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Efficacy of Deep Brain Stimulation for the Treatment of Monogenic Dystonia Symptoms: A Systematic Review

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ABSTRACT

Background: Deep brain stimulation (DBS) is an essential treatment option for disabling segmental or generalized dystonia. An underlying monogenic etiology is increasingly recognized as an important predictor of DBS outcomes. Moreover, the genetic background of dystonia is continuously expanding, posing new challenges in the tailored counseling of patients regarding advanced therapies.

Methods: To improve the quality of available evidence on the efficacy of DBS for treating monogenic dystonia, we conducted a systematic review in accordance with PRISMA guidelines. We applied a rigorous methodology and maximized the amount of information provided by including all patients, regardless of age or applied rating scale.

Results: Our findings confirm the high probability of a good DBS outcome in patients harboring *TOR1A, SGCE, PANK2*, and *TAF1* variants. An intermediate response was associated with *KMT2B* and *THAP1* variants. A particularly favorable outcome with > 80% improvement in dystonia symptoms was associated with a subset of DYT-*TOR1A* patients and few cases with *SGCE-, KMT2B-, THAP1-*, *GNAO1-*, and *TAF1*-related disease. Poor study quality, non-systematic assessment of DBS response, and pooling of patients with different genetic etiologies were among the encountered limitations.
Conclusions: Based on the collected evidence, we formulated recommendations for applying DBS in monogenic dystonia. Our findings, together with the cumulative literature, advocate the introduction of genetic testing in the pre-DBS work-up. They furthermore highlight the need to implement and report on systematic assessments of DBS outcomes, including mandatory patient-reported outcomes. These steps will ensure optimal counseling and continuous improvement in the care of patients with monogenic dystonia.

1 | Introduction

Dystonia is a movement disorder characterized by the occurrence of sustained or intermittent abnormal movements that result in abnormal posturing, twisting, or patterned movements that can affect the entire body [1]. Deep brain stimulation (DBS) is an essential option in the treatment of disabling segmental or generalized dystonia, where the effectiveness of medical therapy is limited [2]. DBS was approved for the treatment of dystonia by the Food and Drug Administration in 2003 (Humanitarian Device Exemption number, H020007). The efficacy of DBS for the treatment of dystonia has been supported by a number of randomized clinical trials and more than 20 years of clinical experience. Cumulative evidence has also shown that, beyond an overall good DBS outcome, up to 25% of patients with isolated dystonia show an insufficient, or even lacking, benefit [3, 4]. The role of genetics was recognized early on, with the presence of a "DYT1-positive" status (according to the current nomenclature, DYT-*TOR1A* disease) generally predicting a good DBS outcome [5]. In the meantime, the molecular background of monogenic dystonia has expanded significantly [6]. Particularly, the availability of next-generation sequencing-based diagnostics has accelerated the molecular identification of dystonia-causing variants, allowing diagnostic assignment early in the disease. Genes involved in the pathogenesis of dystonia are associated with multiple, seemingly unrelated pathways that converge on dysfunction of the basal ganglia and related circuits [6]. Despite the common clinical presentation as "dystonic phenotype", the neurophysiological alterations in these networks can be very different and thus show a different response to modulation by DBS [7].

The limited availability of evidence and clinical trials is a major hurdle in counseling patients with rare diseases. This problem is also faced by clinicians involved in the selection and counseling of dystonia patients for DBS [8].

A number of previous reviews have addressed the efficacy of DBS in the treatment of monogenic dystonia. However, they focused on single outcome measures to assess efficacy [5], reported findings in single dystonia genes [9], or in defined age groups [10].

As part of a project initiated by the European Reference Network for Rare Neurological Diseases (ERN-RND), we conducted a systematic review of the literature with the support of methodological experts with the aim of maximizing the available evidence for the use of DBS in monogenic dystonia. As our goal is to improve the evidence base for counseling, we aimed to collect the largest number of responses from individual patients to define the frequency and magnitude of clinical response in individual dystonia genes. Based on this information, we formulated recommendations based on a clinical consensus to guide the use of DBS in the treatment of monogenic dystonia. Furthermore, we identified and discussed critical gaps for future clinical research in this area.

2 | Methods

We performed a systematic review of the efficacy of DBS for the treatment of monogenic dystonia symptoms. Our research question was formulated following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [11] (Table S1). The disease nomenclature used is consistent with the recommendations of the International Parkinson and Movement Disorder Society [12]. We addressed dystonia genes as reported in the MDS database at the time of the study initiation [12].

2.1 | Research Question and Eligibility Criteria

The initial clinical question was translated into a PICO (Population-Intervention-Comparator-Outcome) format to guide the literature search: "What is the efficacy of deep brain stimulation for the treatment of monogenic dystonia symptoms?" The systematic review protocol was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) repository with the identification CRD42023448145.

Specific inclusion criteria were used to select relevant studies for the systematic review. These criteria are described in Table 1 and reported in detail in the previously published protocol [13]. We only included studies written in English. We excluded studies that did not report clinical data, non-peer-reviewed studies such as conference abstracts, editorials, and letters to the editor, and those for which full text was not available for retrieval. Non-human studies and patients without genetic confirmation of the disease were also excluded. In addition, only studies with ≥ 3 months of follow-up after surgery were included. We considered patients with clinical improvement of ≥ 50% as good responders, patients with improvement of 25%–49% as partial responders, and patients with improvement of < 25% as non-responders [3, 4]. Among the good responders, we identified patients with an excellent response, defined as an improvement of greater than 80% [14]. We calculated the percentage improvement in each outcome measure, and when more than one tool was used to assess efficacy, the average percentage improvement of all scales used was calculated and considered for further analysis.

TABLE 1 | PICO question with the specific inclusion criteria defined for this study.

