Deep brain stimulation for monogenic Parkinson’s disease: a systematic review

Tomi Kuusimäki1,2* · Jaana Korpela1,2 · Eero Pekkonen3,4 · Mika H. Martikainen1,2 · Angelo Antonini5 · Valtteri Kaasinen1,2

Abstract
Deep brain stimulation (DBS) is an effective treatment for Parkinson’s disease (PD) patients with motor fluctuations and dyskinesias. The key DBS efficacy studies were performed in PD patients with unknown genotypes; however, given the estimated monogenic mutation prevalence of approximately 5–10%, most commonly LRRK2, PRKN, PINK1 and SNCA, and risk-increasing genetic factors such as GBA, proper characterization is becoming increasingly relevant. We performed a systematic review of 46 studies that reported DBS effects in 221 genetic PD patients. The results suggest that monogenic PD patients have variable DBS benefit depending on the mutated gene. Outcome appears excellent in patients with the most common LRRK2 mutation, p.G2019S, and good in patients with PRKN mutations but poor in patients with the more rare LRRK2 p.R1441G mutation. The overall benefit of DBS in SNCA, GBA and LRRK2 p.T2031S mutations may be compromised due to rapid progression of cognitive and neuropsychiatric symptoms. In the presence of other mutations, the motor changes in DBS-treated monogenic PD patients appear comparable to those of the general PD population.

Keywords Parkinson’s disease · Monogenic · Genetic · Deep brain stimulation

Introduction
Deep brain stimulation (DBS) provides symptomatic motor benefit for patients with advanced Parkinson’s disease (PD) [1–4]. The benefit of symptom control through DBS surpasses that of optimal medical treatment in patients with motor fluctuations and dyskinesias, and it is a relatively safe treatment option for motor complications of idiopathic PD [1–5]. DBS is often performed in relatively early-onset PD, a population in which it has been estimated that at least 5–10% of cases are not sporadic, but may carry genetic mutations [6, 7]. Genetic cases often are phenotypically different compared to sporadic patients, and this factor may influence clinical outcome [6, 8].

Though DBS has demonstrated efficacy, randomized studies have been performed in PD patients without genetic characterization raising questions of suitability of various monogenic forms and their relevance in DBS outcome. It is known that medication effects may vary between different mutations. For example, patients with PRKN mutations generally are particularly prone to levodopa-induced dyskinesias, whereas patients with LRRK2 mutations tend to show a normal sustained benefit for levodopa [8–11]. The effects of other antiparkinsonian drugs, such as rasagiline, may also be modulated by the genotype [12]. Given the variability in medication effects, it is conceivable that there are also differences in the treatment response to DBS in advanced monogenic PD. There are several case reports and small case series of DBS outcomes in patients with genetic
PD, but due to a lack of information synthesis, we performed a systematic review on the effects of DBS in genetic PD.

**Methods**

**Search strategy**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed [13]. We performed a PubMed search from inception to June 26, 2018 with keywords “deep brain stimulation or DBS”, “Parkinson’s or Parkinson or Parkinsonism” and “genetic or gene or GBA or PRKN or PARKIN or LRRK2 or SNCA or PINK1 or VPS35 or DJ-1 or UCHL1 or GIGYF2 or HTRA2 or TMEM230 or CHCHD2 or RIC3 or ATP13A2 or PLA2G6 or FBX07 or SYNJ1 or VPS13C or DNAJC6”. All original English language articles concerning genetic PD patients treated with DBS were included. Animal studies and review articles were excluded.

The initial search identified 220 articles, and we included an additional 16 relevant studies found in the manual search of reference lists (Fig. 1). All abstracts of these studies were screened, and 184 studies were excluded in the first round (no monogenic PD patients or not treated with DBS \( n = 64 \), review or commentary article \( n = 92 \), animal study \( n = 28 \)). The remaining 52 studies were assessed fully for eligibility and six more studies were excluded in the second round (genetic test negative \( n = 2 \), no genetic testing \( n = 1 \), review or commentary article \( n = 3 \)). Finally, 46 studies of these
236 studies met all selection criteria and were included in the systematic review (Table 1). A summary of the included studies is presented in Table 2. The included studies reported 221 genetic PD patients who were treated with DBS. However, two studies reported partially the same patients [14, 15].

**Specific aims**

This review of evidence aimed to systematically investigate DBS outcome in monogenic PD compared to the general PD population. The primary aim was to evaluate the motor benefit of the DBS operation in each monogenic PD type. An additional aim was to evaluate effects on non-motor symptoms, including possible cognitive and neuropsychiatric symptoms.

**Selection criteria**

Search terms and the PubMed search were planned by two authors (T.K. and V.K.). All titles and abstracts were reviewed by one investigator (T.K.). Studies were excluded if the title and/or abstract were not suitable for the aim of the review. Full texts were obtained for appropriate studies or if the relevance of an article was uncertain. The inclusion criteria for the selected studies were as follows: (1) a human study, (2) genetic PD patients treated with DBS, and (3) English language. The data extracted from each study were study year, first author’s family name, number of patients, mutated gene, specific mutation, patient age at disease onset and DBS implantation, target nucleus of DBS, more specific lead positioning, pre- and postoperative UPDRS-III scores, follow-up time and outcome (Table 1). UPDRS-III scores of control cohort’s (mutation non-carriers, NC) are also reported in Table 1 if the information was available. In the outcome evaluation, an improvement of 30% or more in the UPDRS-III motor score was considered to indicate favourable outcome; 20–30%, moderate outcome; and < 20%, poor/mild outcome [58–60].

**Quality control**

The quality of the included studies was evaluated according to the Newcastle-Ottawa Scale (NOS) [61]. NOS includes selection, comparability, and exposure or outcome. The scale ranged from 0 to 11 stars, with the highest rating representing the greatest quality. Six months or more was a limit for the adequate follow-up time. Pre- and postoperative evaluation was thought to be accomplished if the outcome was reported properly with percentage improvement of the UPDRS-III score or verbally. A total score of 0–3 was considered to indicate to poor quality; 4–7, moderate quality; and 8–11, good quality. The NOS total score is presented in Table 1 and the scale is presented more accurately in Supplementary Table 1. A summary of the assessed quality of the studies is presented in Supplementary Table 2.

**Results**

A summary of the primary results is presented in Table 2. Altogether, 46 studies and 221 monogenic PD patients treated with DBS were included in the systematic review (Table 1).

**LRRK2**

Seventeen studies [9, 15–30] reported 87 patients (target: subthalamic nucleus (STN) n = 79, not available (NA) n = 8). The outcome was reported in 73 patients (83.9% of patients); with percentage improvement of the UPDRS-III score in 49 patients and verbally in 24 patients. The motor outcome was mostly favourable in patients with LRRK2 mutation. Only five studies with ten patients reported poor/mild/moderate outcomes. Both patients with the p.T2031S (c.6091A > T) mutation (n = 2) developed neuropsychiatric problems 5–7 years after implantation. The outcome appeared poor in patients with p.R1441G (c.4321C > G) mutations whereas it appeared excellent in patients with p.G2019S (c.6055G > A) mutations.

