Motor response in monogenic LRRK2 parkinson's disease after deep brain stimulation: A systematic review and meta-analysis

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ABSTRACT

Introduction: Genetic factors are increasingly recognized as crucial contributors to both familial and sporadic forms of Parkinson's disease (PD), including mutations in LRRK2 (Leucine-rich Repeat Kinase 2). Previous studies have indicated that the G2019S variant results in more favorable motor outcomes post-deep brain stimulation (DBS) compared to the R1441G variant. This study was aimed at investigating whether different LRRK2 variants in Parkinson's disease patients with LRRK2 mutations (LRRK2 PD) produce distinct motor responses following DBS.

Materials and Methods: A literature search was conducted across three databases using keywords related to Parkinson's disease, deep brain stimulation, and LRRK2. The inclusion criteria involved studies focusing on LRRK2 PD with DBS intervention, specifically comparing LRRK2 variants, and measuring motor responses pre- and post-DBS using the UPDRS III. A meta-analysis was performed to compare motor responses using a random effects model.

Results: Out of 325 search results, eleven articles were included in the review. Three LRRK2 PD variants—G2019S, R1441G, and G2385R—were associated with DBS intervention. The overall effect of DBS in LRRK2 PD compared to idiopathic PD was not statistically significant, with a mean difference (MD) of -3.00 (-8.52; 2.52). High overall heterogeneity was observed (I^2 = 63.1%; P < 0.05). Subgroup analysis revealed significant differences (P < 0.05), suggesting that different LRRK2 variants may result in varying motor outcomes post-DBS.

Conclusion: LRRK2 PD exhibited diverse motor outcomes depending on the specific mutation variant when subjected to DBS. Patients with LRRK2 variants G2019S and G2385R demonstrated clinically significant improvements in motor responses, while those with the R1441G variant showed inadequate motor response.

KEYWORDS:
Monogenic Parkinson's Disease, LRRK2, motor response, deep brain stimulation

INTRODUCTION

The majority of Parkinson's Disease (PD) cases are idiopathic, although 5–10% of cases are familial, involving mutations in various genes.[1] Among the genes most studied in monogenic PD are SNCA (Synuclein alpha), LRRK2 (Leucine-rich Repeat Kinase 2), GBA (Glucocerebrosidase), VPS13C (Vacuolar Protein Sorting 13 Homologue C), PRKN (Parkin RBR Ubiquitin Protein Ligase), and PINK1 (PTEN Induced Kinase 1).[2-4] Although monogenic PD is relatively rare epidemiologically, studies recruiting individuals with LRRK2 gene mutations, regardless of whether they exhibit PD symptoms, have shown that these mutations are relatively common in certain populations.[2]

The G2019S variant is one of the most commonly identified LRRK2 mutations, contributing to 6–40% of familial Parkinson's Disease cases depending on the ethnic group and accounting for 2% of sporadic cases.[5-8] This mutation has been widely reported in European populations and is particularly common in specific populations, such as Ashkenazi Jews in Israel and Berbers in North Africa.[9-11] However, the G2019S variant is rarely found in Asia. Other notable mutations of LRRK2 PD include the R1441C/G/H, N1437H, Y1699C, I2020T, R1628P, and G2385R variants.[12-13] Among these, the R1441G variant is predominantly found in the Basque population of northern Spain.[14]

Current treatments for PD focus on restoring dopaminergic activity in the striatum, aiming to alleviate motor symptoms effectively.[15] Non-pharmacological approaches, such as basal ganglia surgery, have been utilized as therapeutic modalities for tremors in PD, even before the discovery of levodopa therapy.[16] Deep brain stimulation (DBS) has emerged as a surgical treatment for Parkinson's Disease, initially used exclusively for managing chronic tremors and advanced stages of the disease. However, its application has expanded to include early-stage Parkinson's Disease.[16] This procedure involves implanting electrodes in specific brain regions, primarily targeting the subthalamic nucleus (STN) and the globus pallidus internus (GPi), both of which are recognized as the recommended targets for DBS in Parkinson's Disease.[17-18]

