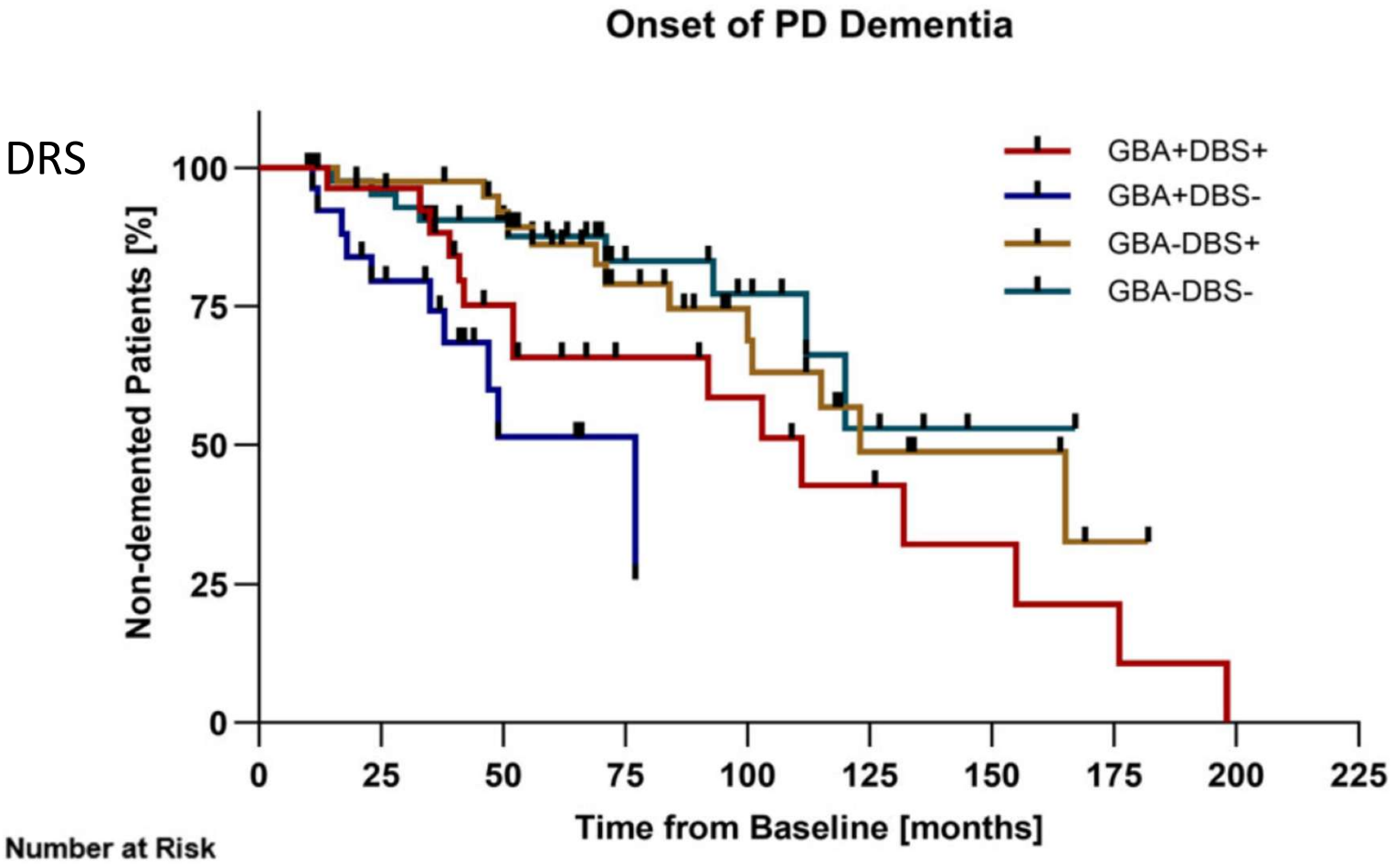
- N=371
- 54 GBA1 variant carriers
- 5 years f/u
- GBA1 carriers had worse motor symptoms in the med-OFF/DBS-OFF state.
- LEDD was significantly reduced in both groups.
- MMSE remained stable in both groups.



Kamo H, Oyama G, et al.MDCP. 2025.