**PRKN**

Eighteen studies [11, 15, 16, 19, 21, 31–43] reported 67 patients (STN n = 51, globus pallidus interna (GPi) n = 5, zona incerta n = 1, NA n = 10). The outcome was reported in 57 patients (85.1%); UPDRS-III percentage improvement was reported in 45 patients and the outcome was described verbally in 12 patients. Fifty-one patients (76.1%) had favourable long-term motor outcomes. Six patients in three different studies were reported to have modest or poor outcomes.

**GBA**

Five studies [14, 15, 19, 44, 45] reported 50 patients (STN n = 33, GPi n = 4, ventral intermediate nucleus (VIM) n = 1, NA n = 12). Samples partially consisted of same patients in two studies [14, 15]. The outcome was reported in 30 patients (60.0%); UPDRS-III percentage improvement in 28 patients and the outcome was described verbally in 2 patients. Eighteen patients were reported to have favourable, three patients moderate and nine patients poor long-term motor outcomes. One study reported better outcomes with STN-DBS and VIM-DBS than with GPi-DBS.
| Study              | N   | Gene  | Mutation\(^b\)          | AAO\(^a\) | AAD\(^a\) | Target\(^a\) | LP   | PRE-UPDRS III\(^a\) | POST-UPDRS III\(^a\) | %\(^b\) | FU  | NOS | Outcome |
|--------------------|-----|-------|--------------------------|-----------|-----------|-------------|------|---------------------|----------------------|--------|-----|-----|---------|
| Healy et al. [9]   | 18  | LRRK2 | p.G2019S                 | NA        | NA\(^a\)  | STN         | NA   | NA                  | NA                  | NA     | NA  | 4   | Good or excellent 
|                   |     |       |                          |           |           |             |      |                     |                      |        |      |     | (n=8), moderate (n=2) and NA (n=6) |
| Sayad et al. [16]  | 15  | LRRK2 | p.G2019S                 | 40.1±9.4  | NA        | STN bilat.  | +   | 55.8±16.4 M–, 25.0±13.2 M+ (NC: 51.7±14.4 M–) | 27.3±20.6 M–S+, 19.7±18.8 M+S+ (NC: 38.5±16.6 M–S+) | 51.1 (NC: 25.5) | 2   | 10  | Favourable and better outcome compared to patients without mutation |
| Greenbaum et al. [17] | 13  | LRRK2 | p.G2019S                 | 49.5±6.8  | 61.1±6.6  | STN bilat.  | +   | 42.5±11.8 M–, 19.5±13 M+ (NC: 43.4±12.3 M–) | Short FU 28.5±13.1 M–S+, 17.4±12.9 M+S+ (NC: Short FU 30.5±12.8 M–S+, 21.2±9.2 M+S+ (NC: Short FU 27.2±14.1 M–S+, Long FU 33.9±16.1 M–S+) | 50±36 (NC: 64) | 9–10 | 10  | Favourable and comparable to patients without mutations. One patient reported new/worse psychiatric symptoms after 5 years |
| Schüpbach et al. [18] | 9   | LRRK2 | p.G2019S (n=7) p.G2019S + het. PRKN mutation (n=1), p.T2031S (n=1) | 33–48     | 38–65     | STN bilat.  | NA  | 41.4±12.4 M–, 8.2±4.6 M+ (NC: 43.4±17.0 M–) | 47.7±13.1 M–S–, 17.8±9.6 M–S+, 11.8±4.5 M+S–, 6.2±3.9 M+S+ (NC: 15.7±9.0) | 53 (NC: 48) | 1–5 | 9   | Favourable and comparable to patients without mutations. No reported cognitive problems |
| Pal et al. [19]    | 5   | LRRK2 | NA                       | 47.5±11.0 | 60.8±9.0  | NA          | NA   | 30.8±11.7 M+S+ (n=4) | NA                  | 3.5±2.4 (n=4) | 6   | 9   | The outcome is not reported. Clinical data before DBS is not available, but UPDRS III score was higher in LRRK2 -patients compared to patients without mutations at follow-up |
| Angeli et al. [15] | 5   | LRRK2 | p.G2019S (n=4), p.G2019S + GBA-E326K (n=1) | 35–55     | NA\(^b\)  | STN         | NA   | 65.4±14.9 M–, 10.8±5.1 M+ (NC: 47.6±14.8 M–) | 69.2±21.4 M–S–, 30.6±16.1 M–S+ (24.6±11.3 M–S+) | 53 (NC: 48) | 1–5 | 9   | Favourable and comparable to patients without mutations. No reported cognitive problems |
| Gómez-Esteban et al. [20] | 4   | LRRK2 | p.R1441G                 | 29–55     | 41–65     | STN bilat.  | +   | 48.5±18.5 M–, 18.0±7.6 M+ (NC: 42.5±10.6 M–) | 39.7±17.7 M–S+, 16.0±7.7 M+S+ (NC: 26.1±6.4 M–S+) | 18 (NC: 39) | 0.5 | 10  | Poorer response compared to patients without mutation |
| Johansen et al. [21] | 3   | LRRK2 | p.G2019S                 | 43–57     | 50–69     | STN bilat.  | +   | NA for individual genes (NC: 35.7±6.7 M–) | NA for individual genes (NC: 19.7±5.5 M–S+) | NA (NC: 44.8) | 5   | 9   | Favourable and comparable to patients without mutations |
| Study                | N  | Gene     | Mutationa | AAOa | AADa | Targeta | LP   | PRE-UPDRS IIIa | POST-UPDRS IIIa | %b  | FU  | NOS | Outcome                                                                 |
|---------------------|----|----------|-----------|------|------|---------|------|----------------|-----------------|-----|-----|-----|--------------------------------------------------------------------------|
| Lesage et al. [22]  | 3  | LRRK2    | p.G2019S (n = 2), p.T2031S (n = 1) | 34–45 | 41–66 | STN     | NA  | 14 M+ (n = 1), NA (n = 2) | 27 M–S+ (n = 1), 17 M–S+ and 32 M–S– (n = 1) | NA  | 7   | 9   | Favourable to motor symptoms, but depression and psychosis in the patient with p.T2031S mutation for one patient |
| Gaig et al. [23]    | 3  | LRRK2    | p.G2019S | 33–62 | NA   | STN bilat. | NA | NA | NA | NA | NA | 5 | Favourable to motor symptoms |
| Goldwarm et al. [24] | 3  | LRRK2    | p.G2019S | NA | NA | NA | NA | NA | NA | NA | NA | 2 | NA |
| Hatano et al. [25]  | 1  | LRRK2    | p.R1441G and p.G2385R | 28 | 39 | STN bilat. | + | NA | NA | NA | 2 | 7 | Poor motor response with severe psychiatric problems at 1 year after operation |
| Stefani et al. [26] | 1  | LRRK2    | Het. p.G2019S | 49 | 56 | STN bilat. | + | 27 M–, 12 M+ | 25 M–S–, 8 M–S+, 5 M+ | 70.4 | 0.25 | 8 | Favourable outcome |
| Puschmann et al. [27] | 1  | LRRK2    | p.N1437H(c.-4309A>C) | 50 | 69 | STN bilat. | + | NA | 65 M–S+ | NA | 0.5 | 8 | Poor motor outcome. Patient had also severe depression and suicidality and she finally committed suicide 6.5 months after DBS implantation |
| Perju-Dumprava et al. [28] | 1  | LRRK2    | p.Y1699C | 43 | 48 | STN bilat. | NA | 54 M–, 32 M+ | 26 M–S+, 15 M+S+ | 52 M–, 53 M+ | 2.5 | 10 | Favourable outcome. No changes in neuropsychological test parameters 6 months postoperatively |
| Briët et al. [29]   | 1  | LRRK2    | p.R793M | 42 | 60 | STN bilat. | NA | NA | NA | 64 (1 year), 56 (8 year) | 8 | 8 | Favourable outcome |
| Aasly et al. [30]   | 1  | LRRK2    | p.Asn1437His | NA | NA | STN | NA | NA | NA | NA | NA | 4 | Favourable outcome |
| Lohmann et al. [31] | 14 | PRKN     | One mutation: ex6hetdupl, ex6hetdel, Arg256Cyshet [n = 2], Ala398Thrhet, ex7hetdupl, and ex3hetdel; Hom. or compound het.: ex5hetdel—c.255delAhet, ex3hetdel—prom-ex1hetdel, ex2–4hetdupl—ex3hetdel, Cys289Glyhom, ex3hetdel—Cys441Arghet, ex2hetdel—ex3hetdel and ex4–7hetdel—IVS7-1GC | 14–52 | 32–67 | STN | NA | One mutation | 54.3 ± 13.9 M–, 11.6 ± 12.7 M+ | Two mutations | 55.4 ± 17.3 M–, 14.5 ± 10 M+ (NC: 51.9 ± 18.3 M–) | One mutation | 38.4 ± 16.8 M–S–, 12.7 ± 11.2 M+S–, 17.8 ± 11.2 M–S+, 10.8 ± 10.1 M+S+ | Two mutations | 47.7 ± 12.8 M–S–, 17 ± 10.9 M–S+, 14.5 ± 12.5 M–S+, 9.3 ± 8.6 M+S+ (NC: 17.9 ± 15.1 M–S+) | One mutation | 69 ± 15 Two mutations | 77 ± 14 (MC: 65.5) | 1–2 except 3 years for one patient with two PRKN mutations | 10 | Motor response was favourable and comparable to patients without mutations, but more cognitive problems in homozygous and compound heterozygous patients compared to patients without mutations |
