Parkinsonism and Related Disorders 64 (2019) 8–19

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review article

Genetic background and outcome of Deep Brain Stimulation in Parkinson's disease

Mario Giorgio Rizzone*[,1], Tiziana Martone[1], Roberta Balestrino, Leonardo Lopiano

Department of Neuroscience "Rita Levi Montalcini", University of Turin, via Cherasco 15, 10124, Torino, Italy

ARTICLE INFO

Keywords:
Parkinson's disease
Genetics
Deep brain stimulation
GBA
Parkin
LRKK2

ABSTRACT

Deep Brain Stimulation (DBS) is a well-established therapeutic option for patients with Parkinson's disease (PD). The high variability observed in the outcome demands better prediction criteria to select candidate patients that may obtain the best results from DBS. Recent advances in genetics have provided important tools to investigate variability in clinical features of PD patients, creating the possibility to correlate the patient's individual genotypes with clinical outcome of therapeutic responsiveness. The purpose of this review is to examine current evidence supporting the role of genetic background on the DBS efficacy. Three databases were searched to identify relevant articles reporting the outcomes of DBS in patients with PD and related genetic mutations. Twelve studies that compared the DBS response in different genetic forms of PD and non-mutated cases were found; mutations in PRKN, LRRK2 and GBA were the most common PD-related mutations. All the studies confirmed the effectiveness of DBS to control motor symptoms independently from the genetic status of patients, although some differences in the response to DBS were found. Due to the several limitations of the available data, all the existing evidence is preliminary. Future well-designed studies are needed to draw more consistent conclusions about genotype-related differences on DBS outcome.

1. Introduction

Deep brain stimulation (DBS) is a surgical option to treat Parkinson's Disease (PD) through the high frequency electrical stimulation of a selected target [1]. The most commonly used targets in PD are the subthalamic nucleus (STN), the globus pallidus internus (GPi) and the ventralis intermediate nucleus (Vim) of the thalamus. DBS disrupts the abnormal information flow that occurs through the cortico-basal ganglia loop in PD improving motor symptoms [1] and it is mainly indicated for the treatment of PD with severe motor complications; several studies demonstrated its efficacy in improving motor symptoms and health-related quality of life (HRQoL) [2–4]. The outcome of DBS is determined by different factors such as the patient selection, surgical procedure and electrode placement, postoperative setting of stimulation parameters and adjustment of pharmacological therapy [5].

Patient selection is of pivotal importance, and relevance is given to the disease duration, age, levodopa responsiveness, type and severity of levodopa-unresponsive symptoms, cognitive and psychiatric issues, comorbidities and brain MRI alterations. Generally, the best results are observed in patients with a good response to levodopa, a younger age and no or few axial non–levodopa-responsive motor symptoms [6]. Moreover, optimal candidates must have no cognitive impairment nor significant psychiatric disorders [7].

In spite of these selection criteria, a significant inter-individual heterogeneity can be observed in DBS outcome, both in the control of motor symptoms and the emergence of cognitive/psychiatric disturbances [8]; in this context, adding more information for the characterization of patients could provide a more precise and personalized approach to the treatment of parkinsonian patients with DBS.

Over the last two decades, substantial progress has been made in understanding the genetics of PD; data on both Mendelian genetics and genome-wide association studies (GWAS) led to the identification of several chromosomal loci that cause or modulate the risk for PD [9–13].

In addition, genetic factors can be associated to specific clinical pictures and may also influence the response to the therapy [14]. Mutations of a-synuclein (SNCA; PARK1), parkin (PRKN; PARK2), PTEN-induced putative kinase 1 (PINK1; PARK6), DJ-1 (PARK7) and Leucine-rich repeat kinase 2 (LRRK2; PARK8) genes have been associated with monogenic forms of PD and linked to specific clinical characteristics slightly different from those observed in non-mutated patients. Patients with mutations in PRKN usually show juvenile-PD (JPD, onset < 21 years old) or early-onset PD (EOPD, between 21 and 40 years old) with

* Corresponding author. Department of Neuroscience "Rita Levi Montalcini", University of Turin, via Cherasco 15, 10124, Torino, Italy.
E-mail address: mrizzone@unito.it (M.G. Rizzone).
[1] These authors equally contributed to the paper.

https://doi.org/10.1016/j.parkreldis.2018.08.006
Received 5 March 2018; Received in revised form 26 July 2018; Accepted 7 August 2018

a slow clinical course, excellent response to low doses of levodopa and frequent treatment-induced dyskinesias [15]. Specific characteristics have also been associated to genetic risk factors for PD, such as GBA; PD patients with some GBA mutations (GBA-PD) tend to have an earlier onset of symptoms, more aggressive disease, with more severe and earlier cognitive impairment and psychiatric manifestations [16].

Current evidence suggests that the genetic background may influence the clinical picture, the natural progression of the disease and the individual responsiveness to treatments [17]; however, it is still unclear how genetic factors influence the outcome of DBS. The observation that genetic forms of PD are over-represented among cohorts of patients undergoing DBS [18] raised further interest regarding the relationship between genotype and DBS responsiveness. Data on DBS outcomes in patients with PD-related mutation are still not conclusive; existing studies are highly heterogeneous in the selection of patients, investigated outcomes and duration of the follow-up. The aim of the present review is to summarize the current evidence on relationship between genetic status of PD patients and DBS responsiveness.

2. Material and methods

To identify relevant articles investigating the impact of genetic status on DBS outcome in PD we performed a search on PubMed, Embase and Cochrane Library databases; key words for the search were “Parkinson's Disease”, “Gene”, “Genetic variation” and “Deep Brain Stimulation”; major details of the queries used to interrogate each database and the flow diagram of search strategy are provided in Supplementary File 1. Additional records were identified by searching the literature list of the references cited in relevant studies. The search was updated to 24 October 2017 and was not restricted by year of publication. After removing duplicated articles, two independent authors screened the titles and the abstracts of all the retrieved records. To be included, the studies had to report the score of the motor section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS-III), assessed at baseline and after DBS at least in 1 medication-stimulation (med-stim) condition. Other outcomes of interest were cognitive function (assessed with different instruments), UPDRS part I (non-motor activities of daily living), II (motor activities of daily life) and –IV (motor complications), Hoehn and Yahr (HY) stage, Schwab and England Activities of Daily Living Scale (SE), motor subscores of the UPDRSIII and levodopa equivalent daily dosage (LEDD) before and after DBS. Only full articles published in English were included. The study design, number of subjects, mutational status, follow-up period, assessments tool and outcome measures of each study are reported in Table 1. Case reports, case series and small descriptive studies were briefly discussed, even when they did not fulfill the criteria above reported, if they added further information or referred to other genes not considered in larger studies (Table 2).

3. Results

We identified 30 relevant papers. Twelve of them were comparative studies, either retrospective or prospective, investigating the differences in the outcome between PD patients carrying different genetic mutations (MC) and non-mutation carriers (NC) in the DBS cohorts [19–30]. The main characteristics of these studies are listed in Table 1, the different methods used to screen mutations for each study are reported in Supplementary Table 1 and the individual mutations identified are indicated in Supplementary Table 2. The size of population in comparative studies varied from 14 to 94, the follow-up ranged from six months to 10 years and enrollment criteria and genetic testing methods were different across the several studies. Mutations in PRKN, LRRK2 and GBA genes were found more frequently than in other PD-associated genes. UPDRS-III scores and LEDDs before and after DBS according to genetic mutations are reported in Table 3. Different instruments were used to assess cognitive functions across the studies (Table 1). Among the remaining 18 retrieved articles, 14 were case reports [31–44], one was a case series study [45] and the remaining were studies describing the outcome of patients carrying mutation treated with DBS as a part of other studies [46–48]. These reports are summarized in Table 2.

3.1. PRKN genetic status and DBS outcome

Six studies analyzed the differences in the outcome of DBS between PRKN MC and NC or carriers of other mutations [19,22–24,26,27]. Three of them only included patients with EOPD [23,24,26].

A total of 315 subjects were enrolled; PRKN gene alterations were found in 47 patients, either homozygote/compound heterozygote (24 cases) or single heterozygote mutations (23 cases). In two cases [19,23] the authors did not consider single mutations for the subsequent analysis, so five patients were excluded. In one study [22] patients with mutations of PRKN, PINK1 and LRRK2 were not considered separately. The target of DBS was the bilateral STN in 38 cases, bilateral GPi in three cases and unilateral GPi in one case.

Outcome evaluations across the studies confirmed the effectiveness of DBS; in the majority of studies, there were no significant differences between the improvement in the UPDRS-III scores and the reduction of LEDD after DBS between MC and NC (Tables 1 and 3) [19,22–24,26,27]. Case reports confirmed the efficacy of STN-DBS [34,39,40,48] and GPi DBS [48] in PRKN MC patients, even in a pediatric case [38] (Table 2).

The comparison between MC and NC patients showed significant differences in some studies. PRKN MC patients in the DBS-group tended to have younger age and a longer duration of PD at baseline [19,23]; the age at onset of PD was significantly younger and the disease duration at DBS significantly longer in patients with double PRKN mutations compared to patients with single or no PRKN mutations [24]. In one study, patients with double PRKN mutations showed a lower LEDD than NC after DBS [24]; in another study PRKN MC showed a greater LEDD reduction after DBS compared to NC [27]; a lower LEDD in PRKN MC than in NC were noted, although not confirmed statistically, both at baseline and after DBS, in other two studies [23,27].