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The effectiveness of deep brain stimulation (DBS) therapy for Parkinson's Disease largely relies on the careful selection of appropriate candidates. Only patients diagnosed with primary Parkinson's Disease are eligible for DBS, while individuals with secondary Parkinson's Disease or atypical parkinsonian syndromes are excluded from this treatment.1[6] Monogenic PD, particularly LRRK2 PD, represents one of the most prevalent genetic abnormalities in this form of the disease, with varying effects across different populations. Considering the diversity of LRRK2 mutation variants, further research is essential to understand their impact on monogenic Parkinson's Disease patients undergoing deep brain stimulation (DBS). In this review, we aim to investigate whether different variants of the LRRK2 mutation in Parkinson's Disease patients (LRRK2 PD) result in varying motor responses following deep brain stimulation (DBS).

MATERIALS AND METHODS

Literature Search

This systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with a literature search covering publications up to December 30, 2024. The search was conducted using online databases, including MEDLINE (via PubMed), Google Scholar, and Scopus. Keywords were selected to align with the review's objective of comparing the response to deep brain stimulation (DBS) in patients with LRRK2-mutated monogenic Parkinson's Disease (LRRK2 PD) and those with idiopathic Parkinson's Disease. The search terms used as search query were 'Parkinson', 'deep brain stimulation,' and 'LRRK2.' Before commencing the review, the protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) on April 28, 2022, under registration number CRD42022320770.

Eligibility Criteria

The inclusion criteria for this systematic review were as follows: human studies comparing the effects of deep brain stimulation (DBS) in Parkinson's Disease (PD) patients with LRRK2 mutations versus idiopathic PD. Only articles written in English were included, and studies without full access to the complete text were excluded. The main exposure was the specific LRRK2 variant identified, which was also analyzed separately. The primary outcome was the improvement in motor function, assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III). Pre-DBS motor status (medication-off) was compared with post-DBS motor status in both medication-off and on-stimulation conditions. Exclusion criteria included studies that failed to confirm the presence of LRRK2 genetic mutations, those with incomplete follow-up data, genetic analyses that did not specifically reference LRRK2, studies that did not utilize DBS as the primary therapy, or those that did not employ UPDRS-III for motor response assessment.

Data Extraction and Analyses

Data were manually extracted using a standardized data extraction form, including: source of the article (first author and year of publication), Number of patients with LRRK2 mutations, Number of control patients (non-monogenic Parkinson's disease), Country of origin, LRRK2 mutation variant, DBS target, Age at onset and at DBS therapy, Pre-DBS UPDRS-III score (medication-off), and Post-DBS UPDRS-III score (medication-off and on-stimulation).

The data synthesis strategy for this review involves both quantitative and narrative approaches. For the quantitative analysis, we will calculate the mean difference of motor response, assessed using UPDRS-III, following DBS. Studies with sufficient comparable data will be included in the meta-analysis, where results will be pooled. The meta-analysis will be conducted using a random-effects model, accounting for the expected heterogeneity between studies. Heterogeneity will be assessed using the I^2 statistic, which quantifies the degree of variation across studies due to heterogeneity rather than chance. Studies reporting LRRK2 mutations with different motor outcomes will be compared to each other and to idiopathic PD cases. For studies with data that cannot be quantitatively synthesized, a narrative report will be provided, summarizing the key findings in descriptive terms. Subgroup analysis will be performed for each specific LRRK2 mutation (e.g., G2019S, R1441G, G2385R), with comparisons made between mutations to explore their effects on motor response post-DBS. This will allow us to examine how different genetic variants of LRRK2 affect treatment outcomes and to identify potential patterns in mutation-specific responses to DBS therapy.

Quality Assessment

The quality of the included studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist, which consists of 22 items analyzing abstracts, titles, methodology, results, and potential funding influences.[19]

RESULTS

Included studies

The search process across three databases yielded 325 articles in total: 41 from MEDLINE, 242 from Google Scholar (top 20 pages sorted by relevance), and 42 from Scopus. After removing duplicates, 250 unique articles remained. These were then screened based on titles and abstracts using the inclusion and exclusion criteria, resulting in the elimination of 239 articles. The remaining 11 articles underwent a detailed evaluation against the criteria for systematic review eligibility. Ultimately, 7 articles were included in the systematic review and meta-analysis. The article selection process is summarized in the flowchart presented in Figure 1.