| Study           | N  | Gene | Mutationa | AAOa | AADa | Targeta | LP | PRE-UPDRS IIIa | POST-UPDRS IIIa | %b | FU | NOS | Outcome                                      |
|-----------------|----|------|-----------|------|------|---------|----|----------------|-----------------|----|----|-----|-----------------------------------------------|
| Moro et al.     | 11 | PRKN | One mutation: delEx6, dupEx5, 867C > T, 1306G > C, delEx5-12, Hom. or compound het.: 203delA [n = 2], delEx3-4, delEx3 + 142-3delGA, delEx2-5 + dupEx8, delEx7-9 | 15–40 | 31–66 | STN bilat. | NA | 35–66 (MV = 49.5) | NA               | Short FU | 36 | Long FU | 42 (NC: Short FU 56, Long FU 44) | Favourable and comparable to patients without mutations in long-term follow-up |
| Pal et al.      | 10 | PRKN | NA        | 30.6± 9.1 | 47.0± 11.5 | NA      | NA | 33.8± 20.5M+S+ (n = 6) | NA               | NA | 4.0± 4.2 | 6 | The outcome is not reported. Clinical data before DBS is not available but UPDRS III score was higher in PRKN-patients compared to patients without mutations at follow-up |
| Angeli et al.   | 5  | PRKN | Hom.: c.101_102delAG, c.1209G > A p.G403D and c.823C > T, p.Arg275Trp, c.337_376del and c.465–466del, Hom. deletion of exon 3 and 4, c.823C > T, p.Arg275Trp and het. duplication of exon 6 | 7–36 | NA | GPi (n = 3), STN' (n = 2) | All | 57.0± 11.2 M−, 21.0± 6.4 M+ (GPi) | 43.3± 16.4 M−S− 25.3± 17.6 M+S+ | GPi | 43.3± 16.4 M−S− 25.3± 17.6 M+S+ | 21 | STN | 31 (NC: STN: 48, GPi: − 28) | Good to motor symptoms without cognitive problems. The percentage improvement in the UPDRS III score was better with STN-DBS than with GPi-DBS |
| Romito et al.   | 5  | PRKN | G828A and Dupl ex1, DelAg 202-203, C1101T, G535A, Dupl ex1 | 27–45 | 42–63 | STN bilat. | + | 7.3± 9.3 M− 22.8± 7.3 M+ (NC: 59.7± 11.3 M−) | 25.2± 10.0 M−S− 21.8± 7.5 M+S+ (NC: 29.0± 12.3 M−S+) | 25.2± 10.0 M−S− 21.8± 7.5 M+S+ (NC: 29.0± 12.3 M−S+) | 56 | (NC: 51.4) | 1–3 | 10 | Favourable and comparable to patients without mutations |
| Johansen et al. | 4  | PRKN | Het. c.delEx3, Het. p.R275W, Het. c.dupEx7, Hom. c.delEx5 (GPi) | 35–46 | 50–59 | STN bilat. (n = 3), GPi unilat. (n = 1) | NA for individual genes (NC: 35.7± 6.7 M−) | NA for individual genes (NC: 19.7± 5.5 M−S+) | 35.7± 6.7 M− | NA | 56 | (NC: 44.8) | 5–7 | 9 | Favourable and comparable to patients without mutations |
| Kim et al.      | 3  | PRKN | NA        | 21.7± 8.5 | 49.7± 16.2 | STN bilat. | NA | 49.8± 24.5 M−, 18.3± 7.8 M+ (NC: 38.3± 10.6 M−) | 24.7± 14.0 M−S−, 22.2± 14.9 M+S+ (NC: 17.2± 5.3 M−S+) | 37.1± 45.4 | (NC: 54.6± 13.9) | 2–5 | 10 | Favourable and comparable to patients without mutations |
| Hassin-Baar et al. | 3  | PRKN | Hom. 202 A deletion | 15–28 | 31–54 | STN' | NA | 27–64 M−, 20–48 M+ | NA               | NA | NA | 7 | Modest outcome with improvement in appendicular symptoms, but no change in axial features |
| Study                  | N  | Gene   | Mutation\(^a\)                  | AAO\(^a\) | AAD\(^a\) | Target\(^a\) | LP  | PRE-UPDRS III\(^b\) | POST-UPDRS III\(^b\) | %\(^b\) | FU  | NOS | Outcome                        |
|-----------------------|----|--------|---------------------------------|-----------|-----------|--------------|-----|---------------------|----------------------|---------|-----|-----|--------------------------------|
| Sayad et al. [16]     | 2  | PRKN   | Het. c. 458C>G                   | 48        | NA        | STN bilat.  | +   | 46 M−, 28 M+        | 51 M−S+, 30 M+S+     | −10.1   | 2   | 10  | Poor response            |
|                       |    |        | Het. c. 1230C>T                  | 48        |           |              |     |                     |                      |         |     |     |                                |
| Thompson et al. [35]  | 2  | PRKN   | Hom., specific mutation NA       | 26 (GPi), 30 (STN) | NA        | STN bilat.  | +   | 48 M−, 7 M+         | 57 M−, 50 M+         | 33 M−S+, 21 M+S+   | 0.7  | 10  | 1  | Favourable outcome         |
| Genç et al. [36]      | 1  | PRKN   | Het. c.99G>A and large het.      | 10        | NA        | STN bilat.  | +   | 48 M−, 7 M+         | 57 M−, 50 M+         | 33 M−S+, 21 M+S+   | 0.7  | 10  | 1  | Favourable outcome         |
| Moll et al. [37]      | 1  | PRKN   | Compound het. PRKN mutation      | 35        | 45        | STN bilat.  | +   | 30 M−, 5 M+         | NA                   | NA      |     |     | Favourable to motor         |
| Nakahara et al. [38]  | 1  | PRKN   | Hom. parkin mutation (p.T175P<->T) | 15        | 60        | STN bilat.  | +   | 86 M−, 25 M+        | 57 M−, 50 M+         | 33 M−S+, 21 M+S+   | 0.7  | 10  | 1  | Favourable outcome         |
| Lefaucheur et al. [39]| 1  | PRKN   | Compound het. mutations of the   | 25        | 69        | STN         | NA  | NA                  | NA                   | NA      |     |     | Favourable outcome without  |
|                       |    |        | PRKN gene, c.101_102delAG        |           |           |              |     |                     |                      |         |     |     | cognitive problems          |
| Wickremaratnhi et al. [40] | 1  | PRKN   | Compound het. exon 2/exon 2 to  | 8         | 46        | STN         | NA  | 68 M−, 22 M+        | 57 M−, 50 M+         | 33 M−S+, 21 M+S+   | 0.5  | 9   | 1  | Favourable outcome         |
|                       |    |        | deletion in the PRKN             |           |           |              |     |                     |                      |         |     |     |                                |
| Lesage et al. [41]    | 1  | PRKN   | Compound het. of the PRKN        | 8         | 39        | STN         | NA  | 46 M−, 15.5 M+      | NA                   | NA      |     |     | Favourable outcome         |
|                       |    |        | c.1-?_7+del, c.172-?_412+del     |           |           |              |     |                     |                      |         |     |     |                                |
| Capecci et al. [42]   | 1  | PRKN   | Hom. deletion in exon 3          | 22        | NA        | STN         | +   | 45 M−, 5 M+         | 57 M−S+, 3 M+S+      | 84.4    | 1   | 8   | Favourable outcome         |
| Khan et al. [43]      | 1  | PRKN   | Exon 9 110C->T (Arg334Cys), exon | 30        | 35        | STN         | NA  | NA                  | NA                   | NA      |     |     | Favourable outcome         |
Table 1 (continued)

