ABSTRACT: Background: Pathogenic variants in 5 genes (GCH1, TH, PTS, SPR, and QDPR), involved in dopamine/tetrahydrobiopterin biosynthesis or recycling, have been linked to Dopa-responsive dystonia (DRD). Diagnosis and treatment are often delayed due to high between- and within-group variability.

Objectives: Comprehensively analyzed individual genotype, phenotype, treatment response, and biochemistry information.

Methods: 734 DRD patients and 151 asymptomatic GCH1 mutation carriers were included using an MDSGene systematic literature review and an automated classification approach to distinguish between different forms of monogenic DRDs.

Results: Whereas dystonia, L-Dopa responsiveness, early age at onset, and diurnal fluctuations were identified as red flags, parkinsonism without dystonia was rarely reported (11%) and combined with dystonia in only 18% of patients. While sex was equally distributed in autosomal recessive DRD, there was female predominance in autosomal dominant DYT/PARK-GCH1 patients accompanied by a lower median age at onset and more dystonia in females compared to males. Accordingly, the majority of asymptomatic heterozygous GCH1 mutation carriers (>8 years of age) were males. Multiple other subgroup-specific characteristics were identified, showing high accuracy in the automated classification approach: Seizures and microcephaly were mostly seen in DYT/PARK-PTS, autonomic symptoms appeared commonly in DYT/PARK-TH and DYT/PARK-PTS, and sleep disorders and oculogyric crises in DYT/PARK-SPR. Biochemically, homovanillic acid and 5-hydroxyindoleacetic acid in CSF were reduced in most DRDs, but neopterin and biopterin were increased only in DYT/PARK-PTS and DYT/PARK-SPR. Hyperphenylalaninemia was seen in DYT/PARK-PTS, DYT/PARK-QDPR, and rarely reported in autosomal recessive DYT/PARK-GCH1.

Conclusions: Our indicators will help to specify diagnosis and accelerate start of treatment. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: dopa-responsive dystonia; genetics; GCH1; TH; SPR; PTS; QDPR; MDSGene; automated classification

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Monogenic dopa-responsive dystonia (DRD) comprises a group of rare treatable monogenic dystonia.\(^1\) Even small doses of levodopa (l-Dopa) can tremendously reduce motor symptoms and increase patients’ quality of life.\(^2\) Pathogenic variants in the guanosine triphosphate cyclohydrolase-1 (GCH1) gene are the most frequent causes of monogenic DRD, with the autosomal dominant form with heterozygous variants being the most common subgroup.\(^3,4\) In addition, recessive/biallelic mutations in GCH1 as well as in four other genes (tyrosine hydroxylase [TH],\(^5\) 6-pyruvoyl tetrahydrobiopterin synthase [PTS],\(^6\) sepiapterin reductase [SPR],\(^7\) and quinoid dihydropteridine reductase [QDPR]\(^8\)) have been frequently associated with monogenic DRD. All of these genes encode enzymes involved in tetrahydrobiopterin (BH4) and dopamine biosynthesis or recycling (Figure S1). Previous studies have described early-onset dystonia in combination with parkinsonism as one of the phenotypic hallmarks of DRD.\(^9\) Thus, the Movement Disorder Society Task Force for the Nomenclature of Genetic Movement Disorders recommends the use of the prefix “DYT/PARK” preceding the specific gene name to classify the different DRD syndromes (i.e., DYT/PARK-GCH1, DYT/PARK-TH, DYT/PARK-PTS, DYT/PARK-SPR, and DYT/PARK-QDPR).\(^10\) However, strong phenotypic and genotypic variability with wide within- and between-subgroup differences\(^11\) that can result in long diagnostic delay and high rates of misdiagnoses have been described, hindering early diagnosis and treatment.\(^12\) The identification of subgroup-specific characteristics is important to accelerate the classification of patients to certain DRD subgroups and thus allow for timely initiation of specific treatment.

In this systematic MDSGene review, we aimed for a comprehensive overview and analysis of available information by combining individual genetic, clinical, treatment, and biochemical data in the six most frequent monogenic forms of DRD caused by mutations in five genes, which can guide clinicians to facilitate diagnosis and adequate therapy in these treatable conditions.