A significantly higher UPDRS axial score after DBS in OFFmed/ONstim condition in PRKN MC (5.5 ± 3.1) compared to PRKN NC patients (2.0 ± 1.4) was reported in one study [23]; there was already a difference, although not significant, between PRKN MC (8.0 ± 4.4) and NC (5.3 ± 2.4) at baseline in OFFmed condition. Another study reported a worse response in PRKN MC than NC after DBS (lower improvement in UPDRS total motor scores, akinesia and postural instability and gait disturbance subscores, and H-Y score in OFFmed/ONstim condition) at short-term follow-up (3–12 months), but a comparable response to NC at a longer follow-up (3–6 years) [26].

3.2. LRRK2 genetic status and DBS outcome

The effectiveness of DBS in patients carrying LRRK2 mutations has been investigated in seven studies for a total of 359 PD patients who underwent DBS [19–22,28–30]. The mutations mentioned in the different studies are a combination of clearly established pathogenic mutations and genetic risk factors with variable penetrance and biological effect. Six out of seven studies [19–22,28,29] found heterozygous LRRK2 mutations in a total of 49 patients. Considering that some studies examined only specific LRRK2 mutations, G2019S mutations were found in 44 patients, R1441G mutations in four patients and T2031S mutation in one patient. One study focused on the LRRK2 variant *rs*1491923 [30]. The target of DBS was the bilateral STN in all 49 cases. Among the considered studies no significant difference between LRRK2 G2019S MC and NC was reported in improvement in the UPDRS-III scores, reduction of LEDD, and in cognition or psychiatric symptoms in studies that considered these aspects [21,29] (Tables 1 and 3). A recent study [28] reported a greater improvement in LRRK2 G2019S MC compared to NC.

Table 1
Overview of studies by year of publication investigating the outcomes of PD patients after DBS in relationship to the genetic status.

Authors	Study Design	N	Enrollment Criteria	Investigated Genes	Measures	Conditions	FU	Genetic Status of Patients	Results
Lythe et al., 2017	Retrospective Case-Control Comparative: MC vs NC	34	DBS cohort (GPi and STN) *Patients selection:* GBA-MC and GBA-NC matched for sex and disease duration	GBA SNCA PRKN PINK1 DJ-1 LRRK2 G2019S	UPDRS-III MDS-UPDRS-III (Segmental and Axial Subscores) LED NMSS PDQ39 DRS-2	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim	7.5 y	GBA-NC, n = 17 (n = 16 at FU) GBA-MC, n = 17 (n = 10 at FU) 15 het, 1 hom, 1 hom/comp het *Notes:* GBA-NC did not carry other mutations; GBA-MC also carried PRKN (n = 1) and LRRK2 (n = 1) mutations	GBA-MC worsened in cognitive performance, quality of life scores and non-motor symptoms than NC Comparable motor outcome between GBA-MC and NC after DBS
Weiss et al., 2016	Prospective Comparative: WT vs VAR	85	STN-DBS cohort *Unselected patients*	SNCA Variants (3′UTR, rs356219, *rs*356220) LRRK2 Variants (LRRK2, *rs*1491923) LRRK2 G2019S GBA (N370S; L444P) PRKN PINK1 DJ-1	UPDRS-III PDQ-39 MMSE BDI	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim OFFmed/ OFFstim	2 y	SNCA (*rs*356219, *rs*356220): WT/ WT n = 27; WT/VAR) n = 44; VAR/VAR n = 14 LRRK2, rs1491923 Variant: WT/ WT n = 33; WT/VAR n = 27; VAR/VAR) n = 11 *Notes:* LRRK2 G2019S MC: n = 0 GBA-MC n = 3 (n = 1 N370S; n = 2 L444P carriers)	SNCA, variant carriers: better response in UPDRS-III and axial motor outcome LRRK2 variants were not predictive Both variants were not predictive on motor symptoms progression or non-motor symptoms
Sayad et al., 2016	Clinical Trial Comparative: MC vs NC	27	STN-DBS cohort *Patients selection*: Age at DBS < 60 Good response to levodopa and dyskinesias	LRRK2 G2019S PRKN PINK1 DJ-1	UPDRS-III HY stage SE stage MMSE	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim	2 y	NC, n = 12 MC (LRRK2 G2019S), n = 15 Notes: 2 patients among NC had PRKN mutations (c.1204C > T het in exon 11; c. 458C > G het in exon 4)	Better response in UPDRS III, SE, HY in MC than NC
Kim et al., 2014	Retrospective Comparative: MC vs NC	14	STN-DBS cohort *Patients selection*: AAO < 40 (EOPD)	PRKN LRRK2 G2019S PINK1 DJ-1 SCA2 SCA17	UPDRS-I UPDRS-II UPDRS-III (Scores and Segmental and Axial Subscores) UPDRS-IV (Dyskinesia and OFF periods subscores) HY stage ADL LEDD SF-36	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim	2- 5 y	NC, n = 9 PRKN-MC, n = 3 (out of 5) 3 Hom/Comp Het (included); 2 Het (excluded) Notes: No mutation was identified in the other investigated genes	Axial sub-scores higher in MC than NC post-operatively Other outcomes were comparable between MC and NC
Greenbaum et al., 2013	Retrospective Case-Control (1:2) Comparative: MC vs NC	39	STN-DBS cohort *Unselected patients*	LRRK2-G2019S	UPDRS-III LEDD CGIC	Pre-DBS: OFFmed ONmed Post-DBS: (2 FU points) OFFmed/ ONstim ONmed/ ONstim	6–12 m; 3 y	NC, n = 26 MC (LRRK2-G2019S), n = 13 Notes: Patients with known mutations in Pink and PRKN genes were not included in the study No other LRRK2 mutations were investigated	Comparable outcome between MC and NC
Angeli et al., 2013	Retrospective Comparative different MC and NC (according DBS target selection and genetic subgroups)	94	DBS cohort (STN, GPi, VIM-DBS) *Unselected patients*	PRKN LRRK2 G2019S GBA PINK1 DJ-1 SNCA	UPDRS-I UPDRS-II UPDRS-III (Segmental and Axial Subscores) UPDRS -IV (Dyskinesia and OFF	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim	1-5 y	NC, n = 67 MC, n = 26 MC group included: PRKN-MC, n = 5 (8) 5 Hom/Comp Het (included); 3 Het (excluded)	PRKN: Comparable outcome between MC and NC LRRK2: Comparable outcome between MC and NC GBA: more severe cognitive decline at 5 y FU in DRS-2 score for GBA-MC

(*continued on next page*)

Table 1 (*continued*)

Authors	Study Design	N	Enrollment Criteria	Investigated Genes	Measures	Conditions	FU	Genetic Status of Patients	Results
					periods subscores) LED DRS-2	OFFmed/OFF Stim ONmed/ ONstim		GBA-MC, n = 16 (2 patients had mutations also in PRKN and GBA genes) LRRK2 (G2019S)-MC, n = 5 (1 patient also had E326K-GBA mutation)	treated with STN-DBS than GBA-NC. Comparable motor response
Johansen et al., 2011	Retrospective Comparative: MC vs NC	37	STN-DBS cohort *Patients selection*: AAO FH	LRRK2 (all subjects) PRKN (≤50 or FH + >50) PINK1 (≤50 or FH + >50) SNCA (all subjects) DJ-1 (≤50) MAPT PARK10 PARK13 GBA DCTN1 FMR1, SCA2, SCA3	UPDRS-III (Segmental and Axial Subscores) LEDD	Pre-DBS: OFFmed ONmed Post-DBS: ONmed/ ONstim	1 y; 3 y; 5 y	NC, n = 30 MC, n = 7 3 PRKN-MC (Het Mut), 3 LRRK2 G2019S-MC, 1 PINK1-MC	Comparable between MC and NC
Gomez-Esteban et al., 2008	Clinical trial Comparative: MC vs NC	48	STN-DBS cohort *Patients selection* Only patients with FH were genotypized (n = 8)	LRKK2 R1441G	UPDRS-II UPDRS-III PDQ-39	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim	6 m	Control group not genotyped n = 41 and 3 LRRK2 R1441G-NC MC (LRRK2 R1441G), n = 4 (5) (one was excluded)	Worse response among MC than NC Lower improvement also in UPDRS-II UPDRS-III PDQ-39
Moro et al., 2008	Prospective Comparative: MC vs NC	80	STN-DBS cohort: *Patients selection:* EOPD (AAO ≤ 45)	PRKN PINK1 LRRK2 G2019S	UPDRS-II UPDRS-III (Segmental and Axial Subscores) UPDRS-IV LEDD HY stage SE stage	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim	3–12 m; 3-6 y	NC, n = 68 MC, n = 12 11 PRKN-MC (n = 6 Hom or Comp Het; n = 5 Het), 1 PINK1 MC	Worse response in MC at short-term FU but comparable response at a longer FU
Lohmann et al., 2008	Retrospective Comparative: MC single-MC double-NC	54	STN-DBS cohort *Patients selection* EOPD	PRKN LRRK2 G2019S	UPDRS-II UPDRS-III UPDRS-IV LEDD HY stage DRS-2, Grober/ Buschke Test, Frontal Score	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim OFFmed/ OFFstim ONmed/ OFFstim	1-2 y	NC, n = 39 MC, n = 14 7 Hom/Comp Het), 7 Single (Het) Notes: 1 patient with PRKN rearrangement of consecutive exons was excluded	Higher LEDD reduction in carriers of double PRKN mutation than NC patients Other outcomes were comparable between MC and NC
Schupbach et al., 2008	Clinical Trial Comparative: MC vs NC	69	STN-DBS Cohort *Unselected patients*	LRRK2	UPDRS-I UPDRS-II UPDRS-III UPDRS-IV LEDD MADRS DRS-2	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim	8 y	NC, n- = 60 MC n = 9 8 G2019S, 1 T2013S Notes: 1 patient with LRRK2-G2019S mutation also had PRKN mutation	Comparable outcome between MC vs NC