| Study          | N  | Gene | Mutationa | AAOa | AADa | Targetb | LP | PRE-UPDRS IIIb | POST-UPDRS IIIb | %b | FU | NOS | Outcome                                                                 |
|----------------|----|------|------------|------|------|----------|----|----------------|----------------|----|----|-----|--------------------------------------------------------------------------|
| Lythe et al.   | 17 | GBA  | Het. mutation carriers (n = 15), hom. mutation carrier (n = 1), compound het. (n = 1). Two patients also carried a mutation in another PD-associated gene; PARKIN or LRRK2 | 41.4±5.8 | 53.5±4.5 | STN (n = 15), GPi (n = 2) | NA | 52.4±13.0 M−, 18.4±14.9 M+ (NC: 40.5±12.0 M−) | NA M−S+, 50.0±17.1 M+S+ (n = 9) (NC: NA M−S+, 38.9±140.0 M+S+) | 4.6 M+S+ (n = 9) (NC: 4.0 M+S+) | 7.5 (n = 9) | 9 | Follow-up data available for 9 patients. Poorer outcome compared to patients without mutations. GBA mutation carriers had faster rate of cognitive decline, reported significantly worse quality of life and exhibited a greater burden of non-motor symptoms compared to patients without mutations. During follow-up 3 GBA+ patients were deceased, 2 were unable to complete follow-up due to severe PD-related disability, 2 could not be contacted and 1 DBS hardware was removed |
| Angeli et al.  | 16 | GBA  | R463CR463C, L444P/E326K, N370S, D409H, recNcil, R463C, N188S, R275Q, IVS2+1 G>A, L444P, E326K/E326K, E326K (n = 3), E326K and LRRK2 p.G2019S, T369M and PRKN c.1310C>T | 34–58 | NA | STN (n = 13), GPi (n = 2), VIM (n = 1) | NA | All 51.3±14.0 M−, 18.0±15.4 M+ | GPi 66.5±19.1 M−S−, 50.0±19.8 M−S+, 41.0±15.0 M+S+ | STN 56.1±18.8 M−S−, 28±11.4 M−S+, 15.9±10.4 M+S+ | GPi 22 40 43 (NC: STN: 48, GPi: 28) | 1–5 9 | Favourable motor response, but faster rate of cognitive decline compared to patients without mutations. The percentage improvement in the UPDRS III score “OFF- medication” was better with bilateral STN-DBS and VIM-DBS than with GPi-DBS |
Table 1 (continued)

| Study                  | N  | Gene | Mutationa | AAOa | AADa | Targeta | LP | PRE-UPDRS IIIa | POST-UPDRS IIIa | %b | FU     | NOS | Outcome                                                                 |
|------------------------|----|------|-----------|------|------|----------|----|----------------|-----------------|----|--------|-----|-------------------------------------------------------------------------|
| Pal et al. [19]         | 12 | GBA  | p.N370S (n = 8), p.L444P (n = 3). 1 patient carried both GBA and LRRK2 mutations and was excluded | 41.6 ± 5.3 (n = 11) | 53.9 ± 2.6 (n = 9) | NA | NA | NA | 27.4 ± 14.5 M+S+ (n = 11) | NA | 1.6 ± 3.0 (n = 9) | 6   | The outcome is not reported. Clinical data before DBS is not available, but UPDRS-III score was little higher in GBA -patients compared to patients without mutations at follow-up |
| Weiss et al. [44]      | 3  | GBA  | p.N370S (n = 1) and p.L444P (n = 2) | 47–54 | 65–69 | STN      | NA | 26 and 53 M−, 14 and 19 M+, NA (n = 1) (NC: 31–63 M−) | 56–71 M−S−, 21–45 M−S+, 32–48 M+S−, 20–45 M+S+ (NC: 21–42 M−S+) | 30–75 (NC: 22–54) | 6–10 | 11     | Favourable outcome, but substantial increase of axial motor impairment in the long-term with declining therapeutic response in GBA carriers. GBA carriers developed also a significant cognitive impairment |
| Lesage et al. [45]     | 2  | GBA  | Hom. p.N370S | 52 | NA | STN bilat. | NA | NA | NA | NA | NA | 5   | Favourable outcome                                                                                                     |
|                        |    |      | c.1263del + RecTL | 21 | 24 |               |    |    |    |    |    | 2   | Some clinical benefit 2 years after DBS, but problems with postural instability                                           |
| Martikainen et al. [46] | 1  | SNCA | Het. c.158C > A (p.A53E) | 42 | 46 | STN bilat. | NA | 31 M−, 8 M+ | NA | NA | NA | 3.5 | 9    | Favourable motor outcome in the short-term but poor in the long-term follow-up. Response for motor fluctuations remained satisfactory but the cognitive and mental state of the patient deteriorated to a state of practical immobility |
| Perandones et al. [47] | 1  | SNCA | SNCA duplication | 18 | 26 | GPi bilat. | +  | NA | NA | NA | 0.1 | 6   | Favourable and comparable to patients without mutations                                                                 |
| Shimo et al. [48]      | 1  | SNCA | SNCA duplication | 35 | 41 | STN bilat. | +  | 27 M−, 10 M+ | 13 M−S+ | 51.9 | 4   | 9    | Favourable motor outcome without cognitive or psychiatric problems                                                        |
Table 1 (continued)