LRRK2 variants in PD Patients with DBS

Table I provides an overview of the seven studies included in this systematic review, consisting of longitudinal follow-up, cohort, and case-control studies. Three LRRK2 mutation variants were identified across the studies: G2019S20-24, R1441G25, and G2385R26.

Five studies focusing on the G2019S variant were conducted in diverse regions, including France, North Africa, Israel, and the United Kingdom.[20-24] The study examining the R1441G variant included participants from the Basque region of Spain, where this mutation is believed to have originated.[25] Lastly, the study on the G2385R variant involved individuals of Han Chinese descent.[26]

Table I: Characteristics of the included studies showing LRRK2 mutation variant, origin, DBS target, follow up, and overall outcome

Study	Number of LRRK2 mutation subjects	Number of control subjects	Country/Population origin	LRRK2 mutation variant	DBS target nucleus	Follow-up duration (months)	Outcome
Schüpbach et al., 2007	9	60	France/North Africa (Caucasian)	G2019S (n=7), G2019S + heterozygous PRKN mutation (n=1), T2031S (n=1)	Subthalamic nucleus	6 to 12	LRRK2 PD patients undergoing DBS demonstrated outcomes that were comparable to or better than those of other groups, particularly in terms of motor symptom improvement, daily living activities, and L-DOPA-related complications.
Gómez-Esteban et al., 2008	4	41	Basque Area, Spain	R1441G	Subthalamic nucleus	6	Patients with LRRK2 PD carrying the R1441G mutation variant in the Basque region of Spain experienced poorer outcomes in motor improvement, daily living activities, and quality of life following DBS.
Angeli et al., 2013	5	67	United Kingdom (Caucasian)	G2019S	STN (LRRK2 (+)=5, LRRK2 (-)=65); GPi: (LRRK2 (+)=0; LRRK2 (-)=2)	12	Patients with LRRK2 PD undergoing DBS exhibited superior motor outcomes compared to those with idiopathic Parkinson's disease.
Greenbaum et al., 2013	13	26	Israel (Jewish)	G2019S	Subthalamic nucleus	6 to 12	Patients with LRRK2 PD undergoing DBS demonstrated favorable outcomes, with motor symptom improvements comparable to those seen in idiopathic Parkinson's disease patients.
Sayad et al., 2016	15	12	Algeria, North Africa	G2019S	Subthalamic nucleus	12	Patients with LRRK2 PD exhibited greater motor improvement following DBS compared to those with idiopathic Parkinson's disease.
Chen et al., 2019	8	49	China / Han Chinese	G2385R	Subthalamic nucleus STN (LRRK2 (+) = 18, LRRK2 (-) = 55); STN+GPi (LRRK2 (+) =1;	12	Patients with LRRK2 PD carrying the G2385R mutation variant showed no significant differences in motor function improvement, daily living activities, or L-DOPA dose reduction compared to patients with non-LRRK2 Parkinson's disease.
Anis et al., 2024	19	64	Israel	G2019S	LRRK2 (-) =1); GPi (LRRK2 (-) = 6); VIM (LRRK2(-) = 2)	12	The LRRK2 variant did not influence the motor outcomes of deep brain stimulation (DBS) in Parkinson's disease patients, nor did it increase the risk of psychosis or cognitive decline.

LRRK2: leucine-rich repeat kinase 2; DBS: Deep Brain Stimulation (DBS); STN: Subthalamic Nucleus; GPi: Globus Pallidus Internus; VIM: Ventral intermediate nucleus of thalamus; PRKN: Parkin RBR Ubiquitin Protein Ligase; PD: Parkinson's Disease

The target nuclei for DBS are detailed in Table I. All studies focused on the subthalamic nucleus, although some also targeted the internal Globus Pallidus and the ventral intermediate nucleus of the thalamus. Notably, Sayad et al. (2016)[23] employed a case-control study design with matching between cases and control groups. In contrast, the other studies exhibited class imbalance, with the number of participants in the control group (non-LRRK2/idiopathic PD) exceeding those in the case group (LRRK2 PD). The overall outcomes, encompassing both motoric and non-motoric aspects, are summarized in Table I.