PICO question	What is the efficacy of deep brain stimulation for the treatment of monogenic dystonia symptoms?
Population	• Patients of all ages with monogenic dystonia who have genetic confirmation of the disease • Monogenic dystonia due to variants in: *ADCY5, ANO3, AOPEP, ATP1A3, EIF2AK2, GCH1, GLB1, GNAO1, GNAL, HPCA, KMT2B, PANK2, PRKRA, SGCE, TAF1, TH, THAP1, TOR1A, TUBB4A, VPS16*
Intervention	• Deep brain stimulation (DBS)* ◦ Targets: – Globus pallidus internus (GPi) – Subthalamic nucleus (STN) – Ventral intermediate nucleus (VIM) – Pedunculopontine Nucleus (PPN) – Other targets *Follow-up (at least 3 months after surgery)
Comparator	None
Outcomes	• Clinical response as reported by rating scales assessing: – Motor symptoms: BFMDRS, UMRS, TWSTRS, UDRS, BADS, TSUI, GDSRS – Non-motor symptoms: CCHQ, GQL, AIMS, SF-36, UPDRS, VAS, CGI-S, BPRS, BDI, PRI, WMI, PSI, SBRS, CMS, SEDS, EDCS, MHC, PHC, PSQ, TMCA, VCI • Efficacy of DBS • Safety of DBS • Adverse events of DBS • Quality of life, activities of daily living (ADL) or PROMS • Medication regimen changes

2.2 | Search Strategy

An initial systematic literature search to review the scientific evidence was conducted in July 2023 and updated in June 2024. This review spanned from January 2000 to June 2024. Embase (Elsevier), the Cochrane Library (Wiley), including the CENTRAL clinical trials register, and MEDLINE (Ovid) were searched as reference databases. Other sources included PsyncINFO (EBSCO), CINAHL (EBSCO), and Web of Science (WoS). Subject specific databases were included to retrieve information from rare disease resources such as Orphanet, EURORDIS, NORD, RARE Best Practices and Gene Reviews. Finally, the International Health Technology Assessment (INAHTA) database, a systematic review-specific resource, was also included in the search. Both controlled language (descriptors) and free terminology were used. The initial strategy was carried out in MEDLINE (Ovid) and later adapted to the syntax of each database. The initial search strategy is described in Table S2.

2.3 | Study Screening, Data Extraction, and Quality Assessment

The identified references were imported into the reference management section of the Covidence software application (https://www.covidence.org/) and duplicates were removed. The authors independently filtered the references by title, abstract, and full text according to the inclusion criteria. The excluded studies were classified according to the first criterion that did not fit the PICO format. Disagreements between the reviewers were resolved by another researcher. Data were extracted by independent authors using Covidence software and then recorded in Excel spreadsheets. The quality of the studies was assessed independently by the authors using specific tools for each study type, as described in detail in the published review protocol [13]. Disagreements were resolved by discussion to reach consensus. None of the studies was excluded because of low quality. To address the potential for patient data bias, prior to including a systematic review, its bibliography was reviewed in detail to compare it against all included case series and cohorts, thereby preventing the multiple reanalysis of identical patient data. Second, the publication dates of all included studies in our study were thoroughly analyzed to confirm the timeline and eliminate repetitive inclusions.

2.4 | Expert Recommendation

In the absence of formal guidelines on the topic, the clinical experts involved in the review process agreed upon finalization of the project to develop recommendations based on the findings of the systematic literature review. They agreed to formulate specific recommendations for each monogenic form of dystonia for which at least ten individual ratings were available, developing them in reference to the degrees of recommendation set out in existing dystonia treatment guidelines [15]. The results of the literature search and the recommendations were presented and discussed in two separate online meetings. The recommendations were discussed and approved through a consensus process according to the European Reference Network guidelines (https://health.ec.europa.eu/publications/european-reference-network-clinical-practice-guidelines-and-clinical-decision-support-tools_en).

2.5 | Data Sharing

The data that supports the findings of this study are available in the Tables S1–S5 of this article and on reasonable request from the corresponding author.

3 | Results

3.1 | Study Selection and Characteristics

A total of 1531 records were found in the initial search that began in July 2023. The updated search in June 2024 yielded 273 new records. After two screening steps and removal of coincident references between both searches, $n = 90$ references were finally included in this systematic review. One study [10] reported data from both a cohort of patients and a systematic review conducted by the same authors. Therefore, we considered two parts of this study separately: (i) a cohort study and (ii) a systematic review, resulting in a total of $n = 91$ studies. The screening process according to the PRISMA flowchart [16] is shown in Figure 1.

The majority of included references were from Europe (52.2%, $n = 47$) followed by 26.7% from the Americas ($n = 24$), 17.8% from Asia ($n = 16$), 2.2% from Australia ($n = 2$), and 1.1% from Africa ($n = 1$). Case series and case reports accounted for 70.3% of the selected references ($n = 64$). Of the remaining references, 15.4% were cohort studies ($n = 14$), 11% were systematic reviews ($n = 10$), and 2.2% were qualitative studies ($n = 2$). One study (1.1%) was a randomized controlled trial. The year of publication ranged from 2004 to 2024. Details of included studies are specified in Table S3.

3.2 | Patient Demographics

From an initial cohort of 3215 patients, 2084 were initially identified with a confirmed dystonia-causing variant. The gender distribution was approximately equal, with 36.5% females ($n = 761$) and 41.2% males ($n = 858$). In 22.3% of patients ($n = 465$) the gender was not specified. The mean age at symptom onset was 11.2 years (range: 9.6 months to 64 years). In some studies reporting larger cohorts, the authors did not specify which patients carried which gene variants ($n = 540$ cases in total). Thus, only 1544 patients with monogenic dystonia could ultimately be assigned to a specific gene group. In this collective, *TOR1A* was the most frequently involved gene (56% of cases, $n = 865$), followed by *THAP1* in 13.4% ($n = 207$) and *SGCE* in 12.7% ($n = 196$) (Table 2). No cases with *EIF2AK2*, *GLB1*, or *AOPEP* variants remained in the final cohort.