| Study            | N  | Gene   | Mutationa | AAOa | AADa | Targeta | LPa | PRE-UPDRS IIIa | POST-UPDRS IIIa | %b | FU  | NOS | Outcome                                                                 |
|------------------|----|--------|-----------|------|------|----------|-----|----------------|-----------------|----|-----|-----|--------------------------------------------------------------------------|
| Antonini et al.  | 1  | SNCA   | SNCA duplication at 4q22.1 | 41   | 46   | STN bilat. | +   | 28 M−, 10 M+   | 16 M−S+, 10 M+S+ | 42.9 | 2   | 9   | Favourable outcome in short-term follow-up but patient developed visual hallucinations and cognitive deterioration and died two years after operation due to metastatic breast cancer |
| Ahn et al.       | 1  | SNCA   | SNCA duplication | 40   | 46   | STN bilat. | NA  | 32 M−, 6 M+   | NA              | NA | NA | 6   | Excellent motor response but later patient’s dementia worsened, requiring assistance in daily activities |
| Fleury et al.    | 2  | VPS35  | p.D620N | 49   | 60   | STN bilat. | NA  | 58 M−, 17 M+  | 32 M−S−, 18 M−S+, 18 M+S−, 15 M+S+ | 76 (1 year) 69 (8 years) | 8   | 8   | Favourable outcome |
| Chen et al.      | 1  | VPS35  | p.D620N | 42   | 55   | STN bilat. | +   | 42 M−, 15 M+  | 35 M−S−, 22 M−S+, 15 M+S−, 13 M+S+ | 37  | 5   | 9   | Favourable outcome                                                                 |
| Kumar et al.     | 1  | VPS35  | p.D620N | NA   | NA   | NA       | NA  | NA            | NA              | NA | NA | 3   | Little benefit to motor symptoms, but patient developed significant dysarthria |
| Sheerin et al.   | 1  | VPS35  | p.D620N | 47   | NA   | NA       | NA  | NA            | NA              | NA | NA | 5   | Favourable outcome. No reported cognitive problems                             |
| Borellini et al. | 1  | PINK1  | Hom. L347P | 30   | 49   | GPi       | NA  | 44 M−         | 32 M+S+         | 27  | 0.1 | 7   | Moderate outcome                                                                 |
| Nakahara et al.  | 1  | PRKN+ PINK1 | Hom. parkin mutation (p.T175P) | 15   | 60   | STN bilat. | +   | 86 M−, 25 M+  | 33 M−S+, 21 M+S+ | 62  | 0.7 | 9   | Favourable outcome                                                                 |
Table 1 (continued)

| Study            | N | Gene          | Mutationa | AAOa | AADa | Targeta | LP | PRE-UPDRS IIIa | POST-UPDRS IIIa | %b | FU | NOS | Outcome                                      |
|------------------|---|---------------|-----------|------|------|---------|----|----------------|----------------|----|----|-----|----------------------------------------------|
| Johansen et al. [21] | 1 | PINK1         | Het. p.G411S | 50   | 59   | STN bilat. | + | NA for individual genes (NC: 35.7 ± 6.7 M−) | NA for individual genes (NC: 19.7 ± 5.5 M−) | NA | 44.8 | 5   | 9   | Favourable and comparable to patients without mutations |
| Moro et al. [32]  | 1 | PINK1         | Hom. c.509T > G (p.V170G) | 31   | 61   | STN bilat. | NA | 35.5 M− | NA | Short FU 46.5 Long FU 43.7 (NC: Short FU 56, Long FU 44) | 3–6 | 9   | Favourable and comparable to patients without mutations |
| Valente et al. [56] | 1 | PINK1         | NA         | NA   | NA   | NA      | NA | NA             | NA             | NA | NA | 3   | Motor outcome was not properly reported but patient developed imbalance, gait impairment, dysarthria, and behavioral changes at the age of 54 years. Mental deterioration was documented a few years later. |
| Dufournet et al. [57] | 3 | 22q11.2 Del. Syndrome | 34–38c | NA   | NA   | STN (n = 1) | NA | NA | NA | 30–70 | NA | 7   | Favourable and comparable to patients with idiopathic PD |

AAO age at disease onset (years), AAD age at DBS operation (years), LP specific lead position (reported or not), % the percentage improvement of the UPDRS III score after DBSb, FU follow-up after surgery (years), NA not available, M−/+ medication OFF/ON, S−/+ stimulation OFF/ON, MV mean value, NC mutation non-carriers

a Parameters are reported in the table as in the original articles
b If the percentage improvement was not reported directly in the original article but UPDRS-III scores were available, we calculated the percentage improvement from the change of UPDRS-III score in the preoperative M− condition compared to the postoperative M−S+ condition ((((Pre-op. UPDRS-III M−) − (Post-op. UPDRS-III M−S+))/((Pre-op. UPDRS-III M−) × 100)

c The study did not specify whether the implantation was uni- or bilateral
d Some patients were reported previously by Angeli et al. [15]
e Age at PD diagnosis
GBA mutation carriers developed cognitive impairment faster than patients without mutations.

SNCA

Five patients were reported in five case reports [46–50] (STN n = 4, GPi n = 1). The motor outcome was favourable for all patients in the short-term but 3/5 patients developed cognitive and/or neuropsychiatric problems a few years after implantation. The percentage change in the UPDRS-III score was documented in two patients.

VPS35

Four studies [51–54] reported five patients (STN n = 3, NA n = 2). Favourable motor outcome was reported in four cases and minor motor benefit complicated by dysarthria in one case. The percentage change in the UPDRS-III score was reported in three patients.

PINK1

Five case reports [21, 32, 38, 55, 56] including one patient in each report (STN n = 4, GPi n = 1) were reported. Favourable motor outcome was observed in three patients and moderate outcome in one case. One patient developed imbalance, gait impairment, dysarthria, and behavioral changes after operation and mental deterioration was documented a few years later.