Five of the seven studies included in this systematic review were previously included in the systematic reviews by Kuusimäki et al. (2020) and Artusi et al. (2019).[3,27] These earlier reviews were conducted before the publication of the studies by Anis et al. (2024) and Chen et al. (2019).[24,26] Kuusimäki et al. (2020) and Artusi et al. (2019) focused on all monogenic forms of PD compared to idiopathic PD, with all participants undergoing DBS.[3,27] In their analyses, LRRK2 PD, regardless of mutation variant, was grouped into a single population while comparing various monogenic Parkinson's genes. Additionally, their inclusion criteria encompassed case reports and case series. The current systematic review incorporates the newer studies by Anis et al. (2024) and Chen

Table II: Characteristics of the motoric response of the included studies in LRRK2 PD vs idiopathic PD

Study	LRRK2 Variant	PD Patients with LRRK2 Mutation (LRRK2 PD)				PD Patients without LRRK2 Mutation (Idiopathic PD)			
		Age at DBS	Age at DBS	UPDRS III Pre-DBS (medication-off)	UPDRS III Post-DBS (medication-off, on-stimulation)	Age at onset	Age at DBS	UPDRS III Pre-DBS (medication-off)	UPDRS III Post-DBS (medication-off, on-stimulation)
Schüpbach et al., 2007	G2019S (n=7), G2019S + heterozygous PRKN mutation (n=1), T2031S (n=1)	41.1 (6.1)	54.5 (8.8)	41.4 (12.4)	17.8 (9.6)	43.1 (7.8)	56.1 (9.3)	43.4 (17)	15.7 (9.9)
Gómez-Esteban et al., 2008	R1441G	43.2 (10.8)	56 (10.5)	48.5 (18.5)	39.7 (17.7)	58.03 (1.16)	Duration: 14.19 (6.9)	42.5 (10.6)	26.1 (8.4)
Angeli et al., 2013	G2019S	43 (8.7)	Duration: 12.1 (1.8)	65.4 (14.9)	30.6 (16.1)	40.8 (7.2)	Duration: 15.1 (5.5)	GPi = 40.5 (13.4), STN = 47.8 (14.8)	GPi = 51 (7.1), STN = 24.6 (11.3)
Greenbaum et al., 2013	G2019S	49.5 (6.8)	61.1 (6.6)	42.5 (11.8)	28.5 (13.3)	49.15 (6.6)	62.4 (4.5)	43.4 (12.3)	27.2 (14.1)
Sayad et al., 2016	G2019S	40.1 (9.4)	NA	55.8 (16.4)	27.3 (20.6)	40.3 (8.2)	NA	51.7 (14.4)	38.5 (16.6)
Chen et al., 2019	G2385R	52.13 (7.55)	62.38 (9.84)	43.38 (11.51)	20.5 (7.89)	51.8 (8.51)	61.29 (8.13)	49 (11.62)	29.69 (9.95)
Anis et al., 2024	G2019S	49.6 (7.3)	62.9 (6.8)	49 (40.5 – 50)	19 (14-22)	51.2 (9.8)	61.8 (8.9)	44 (37.2 – 53.7)	22 (16-34)

LRRK2: leucine-rich repeat kinase 2; DBS: Deep Brain Stimulation (DBS); STN: Subthalamic Nucleus; GPi: Globus Pallidus Internus; VIM: Ventral intermediate nucleus of thalamus; PRKN: Parkin RBR Ubiquitin Protein Ligase; PD: Parkinson's Disease

Table III: Quality assessment of the included studies using STROBE

Item STROBE	Schupbäch et al., 2007	Gómez-Esteban et al., 2008	Angeli et al., 2013	Greenbaum et al., 2013	Sayad et al., 2016	Chen et al., 2019	Anis et al., 2024
1	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y
3	U	U	U	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y
5	Y	U	Y	Y	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y
7	U	U	U	U	Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y
9	U	U	U	U	U	U	U
10	U	U	U	U	U	U	U
11	Y	Y	Y	Y	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y
13	U	Y	Y	Y	U	Y	Y
14	Y	Y	Y	Y	Y	Y	Y
15	Y	Y	Y	Y	Y	Y	Y
16	Y	Y	Y	Y	Y	Y	Y
17	U	U	U	U	U	U	U
18	Y	Y	Y	Y	Y	Y	Y
19	U	U	U	U	Y	Y	Y
20	U	U	U	U	U	Y	Y
21	U	U	U	U	U	Y	Y
22	Y	N	N	Y	Y	Y	Y

STROBE: Strengthening the reporting of observational studies in epidemiology; Y: Yes; U: Undetermined; N: No.