### Patients and Methods

Our MDSGene review follows a standardized data extraction protocol based on a systematic literature review as described previously.\(^13\) We searched the PubMed database (http://www.pubmed.ncbi.nlm.nih.gov) by applying gene-specific search terms (Table S1) for publications on GCH1, TH, SPR, PTS, and QDPR mutation carriers until December 2020 in the English literature. A comprehensive, searchable, and filterable overview of abstracted data can be found on the MDSGene website (www.mdsgene.org). Specified inclusion and exclusion criteria as well as pathogenicity scoring of variants were applied to distinguish definitely, probably, or possibly pathogenic from benign variants (www.mdsgene.org/methods). For methodological details including the automated classification approach, see Supplementary Methods.

If not indicated differently, data in percentage refer to the total number of patients with the particular sign/symptom present in correspondence to all included patients per group (including patients without information on the specific variable). The percentage of sex and l-Dopa response was calculated in correspondence to all patients with available information (excluding patients with missing information). Biochemical data were analyzed only if values of at least 3 individuals were reported. Missing data are reported in the text whenever it was greater than 50%.

### Results

Our literature search revealed 3012 articles. After being screened for reported information on genotype and phenotype, 205 articles were included (Table S2), and data of 734 patients (488 autosomal dominant DYT/PARK-GCH1, 25 autosomal recessive DYT/PARK-GCH1, 104 DYT/PARK-TH, 64 DYT/PARK-PTS, 42 DYT/PARK-SPR, and 11 DYT/PARK-QDPR) and an additional 151 heterozygous asymptomatic GCH1 mutation carriers were extracted (Figure S2).

#### Red Flags of DRDs

Within the combined group of all patients (n = 734), we identified clinical characteristics that point toward the presence of a DRD, including an early age at onset (AAO), a good l-Dopa response of symptoms, the presence of a DRD, including an early age at onset (AAO), a good l-Dopa response of symptoms, the presence of dystonia in general, and diurnal fluctuations of symptoms (Table 1). Dystonia, in general, was the most frequent motor sign (80%, n = 587) with a mostly multifocal or generalized distribution (38%, n = 278). Dystonia without parkinsonism was present in 62% (n = 452), but parkinsonism without dystonia was reported in only 11% (n = 84, 63% missing data) and combined with dystonia in 18% (n = 135, 65% missing data). Diurnal fluctuations of symptoms were observed in 31% (n = 231, 63% missing data) (Table 1). All DRD subgroups showed an early AAO between infancy and childhood, with a median AAO across all groups of 6 years (range 0–68 years). There was a diagnostic delay with a median of 5 years and a wide range from 0 to 61 years across all groups (65% missing data) (Table 1). Several patients received misdiagnoses (14%, n = 98; 86% missing data), with cerebral palsy being most frequent (n = 48). Treatment of symptoms with l-Dopa was observed in 90% (n = 663) of all patients, with 86% reporting a positive (n = 572) and 3% reporting a lack of response (n = 17) (Tables 1 and 2). Biochemically, all DRDs showed reduced...
**Table 1: Demographic and clinical data**