Exclusion of poorer quality studies

Unfortunately, many studies (Table 1) lacked important information as shown in the Supplementary Table 1. Poorer quality studies have tendency for bias; therefore, in the Supplementary Table 3, data are presented after exclusion of poorer quality studies such as studies lacking the information about DBS target, pre- and postoperative evaluation, adequate follow-up time or outcome information. Furthermore, as Lythe et al. [14] and Angeli et al. [15] reported partly the same patients, we tested the conclusions also when the smaller study was excluded. Nevertheless, after the

Table 2  Summary of key findings according to the mutated gene

| Gene     | Studies (n) | Patients (n) | Target          | Outcome                                                                 |
|----------|-------------|--------------|-----------------|-------------------------------------------------------------------------|
| LRRK2    | 17          | 87<sup>a</sup> | STN: n = 79 (90.8%) NA: n = 8 (9.2%) | Mostly favourable motor outcome. Four studies with eight patients (9.2%) reported poor motor outcomes and one study reported moderate outcomes for two patients. Both patients with the LRRK2 p.T2031S (c.6091A > T) mutation (n = 2) developed neuropsychiatric problems 5–7 years after implantation. The outcome appears poor in patients with LRRK2 p.R1441G (c.4321C > G) mutations (n = 5), whereas it appears excellent in patients with LRRK2 p.G2019S (c.6055G > A) mutations |
| PRKN     | 18          | 67<sup>b</sup> | STN: n = 51 (76.1%) GPi: n = 5 (7.5%) Zona incerta: n = 1 (1.5%) NA: n = 10 (14.9%) | Fifty-one patients (76.1%) had favourable long-term motor outcomes. Four patients (6.0%) were reported to have modest outcome in two different studies and one study with two patients (3.0%) reported poor benefit |
| GBA      | 5           | 50<sup>c</sup> | STN: n = 33 (66.0%) GPi: n = 4 (8.0%) VIM: n = 1 (2.0%) NA: n = 12 (24.0%) | Eighteen patients were reported to have favourable, three patients moderate and 9 patients poor long-term motor outcomes. One study reported better outcomes with STN-DBS and VIM-DBS than with GPi-DBS. GBA mutation carriers developed cognitive impairment faster than patients without mutations |
| SNCA     | 5           | 5            | STN: n = 4 (80.0%) GPi: n = 1 (20.0%) | Favourable motor outcome but three of five patients developed cognitive or neuropsychiatric problems a few years after implantation |
| VPS35    | 4           | 5            | STN: n = 3 (60.0%) GPi: n = 2 (40.0%) | Favourable motor outcome in four cases and minor motor benefit complicated by dysarthria in one case |
| PINK1    | 5<sup>b</sup> | 5            | STN: n = 4 (80.0%) GPi: n = 1 (20.0%) | Favourable motor outcome in three cases and moderate in one case |
| 22q11.2.Del. Syndrome | 1<sup>d</sup> | 3            | STN: n = 1 (33.3%) GPi: n = 2 (66.6%) | Favourable motor outcome |

STN subthalamic nucleus, GPi globus pallidus interna, VIM ventral intermediate nucleus, NA not available

<sup>a</sup>One patient had also PRKN mutation and one had GBA mutation

<sup>b</sup>One patient had both PRKN and PINK1 mutations

<sup>c</sup>Two studies reported partially same patients, but it was not possible to separate individual patients that were reported twice. One patient had also LRRK2 mutation and one had PRKN mutation
exclusion of these studies, the results remained essentially the same (Supplementary Table 4).

Discussion

We report the following key findings: (1) DBS outcome appears excellent in patients with LRRK2 p.G2019S (c.6055G > A) mutations, good in patients with PRKN mutations and poor in patients with LRRK2 p.R1441G (c.4321C > G) mutations, (2) the overall benefit of DBS in SNCA, GBA and LRRK2 p.T2031S (c.6091A > T) mutations may be decreased due to rapid progression of cognitive and neuropsychiatric symptoms, and (3) in other mutations, the motor outcome in DBS-treated genetic PD patients appears generally comparable to that of sporadic PD patients.

A recent smaller review of 30 studies described the effects of DBS mainly in patients with LRRK2, PRKN and GBA mutations [62]. In the present PRISMA-compliant systematic review of 46 studies and 221 patients, the most comprehensive data were available for patients with LRRK2 and PRKN mutations. The combined evidence suggests that patients with LRRK2 mutations generally have a good response to DBS, and patients with the most common LRRK2 mutation, the p.G2019S mutation [7], may even have better outcome than the general PD population. However, the reported LRRK2 cases of p.R114G, p.T2031S and p.N1437H (c.4309A > C) mutation carriers appeared to have less favourable outcome. This interpretation is limited by the small number of reported DBS-treated cases of rarer LRRK2 mutations. For the PRKN mutations, the literature supports a view that patients with PRKN mutations are optimal candidates for DBS.

Apart from the LRRK2 and PRKN genes, the published literature concerning individual monogenic mutations and DBS is less comprehensive and the data are clearly limited with respect to both the number of patients and duration of follow-up. The available data are limited to five DBS-treated patients with VPS35 mutation, and the patients have shown favourable sustained motor outcome in 4/5 cases. The available literature also suggests that most patients with mutations in GBA tend to achieve favourable long-term motor outcome from STN-DBS. Despite good motor outcome, GBA mutation carriers may develop cognitive impairment after DBS faster than patients without mutations. SNCA patients commonly develop cognitive and neuropsychiatric problems [8]. The literature supported a good motor outcome after DBS also in patients with SNCA mutations; however, 3/5 patients developed cognitive and neuropsychiatric problems a few years after DBS implantation. Indeed, the non-motor features of genetic PD may be a limiting factor in the overall benefit of DBS in some mutations, such as SNCA and LRRK2 p.T2031S. While the motor benefit from DBS may initially be clear, the rapid non-motor progression may lessen the sum value for the quality of life. A recent study in SNCA A53T mutated rodents suggested that DBS may be neuroprotective [63]. Nonetheless, in human PD patients with SNCA mutations, the neuropsychiatric progression appears to be rapid despite DBS. The issue could be the level of damage at the time of implantation, and earlier DBS in these patients might possibly provide different outcomes.

Preoperative response to levodopa is the best single predictor of the postoperative outcome of DBS [64]. This indicator appears useful also in patients with monogenic mutations and the response was reported in practically all included studies. Another relevant predictor is the localization of DBS electrodes [65]. Unfortunately, there were studies, which did not report DBS targets and most studies lacked information about lead positioning. As the literature expands in the future, the effect of targets and lead positioning should be investigated in more detail. In most studies, STN was preferred over GPI as the target. Hence it remains ambiguous whether there are any relevant differences of clinical outcome between STN and GPI stimulation in monogenic PD. One study reported also a patient with VIM stimulation which is an unusual target for PD patients because VIM stimulation improves only tremor, not other PD symptoms [66, 67]. Finally, it is important to note that the genetic status may have a positive as well as a negative influence on outcome of surgery and this issue should be taken into consideration in the interpretation of DBS studies. For example, the EARLYSTIM trial was performed with young-onset PD patients [5] and there could have been an overrepresentation of PRKN patients in the sample.

In conclusion, monogenic PD patients have variable DBS outcomes depending on the mutated gene. Most patients benefit from STN-DBS, at least in the short-term; however, the current evidence does not support or is questionable for DBS implantation for patients with p.T2031S or p.R114G mutations in the LRRK2 gene or mutations in the SNCA or GBA genes. The best outcome from DBS surgery appears to be in patients with LRRK2 p.G2019S or PRKN mutations.

Acknowledgements Open access funding provided by University of Turku (UTU) including Turku University Central Hospital.