3.3 | Deep Brain Stimulation Efficacy

GPi was the primary brain target used for DBS (84.2%, $n = 1754$). The mean age at surgery was 21.2 years (range 4–69 years). Ten studies reported long-term follow-up of ≥ 10 years (8, 23–31). In the remaining studies ($n = 80$), the mean follow-up was 2.1 years (range: 3 months to 9 years). There was high variability in the outcome measures used to assess the efficacy of DBS (see Table 3 for a summary). The most commonly used clinician-reported outcome measure was the motor subscale of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS-M), used in 53.7% of the total number of evaluations, followed by the Unified Myoclonus Rating Scale (UMRS), used in 10.9% of the evaluations. The most commonly used patient-reported outcome measures was the disability subscale of the BFMDRS (BFMDRS-D) (Table 3).

Considering motor outcome, overall, 67.6% of patients ($n = 1408$) showed a good response to DBS, 21.4% ($n = 446$) were partial responders, and 30 patients (1.4%) did not show significant improvement. Considering functional outcome, BFMDRS-D scores showed a good response in 63.9% of patients (60/94), a partial response in 14.9% (14/94), and no significant improvement in 21.2% (20/94). Data from further patient-reported outcome measures were sparse and showed a mean improvement of 52.4%. Data on preoperative pharmacologic treatment were reported for less than half of the patients, with the majority showing no significant clinical benefit. Trihexyphenidyl, levodopa, baclofen, tetrabenazine, haloperidol, valproic acid, botulinum toxin, gabapentin, and biperiden, among others, were the most commonly used medications to treat dystonia symptoms before surgery. Some patients continued treatment after surgery, albeit with dose adjustments, suggesting a partial response to DBS [17–21]. Bradykinesia [22], dysarthria, swallowing and chewing difficulties [23], gait freezing [24–26] were the most common adverse events reported after surgery. Intracerebral hemorrhage, tonic–clonic seizures [24, 27, 28], dizziness, and nausea [29] were other rare adverse events. Battery exhaustion, stimulator malfunction, cable fracture, and lead migration or displacement were common device-related adverse events, most of which resolved with surgical revision after the initial procedure [9, 30–35]. Device-related infection with subsequent clinical worsening of the movement disorder was also reported [21, 26, 28, 36].

3.4 | Efficacy of Deep Brain Stimulation According to the Genotype

The following paragraphs provide a detailed description of DBS efficacy according to genotype, as defined by an analysis of individual patient scores. This resulted in a significant reduction in the available sample size, particularly when considering the functional outcome. Figure 2 and Table S4 graphically summarize these data. For genotypes with ≥ 10 available single patient scores, we report at the end of each paragraph the key findings and the expert recommendation formulated on their basis.

3.4.1 | DYT-*TOR1A*

Detailed preoperative and postoperative individual rating scale scores were available for 96 out of 865 retrieved DYT-*TOR1A* patients. The assessment tools used were the UDRS in $n = 10$ patients and the BFMDRS-M in the remaining cases.