<table>
<thead>
<tr>
<th></th>
<th>DYT/PARK-GCH1 autosomal dominant</th>
<th>DYT/PARK-GCH1 autosomal recessive</th>
<th>DYT/PARK-TH</th>
<th>DYT/PARK-PTS</th>
<th>DYT/PARK-SPR</th>
<th>DYT/PARK-QDPR</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (n)</td>
<td>488</td>
<td>25</td>
<td>104</td>
<td>64</td>
<td>42</td>
<td>11</td>
<td>734</td>
</tr>
<tr>
<td>Age at onset [median (range)]</td>
<td>8 (0–68)</td>
<td>0 (0–8)</td>
<td>0 (0–38)</td>
<td>0 (0–11)</td>
<td>1 (0–7)</td>
<td>0 (0–1)</td>
<td>6 (0–68)</td>
</tr>
<tr>
<td>Sex [% (n male)]</td>
<td>33 (154)</td>
<td>64 (14)</td>
<td>51 (53)</td>
<td>56 (25)</td>
<td>43 (18)</td>
<td>50 (4)</td>
<td>39 (268)</td>
</tr>
<tr>
<td>Diagnostic delay [median (range)]</td>
<td>8 (0–61)</td>
<td>1 (0–6)</td>
<td>4 (0–32)</td>
<td>0 (0–6)</td>
<td>7 (0–24)</td>
<td>0 (0)</td>
<td>5 (0–61)</td>
</tr>
<tr>
<td>Dystonia in general [% (P/A/M)]</td>
<td>86 (421/39/28)</td>
<td>84 (210/4/2)</td>
<td>81 (84/6/14)</td>
<td>38 (241/39)</td>
<td>74 (31/8/3)</td>
<td>55 (6/0/5)</td>
<td>80 (587/54/93)</td>
</tr>
<tr>
<td>Dystonia without parkinsonism [% (P/A/M)]</td>
<td>70 (340/39/28)</td>
<td>60 (150/4/2)</td>
<td>45 (47/6/14)</td>
<td>31 (201/39)</td>
<td>60 (25/8/3)</td>
<td>45 (5/0/5)</td>
<td>62 (432/54/93)</td>
</tr>
<tr>
<td>Parkinsonism without dystonia [% (P/A/M)]</td>
<td>11 (53/46/308)</td>
<td>8 (2/0/17)</td>
<td>12 (12/8/47)</td>
<td>16 (10/1/49)</td>
<td>10 (4/0/32)</td>
<td>27 (3/0/7)</td>
<td>11 (84/55/460)</td>
</tr>
<tr>
<td>Dystonia-parkinsonism [% (P/A/M)]</td>
<td>17 (81/101/306)</td>
<td>24 (6/0/19)</td>
<td>36 (37/15/52)</td>
<td>6 (4/1/59)</td>
<td>14 (6/4/32)</td>
<td>9 (1/0/10)</td>
<td>18 (135/121/478)</td>
</tr>
<tr>
<td>1-Dopa treated [% (P/A/M)]</td>
<td>89 (436/23/29)</td>
<td>92 (23/0/2)</td>
<td>98 (102/1/1)</td>
<td>83 (53/3/8)</td>
<td>93 (39/2/1)</td>
<td>91 (10/0/1)</td>
<td>90 (663/29/42)</td>
</tr>
<tr>
<td>1-Dopa response [% (P/A/M)]</td>
<td>87 (379/5/104)</td>
<td>100 (23/0/2)</td>
<td>94 (96/7/1)</td>
<td>51 (27/3/34)</td>
<td>100 (39/0/3)</td>
<td>80 (8/2/1)</td>
<td>86 (572/17/145)</td>
</tr>
<tr>
<td>Diurnal fluctuation [% (P/A/M)]</td>
<td>31 (153/12/323)</td>
<td>32 (8/1/16)</td>
<td>32 (33/23/48)</td>
<td>14 (9/0/55)</td>
<td>62 (26/6/10)</td>
<td>18 (2/1/8)</td>
<td>31 (231/43/460)</td>
</tr>
<tr>
<td>Dyskinesia [% (P/A/M)]</td>
<td>6 (30/38/420)</td>
<td>24 (6/7/12)</td>
<td>23 (24/6/74)</td>
<td>16 (10/2/52)</td>
<td>29 (12/4/26)</td>
<td>27 (3/2/6)</td>
<td>12 (85/59/590)</td>
</tr>
<tr>
<td>Oculogyric crises [% (P/A/M)]</td>
<td>0 (1/0/487)</td>
<td>12 (3/0/22)</td>
<td>34 (35/15/56)</td>
<td>5 (3/0/61)</td>
<td>62 (26/7/9)</td>
<td>9 (1/0/10)</td>
<td>9 (69/20/645)</td>
</tr>
<tr>
<td>Spasticity [% (P/A/M)]</td>
<td>5 (26/41/241)</td>
<td>8 (2/7/16)</td>
<td>10 (10/0/94)</td>
<td>48 (31/2/31)</td>
<td>29 (12/2/28)</td>
<td>27 (3/0/8)</td>
<td>11 (84/52/598)</td>
</tr>
<tr>
<td>Muscular hypotonia [% (P/A/M)]</td>
<td>1 (5/27/456)</td>
<td>20 (5/7/13)</td>
<td>76 (79/6/19)</td>
<td>69 (44/5/15)</td>
<td>76 (32/3/7)</td>
<td>45 (5/0/6)</td>
<td>23 (170/48/516)</td>
</tr>
<tr>
<td>Seizures [% (P/A/M)]</td>
<td>0 (0/1/487)</td>
<td>0 (0/4/21)</td>
<td>2 (2/3/99)</td>
<td>55 (35/8/21)</td>
<td>10 (4/4/34)</td>
<td>27 (3/1/7)</td>
<td>6 (44/21/669)</td>
</tr>
</tbody>
</table>