Author contributions (1) Research project: (A) Conception, (B) Organization, (C) Execution; (2) Statistical analysis: (A) Design, (B) Execution, (C) Review and critique; (3) Manuscript: (A) Writing of the first draft, (B) Review and critique. TK: 1A, 1B, 1C, 3A, 3B. JK: 1C, 3B. EP: 1C, 3B. MM: 1C, 3B. AA: 1C, 3B. VK: 1A, 1B, 1C, 3B.

Funding No targeted funding reported. Financial disclosures of all authors for the preceding 12 months. T.K.: Travel expenses from Abbott and Zambon. J.K.: Speaker’s honoraria from Allergan and KRKA; travel expenses from Abbott and Bayer; and an advisory board.
membership for Allergan, E.P.: Speaker’s honoraria from Abbott and Abbvie; travel expenses from Abbott, Abbvie, Boston Scientific and Medtronic; an advisory board membership for Abbvie; and consulting fees from NordicInﬁu Care and Zambon. M.H.M.: Speaker’s honoraria from Sanofi Genzyme Finland. A.A.: Honoraria from Sunovion, Lundbeck, Mundipharma, GE, UCB, Zambon, Medtronic, Ever Neuro Pharma and Movement Disorders Society; advisory board membership for AbbVie and Acadia; consulting fees from AbbVie, UCB, Zambon and Angelini; expert testimony and legal consultancy for Boehringer Ingelheim; stock ownership in PD Neurotechnology Limited; grant for Horizon2020 Project No 643706; and patent WO2015110261-A1 An in vitro method of diagnosing Parkinson’s disease. V.K.: Speaker’s honoraria from Orion Pharma, Teva, GE Healthcare, Abbvie and NordicInﬁu Care AB; travel expenses from NordicInﬁu Care AB; and an advisory board membership for Abbvie.

Compliance with ethical standards

Research involving human participants and animals  This manuscript does not contain clinical studies or patient data apart from those identified through literature search.

Conflicts of interest  The authors declare that they have no conﬂict of interest.