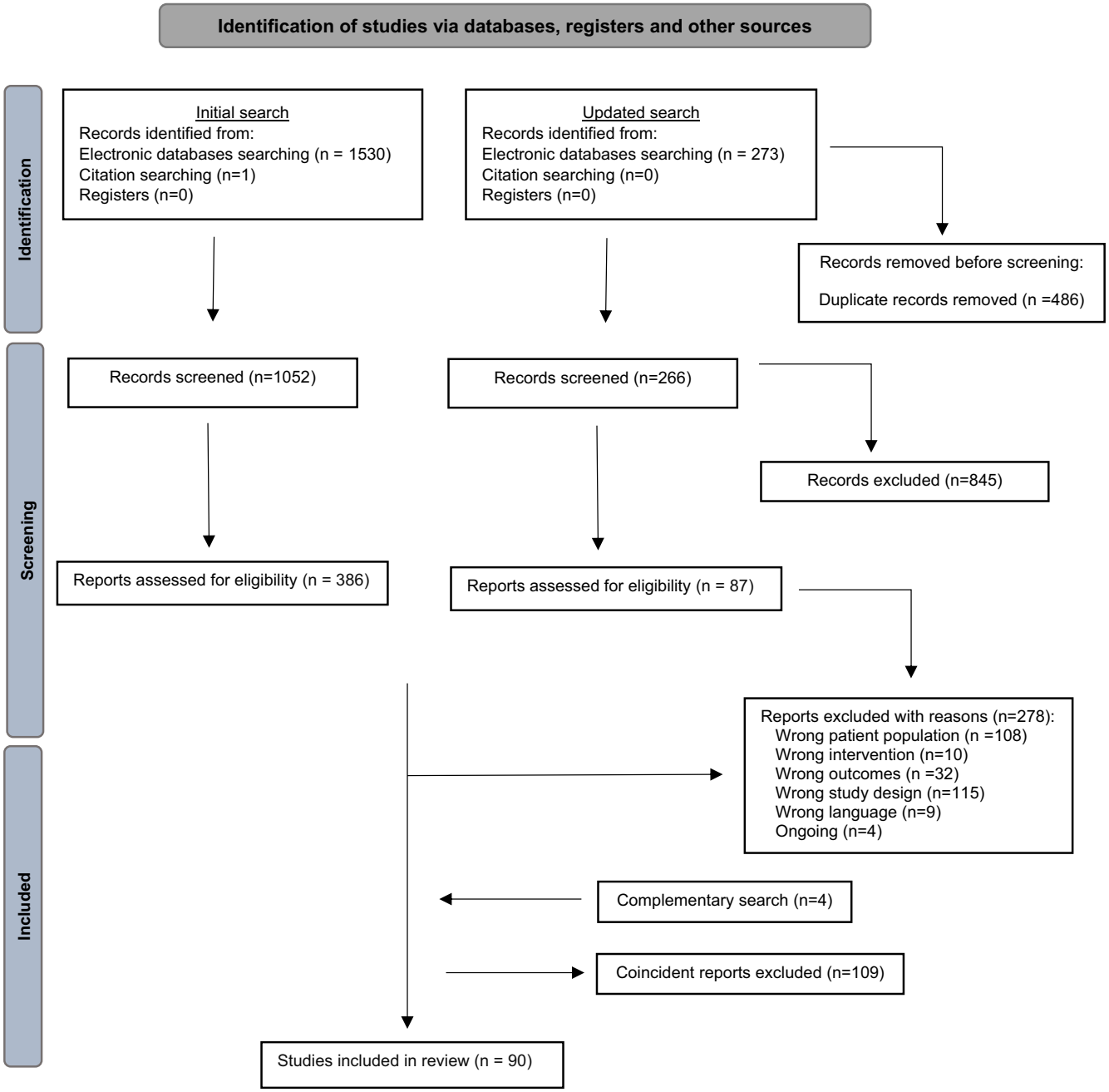

FIGURE 1 | PRISMA flowchart. Illustration of the PRISMA flowchart showing the title-abstract and full-text screening of articles related to the efficacy of deep brain stimulation for the treatment of monogenic dystonia.

The median improvement in motor scales after DBS was 72.8% (interquartile range [IQR] 52.4–94). Looking at individual patient responses, 76% had a good response, 10.4% were partial responders, and 13.5% were classified as non-responders. A subgroup of good responders ($n = 37$, 38.5%) showed excellent dystonia control with DBS with >80% improvement in motor scores. The median improvement in BFMDRS-D was 86%, with 29/31 patients showing a good response (93.5%). GPi was the target of choice except in a few cases. In one case where GPi DBS failed due to non-optimal electrode placement, STN DBS was performed with excellent results (96.6% mean improvement in BFMDRS-M) [37]. In two other cases with poor to partial results, both GPi and STN electrodes were implanted [38]. Intervention in adulthood did not influence the outcome. Reported reasons for lack of response to DBS were non-optimal electrode positioning ($n = 2$), fixed skeletal deformities ($n = 1$). In the remaining $n = 10$ cases, a more aggressive phenotype of DYT-*TOR1A* dystonia characterized by younger age at onset, faster disease progression, and cranial involvement was observed as a possible factor associated with long-term suboptimal responses to DBS. Indeed, these patients experienced >30% improvement in dystonia postoperatively; however, secondary worsening of dystonia began between 6 months and 3 years after DBS [34].

TABLE 2 | Frequency of single gene etiologies in patients with monogenic dystonia considered in the present systematic review.

Gene	Number of patients	Relative frequency (%)
TOR1A	865	56
THAP1	207	13.4
SGCE	196	12.7
PANK2	86	5.6
TAF1	63	4.1
GNAO1	57	3.7
KMT2B	34	2.2
GNAL	10	0.7
ADCY5	9	0.6
PRKRA	4	0.3
TUBB4A	3	0.2
ATP1A3	5	0.3
HPCA	1	0.1
GCH1	1	0.1
TH	1	0.1
ANO3	1	0.1
VPS16	1	0.1

DYT-TOR1A
N = 96
Median improvement: 72.8%
% of good responders: 76%
Loss of efficacy: Reported in 10 patients in the long-term, due to secondary worsening
Recommendation: Pallidal DBS is recommended for the treatment of generalized or segmental dystonia due to DYT-*TOR1A*.

3.4.2 | MYC/DYT-*SGCE*

Detailed individual pre- and post-operative scores were available for 22 MYC/DYT-*SGCE* patients (of whom $n = 20$ underwent GPi DBS and $n = 2$ VIM DBS). The median BFMDRS-M improvement after surgery was 71.8% (IQR 57.2–76.6). The TSUI score was also applied in 6/22 patients, with a mean postoperative improvement of 51.4% (SD 27.6). Looking at individual patient responses, 18 patients (81.8%) had a good response (with an improvement of > 80% in 4/22), three (13.7%) were partial responders, and one (4.6%) was a non-responder. The latter patient was a woman who underwent GPi DBS at the age of 42 years, while the age of onset was 12 years [39]. Her pharmacological treatment prior to DBS included first-generation antipsychotics. She also underwent a wire revision due to scarring. The improvement after DBS was sustained in seven patients with long-term follow-up (range: 7–20 years).

Regarding myoclonus, all patients ($n = 16$) were classified as good responders, with a median UMRS improvement of 67.5% (IQR 56–78.9). A higher probability of a better response of myoclonus than dystonia to DBS was suggested also by a meta-analysis of 51 *SGCE* patients, which, however, did not report individual patient scores [28].

MYC/DYT-*SGCE*
N = 22
Median improvement: 71.8%
% of good responders: 81.8%
Loss of efficacy: None reported
Recommendation: Pallidal DBS is recommended for the treatment of generalized or segmental dystonia and myoclonus due to MYC/DYT-*SGCE*.

3.4.3 | DYT-*THAP1*

Detailed pre- and postoperative motor rating scale scores were available for 18 of 35 DYT-*THAP1* patients who underwent GPi DBS. In the majority of cases, the BFMDRS-M was used, while the TWSTRS scale was used in $n = 2$ cases. The mean improvement after surgery was 44.4% (SD 23.8). Considering the individual patient responses, six patients (33.3%) showed a good response, nine a partial response (50%), and three (16.7%) were classified as non-responders. These latter patients had prominent facial/bulbar symptoms within a segmental/generalized dystonia phenotype, and in one case a delayed intracerebral hematoma developed along a lead. On the other hand, a 12-year-old adolescent who received GPi DBS for severe trunk dystonia that had been present for three years showed an excellent response with > 90% improvement [40]. Of five patients with longer follow-up (5 to 10 years), two showed a sustained benefit, two a partial response, and one no response. Functional scores were available in five patients only. They displayed a mean improvement of 60.7% in BFMDRS-D.

DYT-*THAP1*
N = 18
Mean improvement: 44.4%
% of good responders: 33.3%
Loss of efficacy: None reported
Recommendation: Pallidal DBS can be effective for the treatment of generalized or segmental dystonia due to DYT-*THAP1*.