(*continued on next page*)

Table 1 (*continued*)

Authors	Study Design	N	Enrollment Criteria	Investigated Genes	Measures	Conditions	FU	Genetic Status of Patients	Results
						OFFmed/OFF Stim ONmed/OFF Stim			
Romito et al., 2004	Retrospective Comparative: MC vs NC	36	STN-DBS Cohort *Unselected patients*	PRKN	UPDRS-III LEDD	Pre-DBS: OFFmed ONmed Post-DBS: OFFmed/ ONstim ONmed/ ONstim	1-3 y	NC, n = 31 MC, n = 5 1, Hom/Comp Het, 4 Het	Comparable outcome between MC vs NC

N, Number of subjects; *MC*, mutation carriers; *NC*, non-mutation carriers; *DBS*, Deep Brain Stimulation; *STN*, Subthalamic Nucleus; *VIM*, Ventral Intermediate Nucleus; *GPi*, Globus Pallidus Internus; *AAO*, Age at Onset; *EOPD*, Early Onset PD; *FH*, family history; *PIGD*, Postural Instability and Gait Disturbance); *Hom*, homozygous mutations (double); *Hom/Comp Het*, homozygous or compound heterozygous mutations (double); *Het*, heterozygous mutations (single); *WT*, wild type; *VAR*, variant; *FU*, follow-up; *m*, month(s); *y*, year (s); *Med*, medication state; *Stim*, stimulation state; *LED*, levodopa equivalent daily dose; *LEDD*, levodopa equivalent daily dose; *NMSS*, Non-Motor Symtoms Scale; *MMSE*, Mini Mental State Examination; *PDQ-39*, Parkinson's Disease Quality of Life-39 items; *DRS-2*, Mattis Dementia Rating Scale; *BDI*, Beck Depression Inventory; *HY*, Hoehn and Yahr Stage; *SE*, Schwab and England's Activities of Daily Living Scale; *ADL*, Activities of Daily Living Scale; *SF-36*, Short Form 36 Health Survey; *CGIC*, Clinical Global Impression Change; *MADRS*, Montgomery-Asberg Depression Rating Scale; *UPDRS*, Unified Parkinson's Disease Rating Scale; *UPDRS-I*, Non-Motor Activities of Daily Living; *UPDRS-II*, Activities of Daily Living; UPDRS-III, Motor Activities; UPDRS-IV, Motor Complications; *MDS-UPDRS-III*, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Subscores of UDPRS: items 20–21(tremor), items items 22–26 and 31 (akinesia and rigidity); items 18,19 and 27–30 (axial motor symptoms), items 32–34 (dyskinesias), items 35–39 (OFF periods).

LRRK2 R1441G MC were shown to have a worse response to DBS treatment than NC [20] in relationship to the motor outcome, activities of daily living (ADL) and HRQoL. No difference was observed between wild-type and *rs*1491923 LRRK2 variant carriers [30].

Two case reports showed a positive outcome of DBS in patients with Y1699C or R793 M mutations [33,42], while case reports described satisfactory motor outcome but the development of levodopa-related dystonia in a patient carrying LRRK2 G2019S [44] and severe motor complications and psychiatric symptoms in a patient carrying a double LRRK2 R1441G and G2385R mutation [49].

3.3. GBA genetic status and outcome

Till date, only two studies have analyzed the genetic status of GBA in the patients undergoing DBS [19,25]. In a study performed on a DBS cohort of 94 patients, 16 patients with at least one mutation in the GBA gene (17%) were found, with E326K being the most common GBA alteration; among GBA MC, the target for DBS was the STN in 13 patients, the GPi in two patients and the Vim in one patient. GBA MC underwent DBS earlier (either in terms of age at DBS or PD duration). At a short follow-up the outcome was comparable between MC and NC, independently from the DBS target while at a longer (5 years) follow-up, MC showed a faster cognitive decline after DBS compared to NC (Mattis DRS-II score, MC = 4.4 ± 7,3 vs NC = 0.5 ± 0.9 points per years) [19].

In another study, 10 GB A MC patients were selected and matched with 16 controls; GBA MC underwent earlier to DBS (either in terms of age at DBS and PD duration), showing more severe motor symptoms at baseline [25]. At a mean follow-up of 7,5 years the authors reported more severe decline in cognitive functions and lower HRQoL in GBA MC than in NC; a more sever burden of NMS in GBA MC than in NC was also reported although, given the lack of pre-operative data, it is difficult to interpret this information [25]. In a case series of three GBA MC (1 GB A N370S and 2 GB A L444P) followed for 6–10 years after DBS, cognitive decline was reported in all cases [45].

3.4. Alpha-synuclein genetic status and DBS outcome

A recent study [30] performed on a cohort of 85 PD patients treated with STN-DBS, suggested that SNCA *rs*356219 and *rs*356220 single nucleotide polymorphisms may have a predictive value on the DBS outcome. Namely, patients carrying these SNCA variants, especially homozygous carriers, showed a more favorable response to DBS of motor and axial symptoms after two years when compared to wild-type (*P = 0,030* improvement total UPDRS-III and *P = 0,026* improvement axial UPDRS-III). Genetic variants were not predictive on motor or non-motor symptoms progression.

Two case reports on patients with SNCA duplication who underwent STN-DBS reported a satisfactory response after one and four years [31,43], although in one case decline in verbal fluency and shifting of attention were described after DBS; a case of SNCA duplication mosaicism who underwent successful GPi DBS has also been described [41].

3.5. Other genes

The DBS outcome in patients with PD linked to other mutations has been reported only as case reports. Three cases with VPS35 D620N mutation [35,37], three cases with 22q11.2 [46] and a single case report with C9ORF72 expansion [36] were reported. No adverse events have been reported in any of these cases. Motor improvement ranged from 30 to 70% in 22q11.2, from 36% to 75% in VPS35 after one year -with sustained benefit reported after five and eight years- and it was of 67% in the case of C9ORF72 expansion after one year. In all the cases, the authors concluded that DBS was successful, with comparable results and side effects to those seen in NC (Table 2). No data are available on

Table 2
Summary of data collected from case reports, case series and small descriptive studies investigating the outcome of PD patients after DBS. Data are listed by genetic status.

Genetic Status	Authors	Type of study	N	Age at onset (y)	Age at DBS (y)	PD Duration at DBS (y)	DBS Target	FU	Results	Remarks
SNCA duplication mosaicism	Perandones et al., 2015	CR	1	18	26	8	GPi	1 m	Satisfactory response	Improvement in motor features and complete abolition of peak-dose dyskinesia
SNCA duplication	Shimo et al., 2014	CR	1	35	41	6	STN	4 y	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 27 to 13 LEDDD reduction from 925 mg to 650 mg (30%) No cognitive or psychiatric impairment
SNCA duplication	Antonini et al., 2012	CR	1	41	46	5	STN	1 y	Satisfactory response	UPDRS-III improvement from from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 28 to 16 (64%) LEDD reduction from 600 mg to 300 (50%) Complete abolition of peak dose dyskinesias Improvement of depression, impulse control disorder and memory; Decline in verbal fluency and shifting attention
LRRK2 (R1441G and G2385R)	Hatano et al., 2014	DS as a part of a family study	1	28	39	11	STN	2 y	Unsatisfactory response	No data on UPDRS-III or LEDD; Severe motor fluctuations; Exacerbated psychiatric problems
LRRK2 (G2019S)	Stefani et al., 2013	CR	1	49	56	7	STN	1 m; 3 m; 6 m	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 27 to 7 (after 1 m) and to 8 (after 3 m); No cognitive impairment; development of L-dopa dose-dependent painful dystonia in neck, left shoulder and proximal arm in ONmed/ONstim, relieved by L-Dopa withdrawal and introduction of rotigotine
LRRK2 (Y1699C)	Perju-Dumbrava et al., 2012	CR	1	43	48	5	STN	2,5 y	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 49 to 26 UPDRS II from 5 to 5 UPDRS IV from 3 to 2
LRRK2 (R793 M)	Breit et al., 2010	CR	1	42	60	18	STN	1 y, 8 y	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 64% (1 y FU) and 56% (8 y FU); LEDD reduction from 900 mg to 500 mg (66%) at 1 y FU and from 900 mg to 650 mg (27%) at 8 y FU
PRKN het c.458C > G PRKN het c.1204C > T	Sayad et al., 2016	DS as part of another study	2	48 48	58 61	10 13	STN STN	2 y	Unsatisfactory response	No UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 46 to 51 (patient 1) and from 49 to 51 (patient 2). The best motor outcome after DBS was observed in ONmed/OFFstim situation compared to other situations No differences observed between MC and NC
PRKN het comp: c89G > A + del exons 2,3,4, 5	Genç et al., 2016	CR	1	10	14	4	STN	nr	Satisfactory response	UPDRS-III Improvements from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 48 to 7 (85%); LEDD reduction of 50%
Digenic: PRKN hom (T175PfsX2) + PINK1 Het (R58-V59insGR)	Nakahara et al., 2014	CR	1	15	60	45	STN	8 m	Satisfactory response	UPDRS-III improvements from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 62% UPDRS-I 67%; UPDRS-II 61%; UPDRS-IV 80% LEDD reduction from 700 mg to 300 mg (57%)