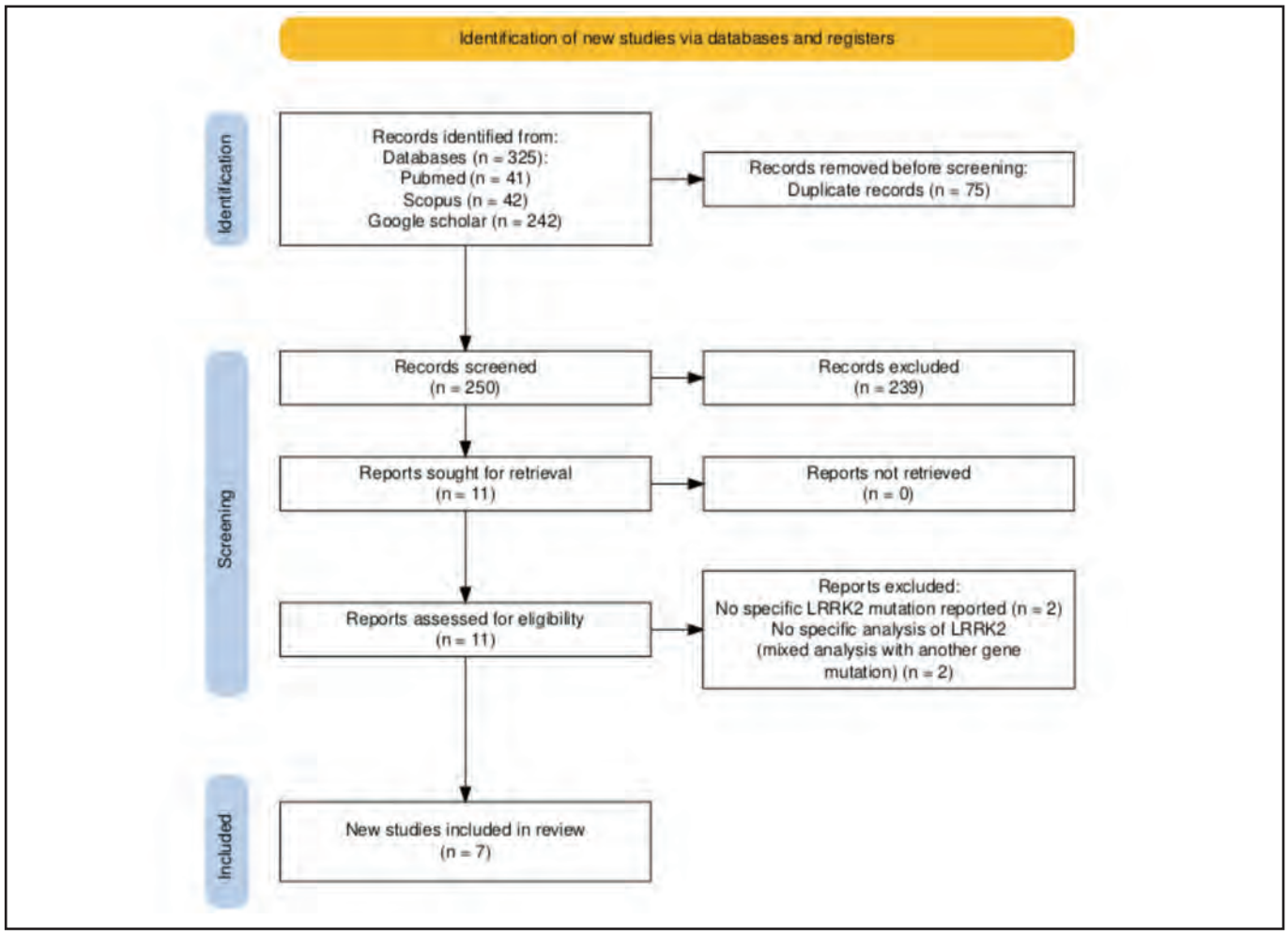

Fig. 1: PRISMA flowchart diagram of the included studies

et al. (2019).[24,26] Furthermore, it distinguishes each LRRK2 mutation variant to specifically evaluate motor responses to DBS treatment, as assessed by UPDRS III scores.