3.4.4 | DYT/PARK-*TAF1*

Detailed pre- and postoperative rating scale scores were available for 15 DYT/PARK-*TAF1* patients who underwent GPi DBS.

TABLE 3 | Use of rating scales to assess the efficacy of DBS in patients with monogenic dystonia.

Acronym	Full scale name	*n*/%	Acronym	Full scale name	*n*/%
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale	1673/53.7	UPDRS	Unified Parkinson's Disease Rating Scale	28/0.9
UMRS	Unified Myoclonus Rating Scale	339/10.9	VAS	Visual Analogue Scale	16/0.5
BADS	Barry-Albright Dystonia Scale	162/5.2	SEDS	Schwab England Disability Scale	16/0.5
TWSTRS	Toronto Spasmodic Torticollis Rating Scale	141/4.5	GDSRS	Global Dystonia Severity Rating Scale	1/0.03
UDRS	Unified Dystonia Rating Scale	129/4.1	CCHQ	Care and Comfort Hypertonicity Questionnaire	14/0.4
TSUI	TSUI Rating Scale	113/3.6	GQL	Global Quality of Life	14/0.4
AIMS	Abnormal Involuntary Movement Scale	110/3.5	CMS	Children's Memory Scale	13/0.4
SF-36	Short Form-36	113/3.6	BDI	Beck Depression Inventory	6/0.2
EDCS	Everyday Cognition Score	37/1.2	PRI	Perceptual Reasoning Index	9/0.3
MHC	Mental Health Composite score	37/1.2	WMI	Working Memory Index	9/0.3
PHC	Physical Health Composite	37/1.2	PSI	Processing Speed Index	9/0.3
PSQ	Parkinsonian Symptom Questionnaire Score	37/1.2	SBRS	Subjective Benefit Rating Scale	4/0.1
TMCA	Telephone Montreal Cognitive Assessment	37/1.2	VCI	Verbal Comprehension Index	9/0.3

Note: N = number of times each scale was used. % = percentage of times each scale was used in relation to the total number of assessments.

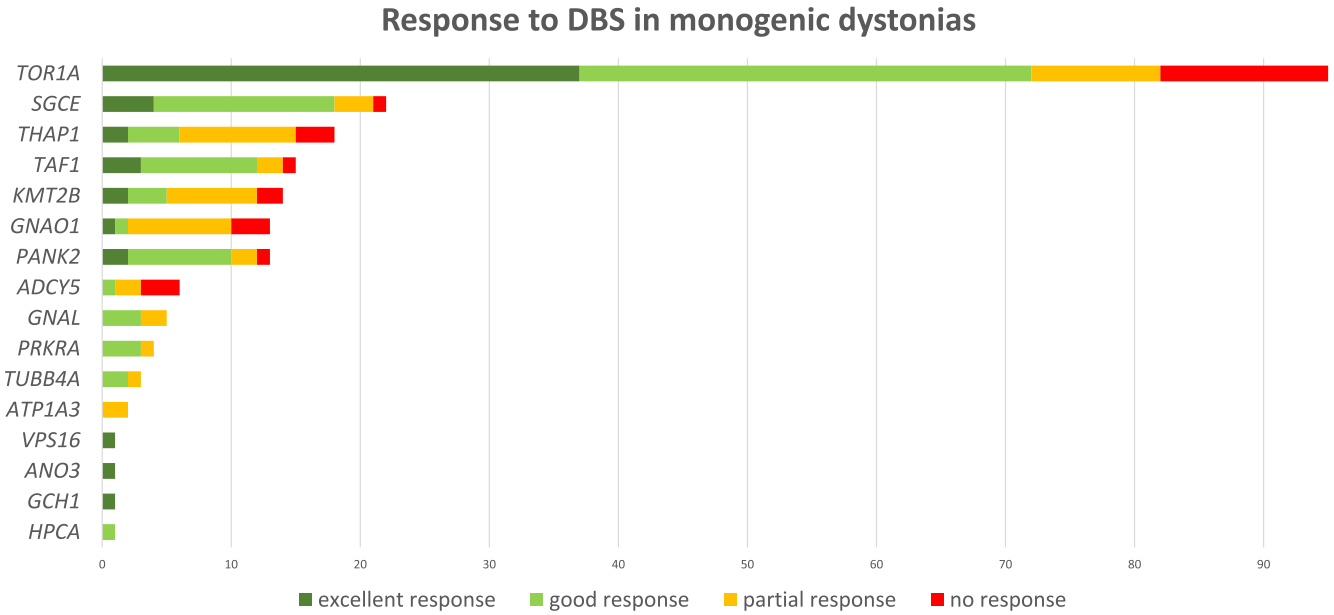

FIGURE 2 | Response to DBS in monogenic dystonia according to changes in dystonia motor scores. The graphic summarizes the responses of individual patients to DBS according to their genotype. The absolute patient number is described by the horizontal axis. The responder classification, according to changes in motor scores, is defined as follows: Excellent response: > 80%; Good response: 50%–80%; Partial response: 25%–49%; No response: < 25%.

The majority of patients (80%, 12/15) were good responders with a mean post-DBS improvement in BFMDRS-M of 64.2% (SD 23.5). Three patients showed an improvement of > 80%. A 45-year-old man who had experienced symptoms for one year, with no apparent atypical features or adverse events related to DBS, was classified as a non-responder [31]. A larger study with

$n = 16$ patients reported a mean BFMDRS-M improvement of 59% at 6 months. This study only reported detailed scoring data graphically. Thus, it was not possible to extrapolate individual patient scores.

DYT/PARK-*TAF1*
N = 15
Mean improvement: 64.2%
% of good responders: 80%
Loss of efficacy: Data not available
Recommendation: Pallidal DBS is recommended for the treatment of generalized or segmental dystonia due to DYT/PARK-*TAF1*.