**Initial signs and symptoms**

<table>
<thead>
<tr>
<th></th>
<th>Dystonia foot (91)</th>
<th>Dystonia in general (6)</th>
<th>Muscular hypotonia (23)</th>
<th>Muscular hypotonia (17)</th>
<th>Muscular hypotonia (15)</th>
<th>Global developmental delay (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common (n)</td>
<td>Dystonia leg (34)</td>
<td>Tremor (5)</td>
<td>Dystonia in general (22)</td>
<td>Global developmental delay (9)</td>
<td>Global developmental delay (7)</td>
<td>Muscular hypotonia (2)</td>
</tr>
<tr>
<td>Second most common (n)</td>
<td>Dystonia unspecified (20)</td>
<td>Motor delay (3)</td>
<td>Developmental delay (12)</td>
<td>Dystonia in general (7)</td>
<td>Oculogyric crises (5)</td>
<td>Microcephaly/dystonia (2)</td>
</tr>
<tr>
<td>Third most common (n)</td>
<td>Dystonia unspecified (20)</td>
<td>Motor delay (3)</td>
<td>Developmental delay (12)</td>
<td>Dystonia in general (7)</td>
<td>Oculogyric crises (5)</td>
<td>Microcephaly/dystonia (2)</td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th></th>
<th>DYT/PARK- GCH1 autosomal dominant</th>
<th>DYT/PARK- GCH1 autosomal recessive</th>
<th>DYT/ PARK-TH</th>
<th>DYT/ PARK-PTS</th>
<th>DYT/ PARK-SPR</th>
<th>DYT/ PARK-QDPR</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmotor signs and symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global developmental delay [% (P/A/M)]</td>
<td>2 (9/23/456)</td>
<td>36 (9/3/13)</td>
<td>63 (66/6/32)</td>
<td>77 (49/3/12)</td>
<td>83 (35/1/6)</td>
<td>55 (6/0/5)</td>
<td>24 (174/36/524)</td>
</tr>
<tr>
<td>Cognitive impairment [% (P/A/M)]</td>
<td>2 (11/111/366)</td>
<td>8 (2/6/17)</td>
<td>27 (28/14/62)</td>
<td>78 (50/8/6)</td>
<td>52 (22/8/12)</td>
<td>64 (7/0/4)</td>
<td>16 (120/147/467)</td>
</tr>
<tr>
<td>Motor development delay [% (P/A/M)]</td>
<td>2 (12/22/454)</td>
<td>48 (12/4/9)</td>
<td>67 (70/5/29)</td>
<td>11 (7/3/54)</td>
<td>81 (34/1/7)</td>
<td>45 (5/0/6)</td>
<td>19 (140/35/559)</td>
</tr>
<tr>
<td>Microcephaly [% (P/A/M)]</td>
<td>0 (0/1/487)</td>
<td>4 (1/1/23)</td>
<td>2 (2/12/90)</td>
<td>28 (18/15/31)</td>
<td>7 (3/4/35)</td>
<td>27 (3/1/7)</td>
<td>4 (27/34/673)</td>
</tr>
<tr>
<td>Autonomic symptoms [% (P/A/M)]</td>
<td>2 (8/21/459)</td>
<td>0 (0/0/25)</td>
<td>24 (25/1/78)</td>
<td>28 (18/7/39)</td>
<td>17 (7/0/35)</td>
<td>9 (1/1/9)</td>
<td>8 (59/30/645)</td>
</tr>
</tbody>
</table>

The percentage values of all variables in this table except sex and L-dopa response were calculated with all patients (including those with missing information). The percentage of the variable sex was calculated in correspondence to all patients with available information (excluding patients with missing information). L-Dopa response refers to the number of treated patients who reported a positive response. Information on additional motor and nonmotor signs/symptoms is presented in Table S6.