OpenAccess  This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Deuschl G, Schade-Brittinger C, Krack P et al (2006) A randomized trial of deep-brain stimulation for Parkinson’s disease. N Engl J Med 355:896–908
2. Obeso JA, Olanow CW, Rodriguez-Oroz MC et al (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson’s disease. N Engl J Med 345:956–963
3. Weaver FM, Follett K, Stern M et al (2009) Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 301:63–73
4. Antonini A, Moro E, Godeiro C, Reichmann H (2018) Medical and surgical management of advanced Parkinson’s disease. Mov Disord 33:900–908
5. Schuepbach WM, Rau J, Knudsen K et al (2013) Neurostimulation for Parkinson’s disease with early motor complications. N Engl J Med 368:610–622
6. Kasten M, Marras C, Klein C (2017) Nonmotor signs in genetic forms of Parkinson’s disease. Int Rev Neurobiol 133:129–178
7. Deng H, Wang P, Jankovic J (2018) The genetics of Parkinson disease. Ageing Res Rev 42:72–85
8. Puschmann A (2013) Monogenic Parkinson’s disease and parkinsonism: clinical phenotypes and frequencies of known mutations. Parkinsonism Relat Disord 19:407–415
9. Healy DG, Falchi M, O’Sullivan SS, et al (2008) Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson’s disease: a case-control study. Lancet Neurol 7:583–590
10. Alcalay RN, Mirelman A, Saunders-Pullman R et al (2013) Parkinson disease phenotype in Ashkenazi Jews with and without LRRK2 G2019S mutations. Mov Disord 28:1966–1971
11. Romito LM, Contarino MF, Ghezzi D, Franzini A, Garavaglia B, Albanese A (2005) High frequency stimulation of the subthalamic nucleus is efficacious in Parkinson disease. J Neuro 252:208–211
12. Maselis M, Collinson S, Freeman N et al (2016) Dopamine D2 receptor gene variants and response to rasagiline in early Parkinson’s disease: a pharmacogenetic study. Brain 139:2050–2062
13. Moher D, Shamseer L, Clarke M et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1
14. Lythe V, Athauda D, Foley J et al (2017) GBA-associated Parkinson’s disease: progression in a deep brain stimulation cohort. J Parkinsons Dis 7:635–644
15. Angeli A, Mencacci NE, Duran R et al (2013) Genotype and phenotype in Parkinson’s disease: lessons in heterogeneity from deep brain stimulation. Mov Disord 28:1370–1375
16. Sayad M, Zouambia M, Chaouch M et al (2016) Greater improvement in LRRK2 G2019S patients undergoing Subthalamic Nucleus Deep Brain Stimulation compared to non-mutation carriers. BMC Neurosci 17:6
17. Greenbaum L, Israeli-Korn SD, Cohen OS et al (2013) The LRRK2 G2019S mutation status does not affect the outcome of subthalamic stimulation in patients with Parkinson’s disease. Parkinsonism Relat Disord 19:1053–1056
18. Schüpbach M, Lohmann E, Anheim M et al (2007) Subthalamic nucleus stimulation is efficacious in patients with Parkinsonism and LRRK2 mutations. Mov Disord 22:119–122
19. Pal GD, Hall D, Ouyang B et al (2016) Genetic and clinical predictors of deep brain stimulation in young-onset Parkinson’s disease. Mov Disord Clin Pract 3:465–471
20. Gómez-Esteban JC, Lezcano E, Zarranz JJ et al (2008) Outcome of bilateral deep brain subthalamic stimulation in patients carrying the R1441G mutation in the LRRK2 dardarin gene. Neurosurgery 62:857–862 (discussion 862–853)
21. Johansen KK, Jergensen JV, White LR, Farrer MJ, Aasly JO (2011) Parkinson-related genetics in patients treated with deep brain stimulation. Acta Neurol Scand 123:201–206
22. Lesage S, Janin S, Lohmann E et al (2007) LRRK2 exon 41 mutations in sporadic Parkinson disease in Europeans. Arch Neurol 64:425–430
23. Gaig C, Ezquerra M, Marti MJ, Muñoz E, Valderrriola F, Tolosa E (2006) LRRK2 mutations in Spanish patients with Parkinson disease: frequency, clinical features, and incomplete penetrance. Arch Neurol 63:377–382
24. Goldwurm S, Di Fonzo A, Simons EJ et al (2005) The G6055A (G2019S) mutation in LRRK2 is frequent in both early and late onset Parkinson’s disease and originates from a common ancestor. J Med Genet 42:e65
25. Hatano T, Funayama M, Kubo SI et al (2014) Identiﬁcation of a Japanese family with LRRK2 p.R1441G-related Parkinson’s disease. Neurobiol Aging 35:2656.e2617–2656.e2656.e2623
26. Stefani A, Marzetti F, Pierantozzi M et al (2013) Successful subthalamic stimulation, but levodopa-induced dystonia, in a genetic Parkinson’s disease. Neurol Sci 34:383–386
27. Puschmann A, Englund E, Ross OA et al (2012) First neuro-pathological description of a patient with Parkinson’s disease and LRRK2 p.N1437H mutation. Parkinsonism Relat Disord 18:332–338
28. Perju-Dumbrava LD, McDonald M, Kneebone AC, Long R, Thyagarajan D (2012) Sustained response to deep brain stimulation in LRRK2 parkinsonism with the Y1699C mutation. J Parkinsons Dis 2:269–271
29. Breit S, Wächter T, Schmid-Bielenberg D et al (2010) Effective long-term subthalamic stimulation in PARK8 positive Parkinson’s disease. J Neurol 257:1205–1207
30. Aalsy JO, Vilarinho-Güell C, Dachsel JC et al (2010) Novel pathogenic LRRK2 p.Asn1437His substitution in familial Parkinson’s disease. Mov Disord 25:2156–2163
31. Lohmann E, Welter ML, Fraix V et al (2008) Are parkin patients particularly suited for deep-brain stimulation? Mov Disord 23:740–743
32. Moro E, Volkmann J, König IR et al (2008) Bilateral subthalamic stimulation in Parkin and PINK1parkinsonism. Neurology 70:1186–1191
33. Kim HJ, Yun JY, Kim YE et al (2014) Parkin mutation and deep brain stimulation outcome. J Clin Neurosci 21:107–110
34. Hassan-Baer S, Hattori N, Cohen OS, Hardwick A, McFarland NR, Okun MS (2013) Variability in clinical phenotypes of heterozygous and homozygous cases of Parkin-related Parkinson’s disease. Int J Neurosci 123:847–849
35. Genç G, Apaydın H, Gündüz A et al (2016) Successful treatment of Juvenile parkinsonism with bilateral subthalamic deep brain stimulation in a 14-year-old patient with parkin gene mutation. Parkinsonism Relat Disord 24:137–138
36. Moll CK, Buhmann C, Gulberti A et al (2015) Synchronized cortico-subthalamic beta oscillations in Parkin-associated Parkinson’s disease. Clin Neurophysiol 126:2241–2243
37. Nakahara K, Ueda M, Yamada K et al (2014) Juvenile-onset parkinsonism with digenic parkin and PINK1 mutations treated with subthalamic nucleus stimulation at 45 years after disease onset. J Neurol Sci 345:276–277
38. Lefaucheur R, Derrey S, Guyant-Maréchal L, Chastan N, Maltête D (2010) Whatever the disease duration, stimulation of the subthalamic nucleus improves Parkinson disease. Parkinsonism Relat Disord 16:482–483
39. Wickremaratne MM, Majounie E, Morris HR et al (2009) Parkinson-related disease clinically diagnosed as a pallido-pyramidal syndrome. Mov Disord 24:138–140
40. Lesage S, Magali P, Lohmann E et al (2007) Deletion of the parkin and PARG gene promoter in early-onset parkinsonism. Hum Mutat 28:27–32
41. Capecchi M, Passamonti L, Annese F et al (2004) Chronic bilateral subthalamic deep brain stimulation in a patient with homozygous deletion in the parkin gene. Mov Disord 19:1450–1452
42. Khan NL, Graham E, Critchley P et al (2003) Parkinson disease: a phenotypic study of a large case series. Brain 126:1279–1292
43. Weiss D, Brockmann K, Sruilijes K et al (2012) Long-term follow-up of subthalamic nucleus stimulation in glucocerebrosidase-associated Parkinson’s disease. J Neurol 259::1970–1972
44. Lesage S, Anheim M, Condroyer C et al (2011) Large-scale screening of the Gaucher’s disease-related glucocerebrosidase gene in Europeans with Parkinson’s disease. Hum Mol Genet 20:202–210
45. Martikainen MH, Paivarinta M, Hietala M, Kaasinen V (2015) Clinical and imaging findings in Parkinson disease associated with the A53E SNCA mutation. Neurol Genet 1:e27
46. Perandones C, Araoz Olivos N, Raina GB et al (2015) Successful GPe stimulation in genetic Parkinson’s disease caused by mosaicism of alpha-synuclein gene duplication: first description. J Neurol 262:222–223
47. Shimo Y, Natori S, Oyama G et al (2014) Subthalamic deep brain stimulation for a Parkinson’s disease patient with duplication of SNCA. Neuromodulation 17:102–103
48. Antonini A, Pillieri M, Padoan A et al (2012) Successful subthalamic stimulation in genetic Parkinson’s disease caused by duplication of the α-synuclein gene. J Neurol 259:165–167
49. Ahn TB, Kim SY, Kim JY et al (2008) Alpha-synuclein gene duplication is present in sporadic Parkinson disease. Neurology 70:43–49
50. Fleury V, Wider C, Horvath J et al (2013) Successful long-term bilateral subthalamic nucleus deep brain stimulation in VPS35 Parkinson’s disease. Parkinsonism Relat Disord 19:707–708
51. Chen YF, Chang YY, Lan MY, Chen PL, Lin CH (2017) 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 17:191
52. Kumar KR, Weissbach A, Heldmann M et al (2012) Frequency of the D620N mutation in VPS35 in Parkinson disease. Arch Neurol 69:1360–1364
53. Sheerin UM, Charlesworth G, Bras J et al (2012) Screening for VPS35 mutations in Parkinson’s disease. Neurobiol Aging 33:838.e831–838.e835
54. Borellini L, Cogiamanian F, Carraba G et al (2017) Globus pallidus internus deep brain stimulation in PINK-1 related Parkinson’s disease: a case report. Parkinsonism Relat Disord 38:93–94
55. Valente EM, Salvi S, Ialongo T et al (2004) PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol 56:336–341
56. Dufournet B, Nguyen K, Charles P et al (2017) Parkinson’s disease associated with 22q11.2 deletion: clinical characteristics and response to treatment. Rev Neurol (Paris) 173:406–410
57. Stern MB, Marek KL, Friedman J et al (2004) Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson’s disease patients. Mov Disord 19:916–923
58. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ (2010) The clinically important difference on the unified Parkinson’s disease rating scale. Arch Neurol 67:64–70
59. Rabie A, Verhagen Metman L, Fakhry M et al (2016) Improvement of advanced Parkinson’s disease manifestations with deep brain stimulation of the subthalamic nucleus: a single institution experience. Brain Sci 6:58
60. Wells GA, Shea B, O’Connell D et al (2011) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
61. Rizzone MG, Marione T, Balestrino R, Lopiano L (2018) Genetic background and outcome of Deep Brain Stimulation of Parkinson’s disease. Parkinsonism Relat Disord. https://doi.org/10.1016/j.parkreldis.2018.08.006
62. Musacchio T, Rebenstorff M, Fluri F et al (2017) Subthalamic nucleus deep brain stimulation is neuroprotective in the A53T α-synuclein Parkinson’s disease rat model. Ann Neurol 81:825–836
63. Charles PD, Van Blercom N, Krack P et al (2002) Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 59:932–934
64. Okun MS, Rodriguez RL, Foote KD et al (2008) A case-based review of troubleshooting deep brain stimulator issues in movement and neuropsychiatric disorders. Parkinsonism Relat Disord 14:532–538
65. Wong JK, Cauraugh JH, Ho KWD et al (2018) STN vs. GPi deep brain stimulation for tremor suppression in Parkinson disease: a systematic review and meta-analysis. Parkinsonism Relat Disord. https://doi.org/10.1016/j.parkreldis.2018.08.017
66. Paribar R, Allerman R, Papavassiliou E, Tarsy D, Shih LC (2015) Comparison of VIM and STN DBS for Parkinsonian resting and postural/action tremor. Tremor Other Hyperkinet Mov (N Y) 5:321