3.4.5 | DYT-*KMT2B*

Detailed pre- and postoperative motor scores were available for 14 out of 34 DYT-*KMT2B* patients. The median improvement after GPi DBS was 42.1% (IQR 35.3–75). Five patients (35.7%) were good responders. Eleven patients had childhood onset of dystonia and were treated in childhood/adolescence. One patient with adult-onset dystonia who underwent DBS 12 years after reported onset showed a good response with an improvement of 74.2% [41]. Two patients with < 25% improvement were children with no apparent clinic-demographic peculiarities [10]. However, one of them experienced intracerebral hemorrhage as an adverse event and both underwent multiple surgical revisions compared to their peers. There is limited data on the long-term response to DBS in patients with DYT-*KMT2B*. One study observed a secondary worsening of gait despite initial improvement [42]. Furthermore, laryngeal dystonia may not benefit and even progress under DBS, which is consistent with the progressive nature of the disorder.

DYT-*KMT2B*
N = 14
Median improvement: 42.1%
% of good responders: 35.7% (of all responders: 85.7%)
Loss of efficacy: Few available long-term follow-up data are consistent with secondary worsening
Recommendation: Pallidal DBS can be effective for the treatment of generalized or segmental dystonia due to DYT-*KMT2B*.

3.4.6 | DYT/CHOR-*GNAO1*

Of 13 children with *GNAO1*-related dystonia, two showed a good response and eight a partial response to DBS. The median improvement was 39.4%. One patient showed an improvement of > 80% after receiving acute GPi DBS for a dyskinetic crisis. The DBS target was the STN in one case (with 32.3% improvement in BFMDRS-M).

DYT/CHOR-*GNAO1*
N = 13
Median improvement: 39.4%
% of good responders: 15.4% (all responders: 84.6%)
Loss of efficacy: Data not available
Recommendation: Pallidal DBS might be considered for the treatment of DYT/CHOR-*GNAO1*, particularly during dyskinetic crises.

3.4.7 | DYT-*PANK2*-(NBIA)

Detailed individual scores were available for 13 patients with *PANK2*-related disease (of whom $n = 7$ received STN DBS, the rest GPi DBS). The median percentage improvement in BFMDRS-M after DBS was 58.8%. Ten patients (of whom five had STN DBS) showed a good response (76.9%), two a partial response, and one no response, according to the reported changes on the BFMDRS-M. One patient showed an improvement of > 80% after receiving acute GPi DBS for a dyskinetic crisis.

We did not include in the analysis a study from 2010 that included 23 patients with neurodegeneration with brain iron accumulation (eye of the tiger pattern at brain MRI) and GPi DBS for which single patient scores were not available [26]. Notably, 8/23 patients did not undergo genetic testing and one case had a genetic diagnosis other than DYT-*PANK2*-(NBIA). The mean reported improvement in severity of dystonia in this mixed cohort was 28.5% at 2–6 months and 25.7% at 9–15 months [26].

DYT-*PANK2*-(NBIA)
N = 13
Median improvement: 58.8%
% of good responders: 76.9% (5/10 of good responders received STN DBS)
Loss of efficacy: Data not available
Recommendation: DBS is recommended in the treatment of generalized or segmental dystonia due to DYT-*PANK2*-(NBIA).

3.4.8 | MxMD-*ADCY5*

Detailed rating scale scores were available for six *ADCY5* patients who underwent GPi DBS (age at intervention: 13 to 34 years). The mean improvement in motor scores after DBS was 29.4% (SD 23). One child showed a good response with a 64.6% improvement in BFMDRS-M. Two other patients aged 30 to 34 years showed a partial to good response (27.6% to

49.7% improvement after DBS). The remaining three patients showed no response according to the changes in the motor scores. However, one patient reported an effective reduction of nocturnal dyskinetic exacerbations, contributing to a subjective improvement of up to 40%–60% [30]. Similarly, in two patients with no significant improvement according to motor scores, an exacerbation of dyskinesias was reported after battery depletion.

3.4.9 | DYT-*GNAL*

Of five patients with *GNAL*-related dystonia who received GPi DBS, three showed a good response to DBS and two a partial response. The mean improvement in motor scores (BFMDRS-M or TWSTRS) was 53.4% (SD 11.9).

3.4.10 | DYT-*PRKRA*

Four children with *PRKRA* variants showed a mean improvement of 64.9% at BFMRS-M after GPi DBS. Two were classified as good responders and two as partial responders (range: 45.9% to 72.83% improvement).

3.4.11 | DYT-*TUBB4A*

Of three DYT-*TUBB4A* patients with detailed motor scores, two showed a good response and one a partial response after DBS, with a mean improvement of 43.1% (SD 19.1). Two patients received GPi DBS and one with a good response received DBS in both GPi and STN.

3.4.12 | DYT/PARK-*ATP1A3*

Two patients with DYT/PARK-*ATP1A3* showed partial improvement (26.1%–44%) on dystonia rating scales after GPi DBS.

3.4.13 | DYT-*VPS16*

One adult male patient with *VPS16*-related dystonia showed an excellent response to GPi DBS with a 93.8% improvement in BFMDRS postoperatively.

3.4.14 | DYT/PARK-*GCH1*

An adolescent male showed an excellent response to GPi DBS for treatment of torticollis (87.23% improvement in TWSTRS).

3.4.15 | DYT-*HPCA*

A male child with DYT-*HPCA* showed a 51.3% improvement in BFMDRS after GPi DBS.

3.4.16 | DYT-*ANO3*

One male child with DYT-*ANO3* showed an excellent response on BFMDRS-M (87% improvement) after GPi DBS.

3.5 | Quality Assessment of the Included Studies

The evidence available for this systematic review came from a variety of study types. Case series and reports represented 70.3% ($n=64$) of the selected references, a priori lowering the overall quality of the available evidence. According to the assessment tools used in our systematic review, 52.7% ($n=48$) of the studies were of high methodological quality, 34% ($n=31$) were of fair quality, and 13.2% ($n=12$) were of low quality. The total scores obtained and the quality tool used for each reference are shown in Table S5.