(*continued on next page*)

Table 2 (*continued*)

Genetic Status	Authors	Type of study	N	Age at onset (y)	Age at DBS (y)	PD Duration at DBS (y)	DBS Target	FU	Results	Remarks
PRKN hom (not specified)	Thompson et al., 2013	DS as a part of retrospective Study	2	30 26	NR	NR	STN GPi	3 y 8 y	Satisfactory response	No Individual UPDRS-III data reported after DBS STN-DBS patient had a sustained (3 y FU) benefit GPi-DBS patient had a sustained (8 y FU) benefit
PRKN comp/het: c.101_102delAG (p.Gln34ArgfsX5) + c.155delA (p.Asn52MetfsX29)	Lefaucheur et al., 2010	CR	1	35	69	44	STN	6 m	Satisfactory response	Cognitive impairment at baseline UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim and to ONmed/ONstim post-DBS: 55% and 74%; UPDRS IV improvement: 81% and 84% LEDD reduction of 67% MDRS pre-DBS 99/144 vs post-DBSt 104/144
PRKN (exon 3 del frameshift)	Capecci et al., 2004	CR on JPD	1	26	42	20	STN	1 y	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 45 to 7 LEDD reduction from 900 mg to 308 mg (66%); Improvement of depression and QoL
PINK-1 hom L347P	Borellini et al., 2017	CR	1	30	49	19	GPi	1 m	Satisfactory response	MDS-UPDRS-III improvement from OFFmed pre-DBS to ONmed/ONstim post-DBS: 44 to 32 LEDD reduction from 1029 mg to 779 mg (24%)
PINK1 hom c.509 TG (p.V170G)	Moro et al., 2008	DS as a part of a Prospective Study	1	31	61	30	STN	3–12 m; 3-6 y	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 46.5% (1 y FU),43.7% (3 y and 6 y FU) LEDD reduction NR
GBA N370S GBA L444P GBA L444P	Weiss et al., 2012	CS Prospective Case-Control (1:2)	3 MC (vs 6 NC)	54 48 47	65 69 67	11 21 20	STN	10 y; 7 y; 6 y	Short term FU: Satisfactory motor response; Long term FU: cognitive impairment and decline of axial symptoms for GBA-MC	Satisfying control of motor fluctuations and LEDD reduction in GBA-MC and NC. GBA-MC showed a stable motor outcome In ONmed/ONstim, but after 4–6 y FU they showed sparse response of axial motor symptoms to both L-Dopa and STN-DBS. All GBA-MC developed sever cognitive impairment
VPS35 Het D620 N	Chen et al., 2017	CR	1	42	55	13	STN	1-5 y	Long term satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 37% (1 y and 5 y FU) LEDD reduction from 1435 to 1000 mg (30%) (1 y FU)
VPS35 Het D620 N	Fleury et al., 2013	CR	2	49 45	60 67	11 22	STNSTN	1-8 y	Satisfactory response	Patient 1 had an UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 76% (1 y FU); LEDD reduction from 1540 mg to 400 mg (74%) (1 y FU) and 550 mg (64%) (8 y FU) Patient 2 had an UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 36% (1 y FU) LEDD reduction from 1276,5–300 mg (76%) (1 y FU)

(*continued on next page*)

Table 2 (*continued*)

Genetic Status	Authors	Type of study	N	Age at onset (y)	Age at DBS (y)	PD Duration at DBS (y)	DBS Target	FU	Results	Remarks
C9ORF72 Rep Exp	Danaila et al., 2014	CR	1	29	38	9	STN	12 m	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 67.5%
22q11.2 del Syndrome	Dufournet et al., 2017	DS 3 patients affected by 22q11.2 del syndrome	3	32–48	34 38 37	NR	GPi STN GPi	nr	Satisfactory response	UPDRS-III improvement from OFFmed pre-DBS to OFFmed/ONstim post-DBS: 30–70%

PD, Parkinson's Disease; *JPD*, Juvenile PD; *N*, Number of subjects; *CR*, case report study; *CS*, Case series study; *DS*, descriptive study; *DBS*, Deep Brain Stimulation; *STN*, Subthalamic Nucleus; *GPi*, Globus Pallidus Internus; *AAO*, Age at Onset; *EOPD*, Early Onset PD; *MC*, mutation carriers; *NC*, non-mutation carriers; *Del*, deletion; *Rep Exp*, repeats expansion; *Hom mut*, homozygous mutations (double); *Hom/Comp Het mut*, homozygous or compound heterozygous mutations (double); *Het mut*, heterozygous mutations (single); *FU*, follow-up; *m*, month(s); *y*, year (s); *Med*, medication state; *Stim*, stimulation state; *LEDD*, levodopa equivalent daily dose; *UPDRS*, Unified Parkinson's Disease Rating Scale; *UPDRS-I*, Non-Motor Activities of Daily Living; *UPDRS-II*, Activities of Daily Living; *UPDRS-III*, Motor Activities; *UPDRS-IV*, Motor Complications; *nr*, not reported.

DBS outcome of patients with another well-established genetic risk factor for PD, the MAPT gene haplotype H1, which was considered only in one study [22].

4. Discussion

Several studies have demonstrated the efficacy of DBS in advanced PD to control motor symptoms and complications with a reduction of levodopa intake and an improvement in HRQoL [50–53]. In the long-term follow-up, although DBS continues to be effective on tremor, rigidity, bradykinesia and motor fluctuations, PD-related disability can increase because of the worsening of levodopa-resistant motor symptoms (hypophonia, postural instability, freezing of gait) and cognitive impairment [3,4,54,55]. Considering the clinical heterogeneity of PD in respect to the age of onset, motor phenotype, clinical progression and burden of non-motor-symptoms, an accurate selection of patients is pivotal for a sustained and long-term positive outcome of DBS [6]. The genetic background may influence the natural progression of the disease and contribute to the high heterogeneity of clinical features and treatment outcomes [17]; therefore, a better understanding of whether genetic subtypes of PD may influence the DBS responsiveness is relevant to develop a more personalized and tailored treatment of PD. Data analyzed in this review confirmed that DBS is effective in the control of motor symptoms both in MC and NC patients, although some differences in response to DBS were reported.

The majority of studies [19,22,24,27] confirmed an improvement of PRKN MC from DBS comparable to that observed in NC. Only two studies [23,26] showed less satisfactory improvement in MC patients. Kim et al. reported a significantly higher UPDRS axial score after DBS (in OFFmed/ONstim) in PRKN MC than NC; however, there was already a difference, although not significant, at baseline in OFFmed condition, and this could reflect a heavier burden of axial symptoms responsible for a worse response to DBS [23]. Another study reported a worse response in PRKN MC than NC at a short-term follow-up, but a comparable response to NC at a longer follow-up; as stated by the authors, a possible explanation could be that MC had a more advanced disease at baseline (higher axial scores with poor response to levodopa), while NC had later but faster progression of disease after three to five years of treatment, with a consequent abolition of the initial difference in the responsiveness to STN-DBS [26]. Further studies are needed to clarify the role of PRKN mutations on DBS response, also comparing the response of PRKN MC to DBS versus conventional medical therapy.

The outcome of GBA-PD after DBS is of particular interest, given that approximately 12–17% of DBS PD patients are GBA mutation carriers, and that PD patients carrying some GBA variants seem to be more susceptible to develop cognitive impairments [16,18,19,57]. GBA-PD patients undergo to DBS earlier than NC patients, probably because of a more aggressive disease; although their motor response to DBS is positive, at a longer follow-up they show more complications, particularly a more severe and rapid cognitive impairment. This is consistent with current evidence that suggests that PD patients carrying specific GBA mutations have a greater burden of cognitive impairment than NC patients [16]. However, a comparison with patients with GBA-PD not undergoing DBS has not yet been performed; it is therefore difficult to estimate the relative role of the natural history of GBA-PD and DBS in respect to the cognitive impairment. Moreover, data from currently available studies are insufficient to evaluate a different outcome between GPi-DBS or STN-DBS in these patients, which would be interesting because of a potentially higher risk for neuropsychiatric symptoms observed in STN-DBS compared to GPi-DBS [56]. Further studies are also necessary to elucidate the effect of DBS in patients carrying different GBA variants, considering that specific mutations, as L444P, seem to be related with a higher risk of developing cognitive problems [57]. Given the few studies published, it is not possible to definitely consider GBA-PD patients as poor candidates for DBS.

Interestingly, the response to DBS in LRKK2 mutated patients seems

Table 3
Overview of UPDRS-III scores and LEDD doses assessed pre-DBS and post-DBS with respect to genetic status. Data extracted from comparative studies are listed by gene.