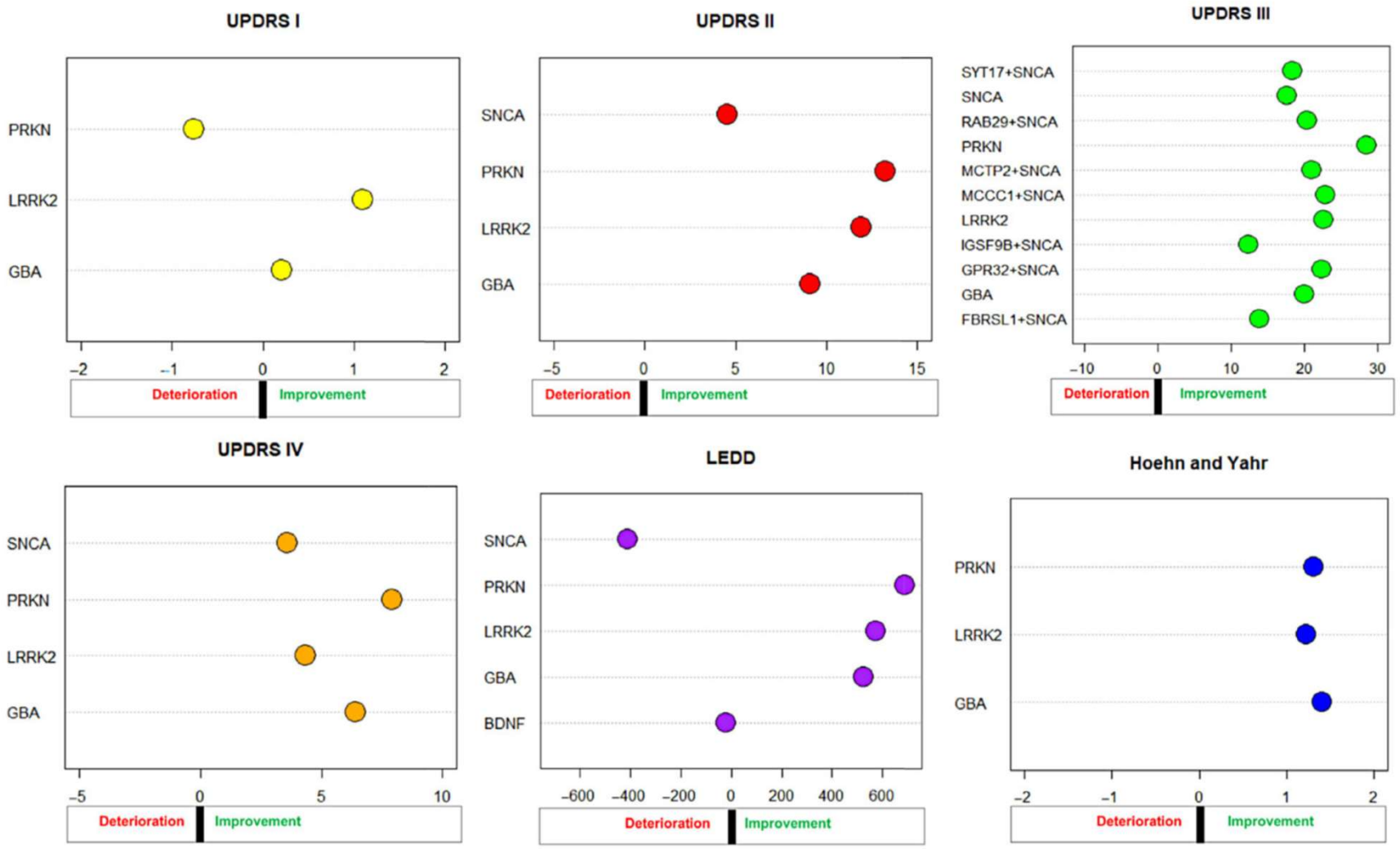
GBA1

- 9 centers in Italy
- GBA+: 75
- GBA−: 278
- Converted MDRS



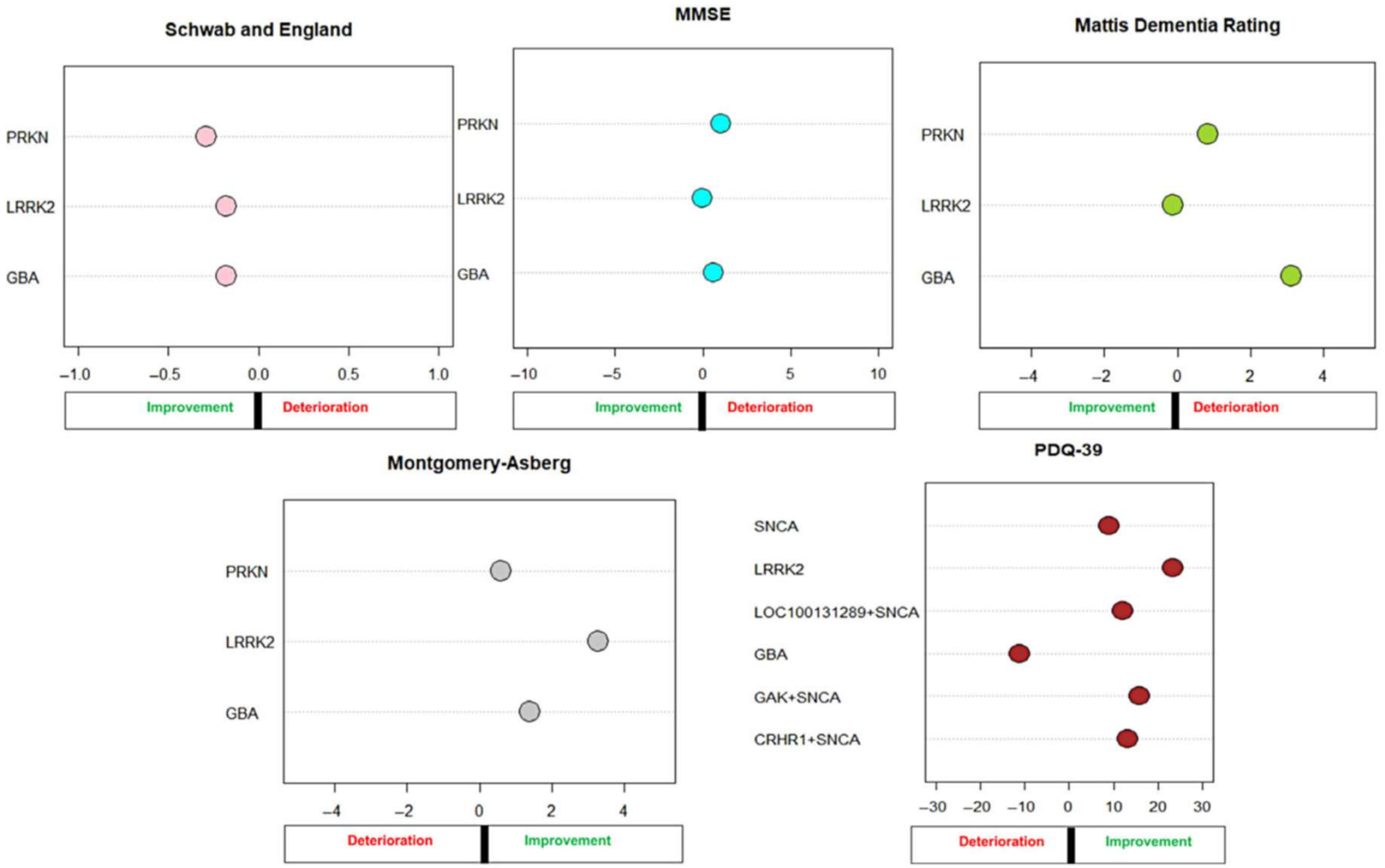
Loeffler MA, et al. ANN NEUROL 2026

Meta-analysis of Genetic Parkinson's disease



Asimakidou, et al. MDCP, 2025

Meta-analysis of Genetic Parkinson's disease



Asimakidou, et al. MDCP, 2025

Key unanswered questions

- Who should undergo genetic testing before DBS?
- Do different variants within the same gene lead to different DBS outcomes?
- Does genotype affect target selection?
- Can genotype predict non-motor and long-term outcomes?
- How should genetics be combined with phenotype and biomarkers?
- Is the evidence strong enough to change practice?

Take home messages

- **Traditional DBS criteria** remain the **gold standard**, but they are no longer sufficient for **precision care**.
- **Surgicogenomics** offers a framework for integrating genetic background into surgical decision-making.
- Although more evidence is needed, genetic background—particularly factors such as GBA1 carrier status—should be taken into account when **evaluating DBS candidacy, discussed with patients during counseling, and carefully monitored after surgery**.

School for Device-Aided Therapies in Parkinson's Disease

Bangkok, Thailand | May 6-7, 2026

International Parkinson and Movement Disorder Society
Asian & Oceanian Section