The main limitations of the reviewed studies were (i) the lack of systematically reported pre- and post-DBS assessment and (ii) the consideration of heterogeneous patient cohorts as a whole, in which it was often not possible to obtain individualized data for patients with different genetic etiologies. Furthermore, the lack of concordance between studies in the age of dystonia diagnosis, the different ages at DBS surgery, the wide range and severity of patients' symptoms, the numerous rating scales used, and the different follow-up times were major sources of variability. Due to the amount of missing information and variability of reported data, it was not possible to quantitatively estimate the risk of bias, inconsistency, indirectness, imprecision, and publication bias of the results.

4 | Discussion

We conducted a systematic review of the evidence on the efficacy of DBS for the treatment of monogenic dystonia symptoms to improve knowledge in this area and to overcome the limitations of previous works. Due to the heterogeneity of the available data, previous literature reviews have often focused on single outcome measures to assess efficacy [5], reported findings in single dystonia genes [9], or from defined age groups [10]. In addition, the ever-increasing number of dystonia gene discoveries, especially in recent years [6], made it necessary to update the available evidence. Our systematic and comprehensive approach allowed us to maximize the amount of information provided.

To optimize search sensitivity, articles were retrieved from a variety of databases using generic and field-specific terms. The external validity of the study was ensured by the diversity of patient age, symptom onset, geographic location, genetic background, and clinical manifestations. Only patients with genetic confirmation of monogenic dystonia were included to ensure internal validity. Trained and impartial reviewers used a rigorous methodology to screen, extract, assess, and synthesize the evidence.

DBS is generally an effective treatment, but results can vary widely among different subtypes of dystonia. The most commonly reported factors influencing DBS response are

patient-related and include age of onset, duration of dystonia, specific characteristics of dystonic movements, and the presence of fixed deformities. Additionally, DBS-related factors such as poor lead placement are also of great importance [14, 32]. The contribution of genetic factors has long received little attention but is now increasingly recognized as an important predictor of outcome [43]. Our review confirms the role of DBS as a mainstay of treatment in monogenic dystonia and refines the available evidence on the association between genotype and DBS outcome. The present results confirm the high probability of a favorable DBS outcome in patients with dystonia harboring *TOR1A*, *SGCE*, *TAF1*, or *PANK2* variants. An intermediate response was associated with *THAP1* and *KMT2B* variants. On average, patients with DYT/CHOR-*GNAO1* disease showed a modest response to pallidal DBS. A particularly favorable outcome with > 80% improvement in dystonia symptoms was associated with a subset of DYT-*TOR1A* patients. Few cases with > 80% improvement were also reported in association with *SGCE*-, *GNAO1*, *KMT2B*-, *THAP1*-, and *TAF1*-related diseases. Based on the consensus that was reached by 20 clinical experts considering the study findings from the systematic review, the following recommendations were established:

- DBS *is recommended* in the treatment of generalized or segmental dystonia due to *TOR1A*, *SGCE*, *TAF1*, and *PANK2* variants after non-invasive therapies have failed to provide adequate improvement.
- DBS *can be effective* for the treatment of generalized or segmental dystonia due to *THAP1* and *KMT2B* variants, after non-invasive therapies have failed to provide adequate improvement.
- DBS *might be considered* for the treatment of DYT/CHOR-*GNAO1*, particularly during dyskinetic crises, when non-invasive therapies have failed to provide adequate improvement.

This latter recommendation is supported also by a previous independent expert consensus [44]. Importantly, the selection of DBS in the specific context of a patient with monogenic dystonia must be made on an individual case-by-case basis, with data-driven information serving as one dimension of the multifaceted decision-making process in the real-world setting.

The heterogeneity of outcome measures and modalities of efficacy assessment is a major obstacle to the systematic investigation of the efficacy of DBS in monogenic dystonia. For this reason, a previous systematic review by Artusi et al. focused on pallidal DBS and included only cases for which the pre- and post-surgical BFMDRS-M scores were available [5]. This enabled them to perform a meta-analysis and compare the outcomes of pallidal DBS between DYT-*TOR1A* and other genotypes. Similar results concerning DBS outcomes of DYT-*TOR1A* and DYT-*THAP1* were yielded in the present review. In contrast, the inclusion of patients in our review, irrespective of the DBS target and the motor scale used, may account for the observed difference in outcomes among patients harboring *PANK2* variants.

Because of the limited, heterogeneous information, we focused on clinician-reported motor outcomes of DBS. These may have limitations in capturing the global impact of DBS on disability and quality of life in all genotypes considered. Another intrinsic challenge in adequately describing outcomes is the frequent coexistence of different movement disorders (e.g., in DYT/CHOR-*GNAO1* or MxMD-*ADCY5*), which may respond differently to DBS and show a different evolution. For instance, patients with DYT/PARK-*TAF1* may experience a sustained response of their dystonia upon DBS, but develop increasingly prominent parkinsonian signs, consistent with the degenerative nature of this disorder [31]. Relevantly, in a case series of pallidal DBS in *ADCY5*-related disease, established motor scales (BFMDRS-M and AIMS) could not reflect the perceived, satisfactory improvement in disability and quality of life related to the reduction or even suppression of mostly nocturnal hyperkinetic episodic exacerbations [30]. From this point of view, functional outcome measures may better reflect a therapeutic effect in complex disorders with a number of different motor manifestations amenable to improvement with DBS, such as several monogenic dystonias. Unfortunately, available patient-reported outcomes, such as the MDS-endorsed BFMDRS-D, were not consistently reported. Based on the consensus that was reached, we defined the following key recommendations:

- We recommend a systematic preoperative and postoperative outcome assessment in patients with monogenic dystonia undergoing DBS.
- Within this assessment, we recommend the regular collection of at least the following: (i) one dystonia rating scale, (ii) one rating scale for each other concomitant movement disorder, and (iii) one patient-reported outcome scale.