The motor response of LRRK2 PD to DBS

All Parkinson's disease (PD) patients included in this review underwent deep brain stimulation (DBS) after a minimum of 10 years of PD progression (Table II). The mean age of onset and the mean age at which DBS was performed were comparable between the LRRK2 PD and idiopathic PD groups across studies. The motor responses, assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) III, are presented in Table II, which includes baseline motor responses before DBS and post-DBS responses (on stimulation).

The meta-analysis revealed no statistically significant difference in the overall effect of DBS between LRRK2 PD and idiopathic PD, with a mean difference (MD) of -3.00 (-8.52; 2.52) (Figure 2). However, the overall heterogeneity was high (I^2 = 63.1%; $P < 0.05$), suggesting variability across studies. When subdividing the LRRK2 variants, substantial heterogeneity remained, even within the G2019S subgroup (I^2 = 56.9%; $p<0.05$). The other variants, R1441G and G2385R, were each represented by a single study. The results showed that the G2385R variant was associated with a significant improvement in UPDRS III (MD = -9.19; -15.33; -3.05), the G2019S variant showed a statistically insignificant improvement (MD = -2.92; -8.51; 2.68), and the R1441G variant demonstrated no significant improvement (MD = 13.6; -3.94; 31.14). The test for subgroup differences indicated a significant effect ($p<0.05$), suggesting that different LRRK2 variants may lead to distinct motor outcomes following DBS.

Quality assessment

The quality assessment of the studies indicated that the core components of the introduction, methods, results, and discussion were adequately addressed in all cases. However, certain studies lacked detailed information on diagnostic criteria, potential confounders, sample size, the workflow of subject selection, subgroup analysis, limitations, and funding sources (Table III). Given the nature of monogenic Parkinson's disease as a rare subset with a limited number of subjects, the absence of these elements may be considered acceptable.

DISCUSSION

This systematic review identifies the following LRRK2 mutation variants in relation to motor response compared to idiopathic Parkinson's disease: G2019S, G2385R, and R1441G, ranked from most to least effective. The G2019S