Gene	Authors	FU	Genetic Status	UPDRS-III PRE-DBS				UPDRS-III POST-DBS				Improvement in UPDRS-III or *MDS-UPDRS-III	LEDD	
				OFFmed		ONmed		OFFmed/ONstim		ONmed/ONstim		OFFmed/ONstim post DBS-*vs* OFFmed pre-DBS[a]	Pre-DBS	Post-DBS
				M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	%	*mg/day*	
PRKN	Kim et al., 2014	2-5 y	NC	38,3	± 10,6	17,7	± 12,6	17,2	± 5,5	15,2	± 5,4	54.6 ± 45,4	1001,1 ± 482,5	316 ± 400,6
			MC	45,8	± 24,5	18,3	± 7,8	24,7	± 14	22,2	± 14,9	37,1 ± 13,9	460 ± 151	141,7 ± 203,6
PRKN	Moro et al., 2008	1 y	NC	48,7	± 13,1	18,6	± 10,2	21,5	± 10,7	15,2	± 9,3	56	1288,6 ± 655,6	722 ± 563,2
			MC	48,4	± 11,3	18	± 7,8	31,8	± 11,7	19,5	± 10,5	36	1066,6 ± 441,1	610,2 ± 360,8
		3-6 y	NC	48,7	± 13,1	18,6	± 10,2	27,4	± 12,1	20,7	± 10,6	44	1288,6 ± 655,6	581,4 ± 365
			MC	48,4	± 11,3	18	± 7,8	28,4	± 13	23,4	± 8,1	42	1066,6 ± 441,1	412,0 ± 262,2
PRKN	Lohmann et al., 2008	1-2 y	NC	51,9	± 18,3	11,2	± 8,5	17,9	± 15,1	7,6	± 6,8	67 ± 21[b]	1355 ± 732	534 ± 439
			MC (One Mut)	54,3	± 13,9	11,6	± 12,7	17,8	± 11,2	10,8	± 10,1	69 ± 15[b]	1089 ± 317	293 ± 196
			MC (Two Mut)	55,4	± 17,3	14,5	± 2,3	14,5	± 12,5	9,3	± 8,6	77 ± 14[b]	1091 ± 267	193 ± 108
PRKN	Romito et al., 2004	1-3 y	NC	59,7	± 11,3	24,5	14,2	29	± 12,3	21,1	± 10,4	51	1306 ± 692	591,2 ± 431,6
			MC	57,3	± 9,3	22,8	7,3	25,2	± 10	21,8	± 7,5	56	1193 ± 463,8	291,8 ± 92,3
PRKN	Angeli et al., 2013	1-5 y	NC	47,6	± 14,8	15,6	± 11,3	24,6	± 11,3	15	± 9	48 (STN); −28 (Gpi)	1259 ± 559	468 ± 494
			MC	62,5	± 3,5	21	± 6,4	43	± 0,0	23,5	± 6,4	31 (STN); 21 (Gpi)	960 ± 611	20 ± 594
LRRK2 G2019S	Sayad et al., 2016	2 y	NC	51,7	± 14,4	30,6	± 16,7	38,5	± 16,6	18,8	± 12,5	25,5	*nr*	*nr*
			MC	55,8	± 16,4	25,8	± 13,2	27,3	± 20,6	19,7	± 18,8	51,1[c]	*nr*	*nr*
LRRK2 G2019S	Greenbaum et al., 2013	6–12 m	NC	43,4	± 12,3	23,6	± 13,2	27,2	± 14,1	21,8	± 10,8	35,6 ± 25,3	1093,5 ± 391,5	612,3 ± 323,1
			MC	42,5	± 11,8	19,5	± 13	28,5	± 13,1	17,4	± 12,9	32,8 ± 31,1	1093,2 ± 458,6	600,4 ± 268,5
		3 y	NC	43,4	± 12,3	23,6	± 13,2	33,9	± 16,1	31,1	± 17,7	17 ± 37,1	1093,5 ± 391,5	662,2 ± 369
			MC	42,5	± 11,8	19,5	± 13	30,5	± 12,8	21,2	± 9,2	28,5 ± 32,9	1093,2 ± 458,6	468 ± 256,7
LRRK2,PRKN, PINK1	Johansen et al., 2011	1 y	NC	35,7	± 6,7	13,8	± 5,3	nr	nr	16,3	± 5,9	nr	1173 ± 463	556 ± 373
			MC	40,5	± 8,1	16,7	± 2,3	nr	nr	12,8	± 2,2	nr	1037 ± 544	480 ± 408
		3 y	NC	35,7	± 6,7	13,8	± 5,3	nr	nr	18,6	± 6,9	nr	1173 ± 463	532 ± 369
			MC	40,5	± 8,1	16,7	± 2,3	nr	nr	14,5	± 0,7	nr	1037 ± 544	700 ± 707
		5 y	NC	35,7	± 6,7	13,8	± 5,3	nr	nr	19,7	± 5,5	nr	1173 ± 463	1100 ± 219
			MC	40,5	± 8,1	16,7	± 2,3	nr	nr	14,5	± 0,7	nr	1037 ± 544	750 ± 777
LRRK2	Schupbach et al., 2008	8 y	NC	43,4	± 17	10,5	± 9,2	15,7	± 9,9	6,7	± 6,0	64 ± 22	*nr*	*nr*
			MC	41,4	± 12,4	8,2	± 4,6	17,8	± 9,6	6,2	± 3,9	50 ± 36	*nr*	*nr*
LRRK2 G2019S	Angeli et al., 2013	1-5 y	NC	47,6	± 14,8	15,6	± 11,3	24,6	± 11,3	15	± 9	48	1259 ± 559	468 ± 494
			MC	65,4	± 14,9	10,8	± 5,1	30,6	± 16,1	14	± 8,1	53	1317 ± 803	586 ± 495
LRRK2 R1441G	Gomez-Esteban et al., 2008	6 m	NC	42,5	± 10,6	17,2	± 6,1	26,1	± 8,4	16,2	± 7,4	39	*na*	*na*
			MC	48,5	± 18,5	18	± 7,4	39,7	± 17,7	16	± 7,7	18[d]	*na*	*na*
GBA	Angeli et al., 2013	1-5 y	NC	47,6	± 14,8	15,6	± 11,3	24,6	± 11,3	15	± 9	48 (STN); −28 (GPi)	1259 ± 559	468 ± 494
			MC	50,5	± 12,4	18	± 15,4	28	± 11,4	15,9	± 10,4	40 (STN); 22 (GPi); 43 (VIM)	1143 ± 540	146 ± 510
GBA	Lythe et al., 2017	7,5 y	NC	40,5	± 12,0	12,6	± 7,4	na	na	*38,9	± 14,0	na	1392 ± 808	790,4 ± 345,7
			MC	52,4	± 13,0	18,4	± 14,9	na	na	*50,0	± 17,1	na	1296,9 ± 665,2	1024,8 ± 755,3
SNCA variants	Weiss et al., 2016	2 y	NC (wt/wt)	46	± 14,5	nr	nr	nr	nr	nr	nr	12 ± 17,1	*na*	*na*
			MC (wt/var)	49,1	± 17,3	nr	nr	nr	nr	nr	nr	22,9 ± 17[e]	*na*	*na*
			MC (var/var)	45,5	± 18,5	nr	nr	nr	nr	nr	nr	29,1 ± 16[e]	*na*	*na*

MC, mutation carriers; *NC,* non-carriers; *M,* mean; *SD*, standard deviation; *var*, variant; *wt,* wild-type; *STN*, Subthalamic Nucleus; *VIM*, Ventral Intermediate Nucleus; *GPi,* Globus Pallidus Internus *nr*, not reported; *na*, not-assessed; *y*, year(s); *m*, month(s); *FU*, follow-up; *LEDD*, levodopa equivalent daily dose; *UPDRS-III*, Motor Activities section of the Unified Parkinson's Disease Rating Scale; *MDS-UPDRS-III*, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS-III); *the authors used the MDS-UPDRS scale for follow-up assessments; [a]Improvement and significant values are those reported by the authors; [b]UPDR-III improvement was related to ONstim/ON med after DBS *vs* OFF med before DBS; [c]The comparison of four UPDRS-III situations were more significant in MC (P = 0,00005) than in NC (P = 0,0003); [d]Intergroup comparison (P = 0.008), [e] Significant prediction of treatment response (P = 0.03).

to be different depending on which mutation is considered. Patients with G2019S mutations seem to have a satisfactory response, even better than NC patients, while a worse response has been reported in patients with R1441G mutations. It is to clarify whether this different response could be related to the different domain involved (the kinase domain for the G2019S mutation, the Ras of complex proteins – ROC - domain for the R1441G) [58].

No differences were observed on cognitive functions between LRRK2 MC and NC. A satisfactory response after DBS was also reported by case report studies in patients carrying R793 M or Y1699C mutations.

An important limit of these studies is that the pathogenicity has not been solidly established for all LRKK2 variants. LRRK2 G2019S, R1441C/G/H and Y1699C variants are reported to be pathogenic, while the role of the LRRK2 R793 M and T2031S variants is not well established. Other variants such as the G2385R and R1628P seem to be only a risk factor for PD in some population [59].

A particularly satisfactory response to DBS has been reported in SNCA *rs*356220 variant carriers; however, this has been observed in an SNCA variant at a short follow-up [30] and this could represent significant limits, especially given that SNCA variability may modulate the cognitive profile in PD [60].

Only case reports are available regarding other mutations; although no conclusion can be deducted, all the studies reported positive outcomes.