Overall, the time of surgery was significantly delayed compared to the reported onset of dystonia symptoms. In fact, the mean age at surgery was 21.3 years, while the reported onset of dystonia symptoms was 11.2 years on average. This may have had a significant impact on the outcome of DBS, as the "window of opportunity", that is, the time interval when the benefit of DBS is greatest, may have been missed. In DYT-*TOR1A*, prolonged disease duration with the onset of fixed skeletal deformities, rather than intrinsic age at intervention, emerged as a key predictor of DBS success [4, 18, 45, 46]. The likelihood of a good DBS outcome did not appear to differ across age groups in our review.

From an initial collective of 2084 monogenic dystonia patients from 90 scientific articles, a significantly reduced sample was available for single patient analysis. This was partly due to the generally poor quality of the data and, conspicuously, to the pooling of patients with different genetic etiologies [36], a practice that should be no more acceptable. In fact, the cumulative evidence, including the present review, clearly highlights the influence of genotype on disease progression and DBS outcome. Additionally, several case reports of patients with monogenic dystonia have described the outcomes of DBS without providing supporting scales.

Although the exact mechanism of action of DBS is complex and not fully understood, there is a broad consensus that its therapeutic effect is related to the desynchronization of the neuronal population and the reduction of pathological oscillations [47, 48]. Cumulative evidence from intraoperative microelectrode recordings reveals marked differences in the

firing patterns of pallidal neurons in different dystonia genes, even those belonging to seemingly related pathophysiological pathways [7] potentially explaining the variability of DBS efficacy across different genetic profiles. Our findings, together with the cumulative literature, support the introduction of systematic genetic testing for dystonia in the pre-DBS work-up [43]. Genetic testing of previously treated cases would also be desirable and should not be limited to "non-responders" [49]. Indeed, a two-sided bias is likely to affect the overall results of our review. We refer on one hand to the likely tendency not to publish cases with a poor outcome and on the other hand to the lack of genetic data for most patients with long-term follow-up in the literature [49]. The consequences of a genetic diagnosis extend far beyond informing counseling for future DBS. Clear criteria have been established to guide the decision to perform genetic testing in dystonia, based on two large, multicenter studies [50, 51]. These criteria should be regularly evaluated as part of routine good practice in managing patients with dystonia.

Based on the consensus that was reached, we defined the following key recommendation:

- In all patients with dystonia, the need for genetic testing should be routinely evaluated according to the criteria defined by Zech et al. [50, 51].
- Regardless of these criteria, genetic testing should be part of the routine workup for all patients with dystonia for whom DBS is considered.

According to Zech's criteria, genetic testing should be performed when specific characteristics are present, such as dystonia onset before age 21, segmental or generalized dystonia distribution, and concomitant non-movement disorders neurological symptoms [50, 51]. Indeed, two large multicenter studies [50, 51] showed that these features are associated with a high diagnostic yield of whole exome sequencing and allow for testing prioritization and optimization of resources in a clinical setting. Nevertheless, there are dystonia cases not contemplated by Zech's criteria, for example, severe, isolated cervical dystonia inadequately controlled with botulinum toxin injections, for which DBS might be evaluated. In these cases, genetic testing should be considered as well.

5 | Conclusion

This systematic review provides an update on the evolving field of DBS for the treatment of monogenic dystonia. Based on this information, we have defined clinical consensus-based recommendations for the use of DBS in the treatment of monogenic dystonia.

The present findings emphasize the importance of early genetic diagnosis, which should become mandatory in the pre-DBS workup. In addition, this review highlights the need for the implementation and reporting of systematic assessment of DBS outcomes, including mandatory patient-reported outcomes. This will allow for optimal counseling and continuous improvement in the clinical care of patients with monogenic dystonia.

Author Contributions

Elisabetta Indelicato: conceptualization, data acquisition, formal analysis, and writing – original draft. **Beatriz Carmona-Hidalgo:** methodology, data acquisition, formal analysis, and writing – review and editing. **Javier Quintero:** methodology, data acquisition, formal analysis, and writing – review and editing. **Juan Darío Ortigoza Escobar:** conceptualization, data acquisition, and writing – review and editing. **Anne Koy:** conceptualization, data acquisition, and writing – review and editing. **András Salamon:** conceptualization, data acquisition, and writing – review and editing. **Pawel Tacik:** conceptualization, data acquisition, and writing – review and editing. **Laura Muñoz-Delgado:** conceptualization, data acquisition, and writing – review and editing. **Giulia Giannini:** conceptualization, data acquisition, and writing – review and editing. **Martin Reich:** conceptualization, data acquisition, and writing – review and editing. **Alberto Albanese, Tobias Bäumer, Francisco Grandas, Robert Jech, Athanasios Leonardos, Pablo Mir, Belén Pérez-Dueñas, Javier Ricardo Perez-Sanchezm Francesc Valldeoriola, Ginevra Zanni, Marie Vidailhet**, and **Carola Reinhard:** conceptualization and writing – review and editing. **Rocío Rodríguez-López:** methodology, search strategy design. **Juan Antonio Blasco-Amaro:** methodology and formal analysis. **Sylvia Boesch:** conceptualization, funding acquisition, data acquisition, and writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** PRISMA checklist. Evidence-based items to report the efficacy of deep brain stimulation for the treatment of monogenic dystonia. **Table S2:** Search strategy. Detailed search strategy used in this study to identify relevant articles related to efficacy of deep brain stimulation for the treatment monogenic dystonia. **Table S3:** Included references. List of final included articles in this study for the purpose of investigating the efficacy of deep brain stimulation as treatment for monogenic dystonia. Author, year of publication, study design, location, and number of patients are specified. **Table S4:** DBS response according to changes in the BFMDRS-D in the different genotypes. The graphic summarizes the responses of individual patients to DBS according to their genotype. The absolute patient number is described by the horizontal axis. The responder classification, according to changes in disability scores, is defined as follows: Excellent response: > 90%; Good response: 50%–89%; Partial response: 25%–49%; No response: < 25%. **Table S5:** Quality assessment. The table displays the quality assessment of the included articles concerning the efficacy of deep brain stimulation for the treatment of monogenic dystonia.