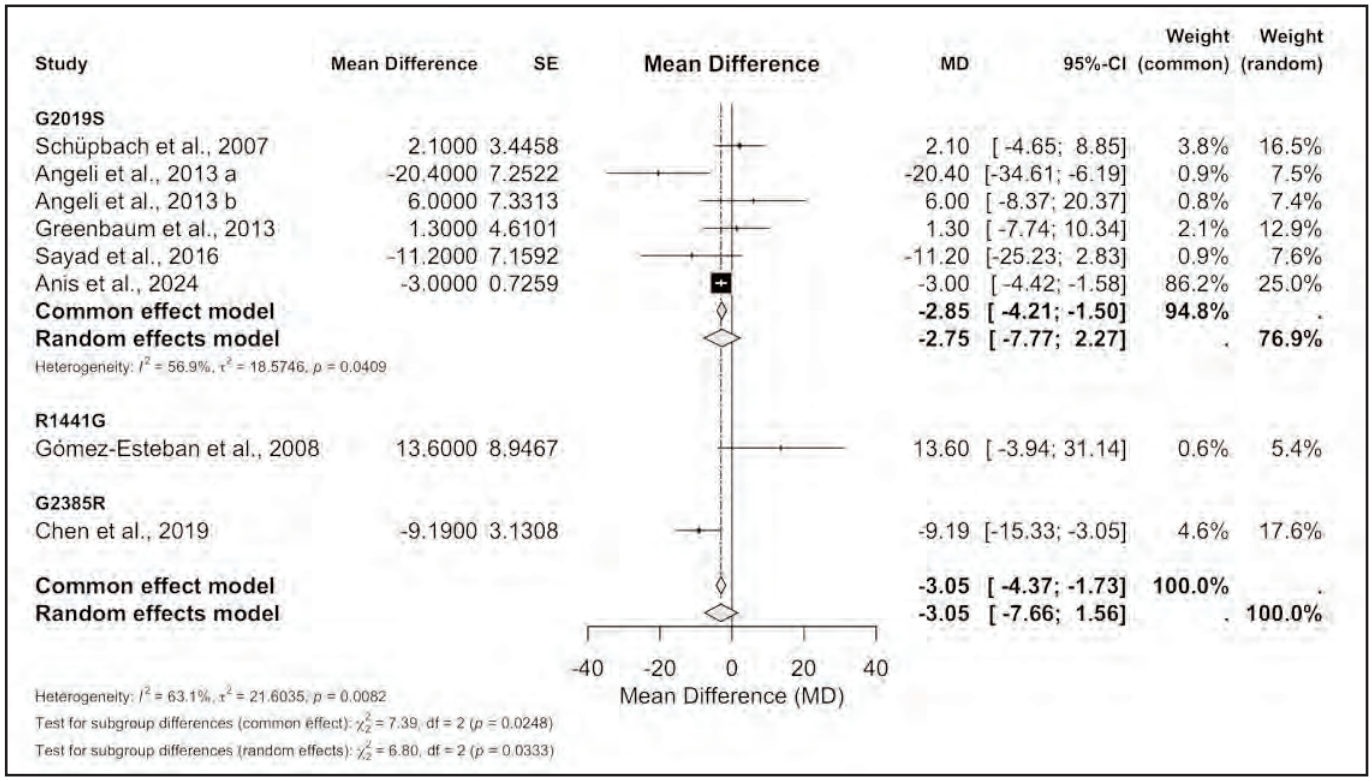

Fig. 2: Forest plot illustrating motor response as assessed by UPDRS III, with subgroup analysis based on specific LRRK2 variants

variant demonstrated a significant motor response, as evidenced by improved UPDRS III scores and reduced levodopa equivalent daily dose (LEDD) after DBS surgery. This mutation, the most common in monogenic PD, was studied in well-established research settings, particularly in regions with a higher prevalence of familial Parkinson's disease. For example, Greenbaum et al. (2013) conducted their study within the Ashkenazi Jewish population in Israel.[22] The G2019S variant showed a superior motor response to DBS when compared to the R1441G variant. In contrast, studies on Parkinson's patients with the LRRK2 R1441G variant indicated clinically insignificant motor improvements, suggesting a limited DBS response.[25] Patients with LRRK2 R1441G Parkinson's disease did, however, show a sustained positive pharmacological response to L-DOPA after DBS surgery.

This finding is supported by evidence suggesting that PD associated with the LRRK2 G2019S variant progresses more slowly in terms of drug-resistant symptoms and experiences milder disease deterioration compared to idiopathic Parkinson's disease.[27] This review includes studies that utilized DBS targeting the subthalamic nucleus in patients with LRRK2 PD. Therefore, the systematic review focuses specifically on this DBS target and its association with motor response, as measured by UPDRS III scores.

A significant limitation identified in nearly all studies included in this systematic review is the class imbalance in the number of subjects between the two groups20-22,24-26, with the exception of the study by Sayad et al. (2013) which reported that 55% of participants had the LRRK2 G2019S variant in comparison to the control group, owing to the case-control study design.[23] The significance of this imbalance lies in its potential to affect statistical analysis, reducing its power due to the unequal distribution of subjects. Class imbalance in genetic research presents notable challenges, mainly due to the rarity of specific genetic mutations. Most studies assessed motor response through UPDRS III scores, which, while practical, may not capture the full spectrum of clinical outcomes, including non-motor symptoms or long-term functional status. The most recent study by Anis et al. (2024) also compared LRRK2 PD with GBA1 PD and idiopathic PD.[24] One key finding was that LRRK2 PD and idiopathic PD exhibited comparable motor, behavioural, and cognitive outcomes after DBS, in contrast to GBA1 PD, which showed an increased risk for psychosis and cognitive decline. Additionally, the studies primarily focused on a single DBS target, the subthalamic nucleus, with less comprehensive exploration of other potential targets, such as the globus pallidus internus. Although detailed reporting of DBS programming parameters and lead placement was limited in the included studies, almost all patients received STN-targeted DBS. The differences in electrode placement or target selection were minimal, thereby reducing the potential impact of such variability on outcomes. This limitation affects the generalizability of the findings to other DBS techniques. Consistent with this limitation, our meta-analysis demonstrated a high degree of heterogeneity (I^2 = 63.1%), likely reflecting the variability introduced by class imbalance and small sample sizes inherent in studies of rare mutations. This high heterogeneity necessitates cautious interpretation of the pooled effect estimates.