Based on the above findings, the available data do not allow a definitive conclusion on the impact of genotype on the DBS outcome and should be interpreted with great caution, given the numerous limitations.

Firstly, the available information on genetic status is limited to a few PD related genes. Selection criteria have made the cohort of DBS patients a valuable resource to identify the genetic forms of PD because of the inclusion of relatively young patients with a long PD duration, and a relative uniformity of clinical features across the groups. Therefore, such consistency may have introduced a bias in the analysis, as most of the available information so far has been limited to a few genes among those more frequently mutated in PD. Also, the variability in the approaches used across the studies to screen PD-related genes may have significantly influenced the results: the techniques used to analyze genetic alterations were not uniform (full sequencing analysis, MLPA or linkage analysis) (Supplementary Table 1) with some studies investigating only specific mutations in some genes (i.e. G2019S for LRRK2) whereas others assessing several known mutations. Some studies on PRKN MC included in the analysis exclusively patients with homozygous mutations, whereas some others considered heterozygous carriers. There is evidence that individuals with two PRKN mutations have younger AAO than those with only one mutation or without mutations, while it is still unclear whether a mutation in only one allele may increase the risk for PD [61].

Other factors that may confound the results of the studies include widely heterogeneous cohorts with respect to the size, the demographic data and the enrollment criteria of patients; in some studies, patients were selected according to clinical features (age of onset, family history), while in other studies they were not selected. Moreover, most studies were retrospective and based solely on recorded medical data; hence, data may be insufficient to completely evaluate the effects of DBS.

Also the lack of data relative to the different conditions of stimulation and drug intake make it difficult to distinguish between the effects of pharmacological therapy and DBS.

The great variability in the length of follow-up and the lack of data on the long-term effects of DBS represent a further significant limitation of the studies.

Also, it is possible to hypothesize a publication bias linked to the report of only positive outcomes in MC.

Several variables should be considered as possible confounding factors in the assessment of the DBS response of patients with different genetic profiles.

For example, it is known that recessive PD is often associated with early onset of symptoms and with a phenotype characterized by the presence of a few motor symptoms, a slow disease progression and a good response to levodopa [61]; on the other hand, there is evidence that the phenotype of EOPD, with a few non-motor symptoms, is not correlated to genotype but with age at onset [62]. It is therefore difficult to attribute the different response to DBS of EOPD to the genotype rather than to the age of onset of the disease.

Another relevant confounding factor is the intrinsic characteristics of DBS, a complex treatment with a wide possibility of modifying stimulation parameters in order to adapt stimulation to the patient's needs. Different parameter settings may determine different side effects: high intensity stimulations can spread to brain areas near to the target, determining the onset of either motor or non-motor adverse effects, and the clinical effect of the diffusion may be different depending on patient's characteristics. For example, the stimulus spread to associative or limbic areas could worsen cognitive functions in patients already at risk for cognitive impairment (eg., older patients or GBA-PD patients) more than in other patients.

The role of the stimulation parameters is often poorly considered in the studies, but it can be a relevant confounding factor when attempting to analyze the outcome of DBS in patients with different genotype. Moreover, most of the studies referred to the effectiveness of STN-DBS, with the lack of comparison of outcome between different targets in different genetic PD forms.

In conclusion, due to the several limitations in the available data, no definitive conclusion can be drawn yet on the genotype impact on DBS outcome. All the existing evidence is preliminary, and well-designed prospective studies, performed on larger cohorts with longer follow-up and assessing a wider PD gene related panel are needed to reliably decipher genotype related differences in DBS outcome and therefore offer new insights to customize the treatment of PD.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

Contribution to the article

All authors have contributed to the conception and design of the study, the acquisition, the analysis and interpretation of data, the draft of the article and its revising, the final approval of the version submitted.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.08.006.

References

[1] S. Chiken, A. Nambu, Mechanism of deep brain stimulation, Neuroscientist 22 (2016) 313–322, https://doi.org/10.1177/1073858415581986.
[2] G. Deuschl, S. Paschen, K. Witt, Clinical outcome of deep brain stimulation for Parkinson's disease, Handb. Clin. Neurol. 116 (2013) 107–128, https://doi.org/10.1016/B978-0-444-53497-2.00010-3.
[3] M.G. Rizzone, A. Fasano, A. Daniele, M. Zibetti, A. Merola, L. Rizzi, C. Piano, C. Piccininni, L.M. Romito, L. Lopiano, A. Albanese, Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? Park. Relat. Disord. 20 (2014) 376–381, https://doi.org/10.1016/j.parkreldis.2014.01.012.

[4] M. Zibetti, A. Merola, L. Rizzi, V. Ricchi, S. Angrisano, C. Azzaro, C.A. Artusi, N. Arduino, A. Marchisio, M. Lanotte, M. Rizzone, L. Lopiano, Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease, Mov. Disord. 26 (2011) 2327–2334, https://doi.org/10.1002/mds.23903.

[5] A.A. Bari, A. Fasano, R.P. Munhoz, A.M. Lozano, Improving outcomes of subthalamic nucleus deep brain stimulation in Parkinson's disease, Expert Rev. Neurother. 15 (2015) 1151–1160, https://doi.org/10.1586/14737175.2015.1081815.

[6] P. Pollak, Deep brain stimulation for Parkinson's disease - patient selection, Handb. Clin. Neurol. 116 (2013) 97–105, https://doi.org/10.1016/B978-0-444-53497-2.00009-7.

[7] J.M. Bronstein, M. Tagliati, R.L. Alterman, A.M. Lozano, J. Volkmann, A. Stefani, F.B. Horak, M.S. Okun, K.D. Foote, P. Krack, R. Pahwa, J.M. Henderson, M.I. Hariz, R.A. Bakay, A. Rezai, W.J. Marks, E. Moro, J.L. Vitek, F.M. Weaver, R.E. Gross, M.R. DeLong, Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues, Arch. Neurol. 68 (2011) 165, https://doi.org/10.1001/archneurol.2010.260.

[8] A. Nassery, C.A. Palmese, H. Sarva, M. Groves, J. Miravite, B.H. Kopell, Psychiatric and cognitive effects of deep brain stimulation for Parkinson's disease, Curr. Neurol. Neurosci. Rep. 16 (2016) 87, https://doi.org/10.1007/s11910-016-0690-1.

[9] V. Bonifati, Genetics of Parkinson's disease–state of the art, 2013, Park. Relat. Disord. 20 (Suppl 1) (2014) S23–S28, https://doi.org/10.1016/S1353-8020(13)70009-9.

[10] D.G. Hernandez, X. Reed, A.B. Singleton, Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance, J. Neurochem. 139 (Suppl 1) (2016) 59–74, https://doi.org/10.1111/jnc.13593.

[11] S. Lesage, A. Brice, Role of Mendelian genes in "sporadic" Parkinson's disease, Park. Relat. Disord. 18 (2012) S66–S70, https://doi.org/10.1016/S1353-8020(11)70022-0.

[12] H. Deng, P. Wang, J. Jankovic, The genetics of Parkinson disease, Ageing Res. Rev. 42 (2018) 72–85, https://doi.org/10.1016/j.arr.2017.12.007.

[13] C.Y. Kim, R.N. Alcalay, Genetic forms of Parkinson's disease, Semin. Neurol. 37 (2017) 135–146, https://doi.org/10.1055/s-0037-1601567.

[14] C. Koros, A. Simitsi, L. Stefanis, Chapter eight - genetics of Parkinson's disease: genotype–phenotype correlations, in: K.P. Bhatia, K.R. Chaudhuri, M. Stamelou (Eds.), International Review of Neurobiology, Academic Press, 2017, pp. 197–231, , https://doi.org/10.1016/bs.irn.2017.01.009.

[15] E. Lohmann, S. Thobois, S. Lesage, E. Broussolle, S.T. du Montcel, M.-J. Ribeiro, P. Remy, A. Pelissolo, B. Dubois, L. Mallet, P. Pollak, Y. Agid, A. Brice, French Parkinson's Disease Genetics Study Group, A multidisciplinary study of patients with early-onset PD with and without parkin mutations, Neurology 72 (2009) 110–116, https://doi.org/10.1212/01.wnl.0000327098.86861.d4.

[16] R. Balestrino, A.H.V. Schapira, Glucocerebrosidase and Parkinson disease: molecular, clinical, and therapeutic implications, Neuroscientist (2018), https://doi.org/10.1177/1073858417748875.

[17] A. Puschmann, Monogenic Parkinson's disease and parkinsonism: clinical phenotypes and frequencies of known mutations, Park. Relat. Disord. 19 (2013) 407–415, https://doi.org/10.1016/j.parkreldis.2013.01.020.

[18] G.D. Pal, D. Hall, B. Ouyang, J. Phelps, R. Alcalay, M.W. Pauciulo, W.C. Nichols, L. Clark, H. Mejia-Santana, L. Blasucci, C.G. Goetz, C. Comella, A. Colcher, Z. Gan-Or, G.A. Rouleau, K. Marder, Consortium on risk for early onset Parkinson's disease (CORE-PD) investigators, genetic and clinical predictors of deep brain stimulation in young-onset Parkinson's disease, Mov Disord Clin Pract 3 (2016) 465–471, https://doi.org/10.1002/mdc3.12309.