The G2019S, G2385R, and R1441G variants are among the reported pathogenic mutations causing LRRK2 PD.[28] All

pathogenic mutations in the LRRK2 gene are located within the ROC (Ras of complex), COR (C-terminal of Roc), and kinase domains.[4] The G2019S variant is situated within the kinase activation loop and leads to increased kinase activity. The R1441G/C/H variants are located in the ROC GTPase domain, resulting in the suppression of GTP hydrolysis and an increased affinity of the LRRK2 protein for GTP, which in turn leads to a three to four fold increase in kinase activity towards the Rab substrate compared to normal. Meanwhile, the N1437H variant of LRRK2 allows the LRRK2 protein to remain bound to GTP by stabilizing the LRRK2 protein dimer, even though the protein's affinity for GTP or its GTPase activity is reduced. The G2385R variant is located in the WD40 domain and disrupts WD40 domain dimerization, thereby enhancing LRRK2 protein activity within the cell.[29] Overall, these pathogenic mutations function by either decreasing GTPase activity encoded by the tandem ROC-COR bidomain or by increasing kinase domain activity.[29-30]

All known pathogenic LRRK2 mutations cluster within a tightly conserved region of the gene that encodes its critical functional domains (ROC, COR, and kinase domains, with risk variants also found in the WD40 domain). According to the NCBI Conserved Domain Database, the most common LRRK2 mutation (G2019S) lies in the kinase domain's activation loop and causes elevated kinase activity, whereas the R1441G mutation in the ROC GTPase domain impairs GTP hydrolysis and similarly results in kinase hyperactivation.[31] The G2385R variant affects the WD40 domain, disrupting normal LRRK2 dimerization and protein interactions, which also enhances LRRK2 activity.[29] These distinct molecular mechanisms trigger different downstream effects – for example, hyperactive LRRK2 leads to excessive phosphorylation of its Rab GTPase substrates and disruption of autophagic pathways – potentially producing variant-specific patterns of neurodegeneration.[28] This provides a biological rationale for the observed differences in DBS outcomes: variants such as G2019S and G2385R, which increase kinase activity but may preserve more typical network function, showed better motor improvement with STN-DBS, whereas the R1441G variant's more disruptive effect corresponded with a relatively limited DBS response.

Subsequent research examining the effects of DBS in monogenic Parkinson's disease associated with LRRK2 mutations should incorporate additional parameters, including various sections of the UPDRS, LEDD, and non-motor outcomes, to yield a more thorough therapeutic response profile. Studies investigating DBS responses in Parkinson's patients with various gene mutations and a detailed analysis of genetic variants are essential for comprehending the broader implications of genetic diversity on therapeutic outcomes.

CONCLUSIONS

Parkinson's disease associated with LRRK2 mutations exhibits diverse motor responses to deep brain stimulation (DBS), depending on the specific mutation variant. Patients with the LRRK2 G2019S and G2385R variants showed clinically significant improvements in motor responses following DBS, as evidenced by the enhancement in UPDRS III scores. These motor responses were either comparable to or superior to those seen in idiopathic Parkinson's disease patients following DBS targeting the subthalamic nucleus. In contrast, Parkinson's disease associated with the LRRK2 R1441G variant demonstrated an inadequate motor response, with no clinically significant improvement in UPDRS III scores. This systematic review highlights the importance of genetic testing in guiding evidence-based decision-making within precision medicine. By providing insight into the genetic foundations and clinical variability of Parkinson's disease, genetic testing enables clinicians to better understand patient responses to DBS, thereby supporting the customization of therapeutic strategies.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare.

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