[19] A. Angeli, N.E. Mencacci, R. Duran, I. Aviles-Olmos, Z. Kefalopoulou, J. Candelario, S. Rusbridge, J. Foley, P. Pradhan, M. Jahanshahi, L. Zrinzo, M. Hariz, N.W. Wood, J. Hardy, P. Limousin, T. Foltynie, Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation: Angeli et al, Mov. Disord. 28 (2013) 1370–1375, https://doi.org/10.1002/mds.25535.

[20] J.C. Gómez-Esteban, E. Lezcano, J.J. Zarranz, C. González, G. Bilbao, I. Lambarri, O. Rodríguez, J. Garibi, Outcome of bilateral deep brain subthalamic stimulation in patients carrying the R1441G mutation in the LRRK2 dardarin gene, Neurosurgery 62 (2008) 857–863.

[21] L. Greenbaum, S.D. Israeli-Korn, O.S. Cohen, S. Elincx-Benizri, G. Yahalom, E. Kozlova, H. Strauss, N. Molshatzki, R. Inzelberg, R. Spiegelmann, Z. Israel, S. Hassin-Baer, The LRRK2 G2019S mutation status does not affect the outcome of subthalamic stimulation in patients with Parkinson's disease, Park. Relat. Disord. 19 (2013) 1053–1056, https://doi.org/10.1016/j.parkreldis.2013.07.005.

[22] K.K. Johansen, J.V. Jørgensen, L.R. White, M.J. Farrer, J.O. Aasly, Parkinson-related genetics in patients treated with deep brain stimulation, Acta Neurol. Scand. 123 (2011) 201–206, https://doi.org/10.1111/j.1600-0404.2010.01387.x.

[23] H.J. Kim, J.Y. Yun, Y.-E. Kim, J.-Y. Lee, H.-J. Kim, J.-Y. Kim, S.S. Park, S.H. Paek, B.S. Jeon, Parkin mutation and deep brain stimulation outcome, J. Clin. Neurosci. 21 (2014) 107–110, https://doi.org/10.1016/j.jocn.2013.03.026.

[24] E. Lohmann, M.-L. Welter, V. Fraix, P. Krack, S. Lesage, S. Laine, M.-L. Tanguy, J.-L. Houeto, V. Mesnage, P. Pollak, Alexandra Durr, Y. Agid, A. Brice, French Parkinson's Disease Genetics study group, Are parkin patients particularly suited for deep-brain stimulation? Mov. Disord. 23 (2008) 740–743, https://doi.org/10.1002/mds.21903.

[25] V. Lythe, D. Athauda, J. Foley, N.E. Mencacci, M. Jahanshahi, L. Cipolotti, J. Hyam, L. Zrinzo, M. Hariz, J. Hardy, P. Limousin, T. Foltynie, GBA-associated Parkinson's disease: progression in a deep brain stimulation cohort, J. Parkinson's Dis. (2017), https://doi.org/10.3233/JPD-171172.

[26] E. Moro, J. Volkmann, I.R. König, S. Winkler, A. Hiller, S. Hassin-Baer, J. Herzog, A. Schnitzler, K. Lohmann, M.O. Pinsker, J. Voges, A. Djarmatic, P. Seibler, A.M. Lozano, E. Rogaeva, A.E. Lang, G. Deuschl, C. Klein, Bilateral subthalamic stimulation in Parkin and PINK1 parkinsonism, Neurology 70 (2008) 1186–1191, https://doi.org/10.1212/01.wnl.0000307748.11216.03.

[27] L.M.A. Romito, M.F. Contarino, D. Ghezzi, A. Franzini, B. Garavaglia, A. Albanese, High frequency stimulation of the subthalamic nucleus is efficacious in Parkin disease, J. Neurol. 252 (2005) 208–211, https://doi.org/10.1007/s00415-005-0638-x.

[28] M. Sayad, M. Zouambia, M. Chaouch, F. Ferrat, M. Nebbal, M. Bendini, S. Lesage, A. Brice, M. Brahim Errahmani, B. Asselah, Greater improvement in LRRK2 G2019S patients undergoing Subthalamic Nucleus Deep Brain Stimulation compared to non-mutation carriers, BMC Neurosci. 17 (2016) 6, https://doi.org/10.1186/s12868-016-0240-4.

[29] M. Schüpbach, E. Lohmann, M. Anheim, S. Lesage, V. Czernecki, S. Yaici, Y. Worbe, P. Charles, M.-L. Welter, P. Pollak, A. Dürr, Y. Agid, A. Brice, Subthalamic nucleus stimulation is efficacious in patients with Parkinsonism and LRRK2 mutations, Mov. Disord. 22 (2007) 119–122, https://doi.org/10.1002/mds.21178.

[30] D. Weiss, S. Herrmann, L. Wang, C. Schulte, K. Brockmann, C. Plewnia, T. Gasser, M. Sharma, A. Gharabaghi, R. Krüger, Alpha-synuclein gene variants may predict neurostimulation outcome, Mov. Disord. 31 (2016) 601–603, https://doi.org/10.1002/mds.26558.

[31] A. Antonini, M. Pilleri, A. Padoan, A. Landi, S. Ferla, R. Biundo, D. D'Avella, Successful subthalamic stimulation in genetic Parkinson's disease caused by duplication of the α-synuclein gene, J. Neurol. 259 (2012) 165–167, https://doi.org/10.1007/s00415-011-6162-2.

[32] L. Borellini, F. Cogiamanian, G. Carrabba, M. Locatelli, P. Rampini, A. Di Fonzo, C. Bana, S. Barbieri, G. Ardolino, Globus pallidus internus deep brain stimulation in PINK-1 related Parkinson's disease: a case report, Park. Relat. Disord. 38 (2017) 93–94, https://doi.org/10.1016/j.parkreldis.2017.02.018.

[33] S. Breit, T. Wächter, D. Schmid-Bielenberg, D. Weiss, P. Leitner, T. Nägele, D. Freudenstein, T. Gasser, R. Krüger, Effective long-term subthalamic stimulation in PARK8 positive Parkinson's disease, J. Neurol. 257 (2010) 1205–1207, https://doi.org/10.1007/s00415-010-5493-8.

[34] M. Capecci, L. Passamonti, F. Annesi, G. Annesi, M. Bellesi, I.C.C. Candiano, R. Ricciuti, M. Iacoangeli, M. Scerrati, M. Zappia, P. Tarantino, E.V. De Marco, D. Civitelli, S. Carrideo, L. Provinciali, M.G. Ceravolo, A. Quattrone, Chronic bilateral subthalamic deep brain stimulation in a patient with homozygous deletion in the parkin gene, Mov. Disord. 19 (2004) 1450–1452, https://doi.org/10.1002/mds.20250.

[35] Y.-F. Chen, Y.-Y. Chang, M.-Y. Lan, P.-L. Chen, C.-H. Lin, Identification of VPS35 p.D620N mutation-related Parkinson's disease in a Taiwanese family with successful bilateral subthalamic nucleus deep brain stimulation: a case report and literature review, BMC Neurol. 17 (2017) 191, https://doi.org/10.1186/s12883-017-0972-5.

[36] T. Danaila, G. Polo, H. Klinger, E. Broussolle, P. Mertens, S. Lesage, A. Brice, S. Thobois, Efficacy of subthalamic nucleus stimulation in C9ORF72 expansion related parkinsonism, Park. Relat. Disord. 20 (2014) 1104–1105, https://doi.org/10.1016/j.parkreldis.2014.07.010.

[37] V. Fleury, C. Wider, J. Horvath, A. Zacharia, J. Bally, P. Pollak, C. Pollo, F.J.G. Vingerhoets, P.R. Burkhard, Successful long-term bilateral subthalamic nucleus deep brain stimulation in VPS35 Parkinson's disease, Park. Relat. Disord. 19 (2013) 707–708, https://doi.org/10.1016/j.parkreldis.2013.04.002.

[38] G. Genç, H. Apaydın, A. Gündüz, Ç. Poyraz, S. Oğuz, S. Yağcı, H. Canaz, S. Aydın, A. Gündoğdu-Eken, A.N. Başak, S. Ertan, Successful treatment of Juvenile parkinsonism with bilateral subthalamic deep brain stimulation in a 14-year-old patient with parkin gene mutation, Park. Relat. Disord. 24 (2016) 137–138, https://doi.org/10.1016/j.parkreldis.2016.01.018.

[39] R. Lefaucheur, S. Derrey, L. Guyant-Maréchal, N. Chastan, D. Maltête, Whatever the disease duration, stimulation of the subthalamic nucleus improves Parkin disease, Park. Relat. Disord. 16 (2010) 482–483, https://doi.org/10.1016/j.parkreldis.2010.04.013.

[40] K. Nakahara, M. Ueda, K. Yamada, T. Koide, G. Yoshimochi, M. Funayama, J.-H. Kim, S. Yamakawa, A. Mori, Y. Misumi, E. Uyama, N. Hattori, Y. Ando, Juvenile-onset parkinsonism with digenic parkin and PINK1 mutations treated with subthalamic nucleus stimulation at 45 years after disease onset, J. Neurol. Sci. 345 (2014) 276–277, https://doi.org/10.1016/j.jns.2014.07.053.

[41] C. Perandones, N. Aráoz Olivos, G.B. Raina, L.A. Pellene, J.C. Giugni, D.S. Calvo, M. Radrizzani, F. Piedimonte, F.E. Micheli, Successful GPi stimulation in genetic Parkinson's disease caused by mosaicism of alpha-synuclein gene duplication: first description, J. Neurol. 262 (2015) 222–223, https://doi.org/10.1007/s00415-014-7576-4.

[42] L.D. Perju-Dumbrava, M. McDonald, A.C. Kneebone, R. Long, D. Thyagarajan, Sustained response to deep brain stimulation in LRRK2 parkinsonism with the Y1699C mutation, J. Parkinson's Dis. 2 (2012) 269–271, https://doi.org/10.3233/JPD-012121.

[43] Y. Shimo, S. Natori, G. Oyama, M. Nakajima, H. Ishii, H. Arai, N. Hattori, Subthalamic deep brain stimulation for a Parkinson's disease patient with duplication of SNCA, Neuromodulation 17 (2014) 102–103, https://doi.org/10.1111/ner.12034.

[44] A. Stefani, F. Marzetti, M. Pierantozzi, S. Petrucci, E. Olivola, S. Galati, M.S. Bassi, P. Imbriani, E.M. Valente, F.S. Pastore, Successful subthalamic stimulation, but levodopa-induced dystonia, in a genetic Parkinson's disease, Neurol. Sci. 34 (2013) 383–386, https://doi.org/10.1007/s10072-012-1014-0.

[45] D. Weiss, K. Brockmann, K. Srulijes, C. Meisner, R. Klotz, S. Reinbold, A.-K. Hauser, C. Schulte, D. Berg, T. Gasser, C. Plewnia, A. Gharabaghi, S. Breit, T. Wächter, R. Krüger, Long-term follow-up of subthalamic nucleus stimulation in glucocerebrosidase-associated Parkinson's disease, J. Neurol. 259 (2012) 1970–1972, https://doi.org/10.1007/s00415-012-6469-7.

[46] B. Dufournet, K. Nguyen, P. Charles, D. Grabli, A. Jacquette, M. Borg, T. Danaila, E. Mutez, S. Drapier, O. Colin, A. Eusebio, N. Philip, J.P. Azulay, Parkinson's disease associated with 22q11.2 deletion: clinical characteristics and response to treatment, Rev. Neurol. (Paris) 173 (2017) 406–410, https://doi.org/10.1016/j.neurol.2017.03.021.

[47] Y. Hatano, Y. Li, K. Sato, S. Asakawa, Y. Yamamura, H. Tomiyama, H. Yoshino, M. Asahina, S. Kobayashi, S. Hassin-Baer, C.-S. Lu, A.R. Ng, R.L. Rosales, N. Shimizu, T. Toda, Y. Mizuno, N. Hattori, Novel PINK1 mutations in early-onset parkinsonism, Ann. Neurol. 56 (2004) 424–427, https://doi.org/10.1002/ana.20251.

[48] A.J. Thompson, S.W. Scholz, A.B. Singleton, A. Hardwick, N.R. McFarland, M.S. Okun, Variability in clinical phenotypes of heterozygous and homozygous cases of Parkin-related Parkinson's disease, Int. J. Neurosci. 123 (2013) 847–849, https://doi.org/10.3109/00207454.2013.810626.

[49] T. Hatano, M. Funayama, S.-I. Kubo, I.F. Mata, Y. Oji, A. Mori, C.P. Zabetian, S.M. Waldherr, H. Yoshino, G. Oyama, Y. Shimo, K.-I. Fujimoto, H. Oshima, Y. Kunii, H. Yabe, Y. Mizuno, N. Hattori, Identification of a Japanese family with LRRK2 p.R1441G-related Parkinson's disease, Neurobiol. Aging 35 (2014), https://doi.org/10.1016/j.neurobiolaging.2014.05.025 2656.e17-2656.e23.

[50] G. Deuschl, C. Schade-Brittinger, P. Krack, J. Volkmann, H. Schäfer, K. Bötzel, C. Daniels, A. Deutschländer, U. Dillmann, W. Eisner, D. Gruber, W. Hamel, J. Herzog, R. Hilker, S. Klebe, M. Kloss, J. Koy, M. Krause, A. Kupsch, D. Lorenz, S. Lorenzl, H.M. Mehdorn, J.R. Moringlane, W. Oertel, M.O. Pinsker, H. Reichmann, A. Reuss, G.-H. Schneider, A. Schnitzler, U. Steude, V. Sturm, L. Timmermann, V. Tronnier, T. Trottenberg, L. Wojtecki, E. Wolf, W. Poewe, J. Voges, German Parkinson Study Group, Neurostimulation Section, A randomized trial of deep-brain stimulation for Parkinson's disease, N. Engl. J. Med. 355 (2006) 896–908, https://doi.org/10.1056/NEJMoa060281.

[51] P. Krack, A. Batir, N. Van Blercom, S. Chabardes, V. Fraix, C. Ardouin, A. Koudsie, P.D. Limousin, A. Benazzouz, J.F. LeBas, others, Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease, N. Engl. J. Med. 349 (2003) 1925–1934.

[52] M.C. Rodriguez-Oroz, J.A. Obeso, A.E. Lang, J.-L. Houeto, P. Pollak, S. Rehncrona, J. Kulisevsky, A. Albanese, J. Volkmann, M.I. Hariz, N.P. Quinn, J.D. Speelman, J. Guridi, I. Zamarbide, A. Gironell, J. Molet, B. Pascual-Sedano, B. Pidoux, A.M. Bonnet, Y. Agid, J. Xie, A.-L. Benabid, A.M. Lozano, J. Saint-Cyr, L. Romito, M.F. Contarino, M. Scerrati, V. Fraix, N. Van Blercom, Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up, Brain 128 (2005) 2240–2249, https://doi.org/10.1093/brain/awh571.

[53] J. Volkmann, A. Albanese, J. Kulisevsky, A.-L. Tornqvist, J.-L. Houeto, B. Pidoux, A.-M. Bonnet, A. Mendes, A.-L. Benabid, V. Fraix, N. Van Blercom, J. Xie, J. Obeso, M.C. Rodriguez-Oroz, J. Guridi, A. Schnitzler, L. Timmermann, A.A. Gironell, J. Molet, B. Pascual-Sedano, S. Rehncrona, E. Moro, A.C. Lang, A.M. Lozano, A.R. Bentivoglio, M. Scerrati, M.F. Contarino, L. Romito, M. Janssens, Y. Agid, Long-term effects of pallidal or subthalamic deep brain stimulation on quality of life in Parkinson's disease, Mov. Disord. 24 (2009) 1154–1161, https://doi.org/10.1002/mds.22496.

[54] A. Castrioto, A.M. Lozano, Y.-Y. Poon, A.E. Lang, M. Fallis, E. Moro, Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation, Arch. Neurol. 68 (2011) 1550–1556, https://doi.org/10.1001/archneurol.2011.182.

[55] A. Fasano, L.M. Romito, A. Daniele, C. Piano, M. Zinno, A.R. Bentivoglio, A. Albanese, Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants, Brain 133 (2010) 2664–2676, https://doi.org/10.1093/brain/awq221.

[56] A. Ramirez-Zamora, J.L. Ostrem, Globus pallidus interna or subthalamic nucleus deep brain stimulation for Parkinson disease: a review, JAMA Neurol (2018), https://doi.org/10.1001/jamaneurol.2017.4321.

[57] R. Cilia, S. Tunesi, G. Marotta, E. Cereda, C. Siri PsyD, S. Tesei, A. Zecchinelli, M. Canesi, C.B. Mariani, N. Meucci, G. Sacilotto, M. Zini, M. Barichella, C. Magnani, S. Duga, R. Asselta, G. Soldà, A. Seresini, M. Seia, G. Pezzoli, S. Goldwurm, Survival and dementia in GBA-associated Parkinson Disease: the mutation matters, Ann. Neurol. (2016), https://doi.org/10.1002/ana.24777.

[58] C. Paisán-Ruiz, LRRK2 gene variation and its contribution to Parkinson disease, Hum. Mutat. 30 (2009) 1153–1160, https://doi.org/10.1002/humu.21038.

[59] K. Nuytemans, J. Theuns, M. Cruts, C. Van Broeckhoven, Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update, Hum. Mutat. 31 (2010) 763–780, https://doi.org/10.1002/humu.21277.

[60] E.S. Fagan, L. Pihlstrøm, Genetic risk factors for cognitive decline in Parkinson's disease: a review of the literature, Eur. J. Neurol. 24 (2017), https://doi.org/10.1111/ene.13258 561-e20.

[61] A. Grünewald, M. Kasten, A. Ziegler, C. Klein, Next-generation phenotyping using the parkin example: time to catch up with genetics, JAMA Neurol 70 (2013) 1186–1191, https://doi.org/10.1001/jamaneurol.2013.488.

[62] E. Lohmann, M. Periquet, V. Bonifati, N.W. Wood, G. De Michele, A.-M. Bonnet, V. Fraix, E. Broussolle, M.W.I.M. Horstink, M. Vidailhet, P. Verpillat, T. Gasser, D. Nicholl, H. Teive, S. Raskin, O. Rascol, A. Destée, M. Ruberg, F. Gasparini, G. Meco, Y. Agid, A. Durr, A. Brice, French Parkinson's disease genetics study group, European consortium on genetic susceptibility in Parkinson's disease, how much phenotypic variation can be attributed to parkin genotype? Ann. Neurol. 54 (2003) 176–185, https://doi.org/10.1002/ana.10613.