*Absent and missing data are referred to all patients without dystonia in general.

†No, negative, or temporary response was classified as lack of response.

‡Includes any kind of dystonia, for example, leg dystonia, cervical dystonia, axial dystonia, dystonia unspecified.

§Includes only dystonia that is not further specified.

Abbreviations: GCH1, guanosine triphosphate cyclohydrolase-1; TH, tyrosine hydroxylase; PTS, 6-pyruvoyl tetrahydrobiopterin synthase; SPR, sepiapterin reductase; QDPR, quinoid dihydropteridine reductase; P, present; A, absent; M, missing data.
<table>
<thead>
<tr>
<th>Gene Type</th>
<th>DYT/PARK-GCH1 autosomal dominant</th>
<th>DYT/PARK-GCH1 autosomal recessive</th>
<th>DYT/PARK-TH</th>
<th>DYT/PARK-PTS</th>
<th>DYT/PARK-SPR</th>
<th>DYT/PARK-QDPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Dopa Treated n (%)</td>
<td>436 (89)</td>
<td>23 (92)</td>
<td>102 (98)</td>
<td>53 (83)</td>
<td>39 (93)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Positive response n (%)</td>
<td>379 (87)</td>
<td>23 (100)</td>
<td>96 (94)</td>
<td>27 (51)</td>
<td>39 (100)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Mean mg/d (range)</td>
<td>236.08 (25-1800)</td>
<td>208 (80-625)</td>
<td>208 (40-800)</td>
<td>100 (100)</td>
<td>95.83 (25-150)</td>
<td>600 (500-700)</td>
</tr>
<tr>
<td>Mean mg/kg/d (range)</td>
<td>5.5 (0.4-20)</td>
<td>8.4 (1.5-20)</td>
<td>5.0 (0.6-34.7)</td>
<td>5.5 (1-10)</td>
<td>4.5 (0.65-20)</td>
<td>5.8 (1-15)</td>
</tr>
<tr>
<td>Pramipexole Treated n (%)</td>
<td>6 (1)</td>
<td>na</td>
<td>na</td>
<td>5 (8)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Positive response n (%)</td>
<td>5 (83)</td>
<td>na</td>
<td>na</td>
<td>5 (100)</td>
<td>na</td>
<td>na</td>
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<tr>
<td>Mean mg/d (range)</td>
<td>1.48 (0.125-3.15)</td>
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<td>na</td>
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<tr>
<td>Mean mg/kg/d (range)</td>
<td>0.032 (0.03-0.033)</td>
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<td>na</td>
<td>na</td>
<td>na</td>
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<tr>
<td>Selegiline Treated n (%)</td>
<td>5 (1)</td>
<td>na</td>
<td>19 (18)</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Positive response n (%)</td>
<td>3 (60)</td>
<td>na</td>
<td>7 (37)</td>
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<td>na</td>
<td>na</td>
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<tr>
<td>Mean mg/d (range)</td>
<td>4.17 (2.5-5)</td>
<td>na</td>
<td>5.0 (2.5-15)</td>
<td>na</td>
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<td>na</td>
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<tr>
<td>Mean mg/kg/d (range)</td>
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<td>1.65 (0.2-3)</td>
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<td><strong>Pathophysiology-based therapies</strong></td>
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<tr>
<td>BH₄ Treated n (%)</td>
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<td>6 (24)</td>
<td>na</td>
<td>45 (70)</td>
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<tr>
<td>Positive response n (%)</td>
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<td>6 (100)</td>
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<td>31 (69)</td>
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<td>na</td>
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<tr>
<td>Mean mg/d (range)</td>
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<td>na</td>
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<tr>
<td>Mean mg/kg/d (range)</td>
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<td>na</td>
<td>6.7 (1.2-21)</td>
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<tr>
<td>5-HTP Treated n (%)</td>
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<td>6 (24)</td>
<td>na</td>
<td>50 (78)</td>
<td>17 (40)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Positive response n (%)</td>
<td>na</td>
<td>6 (100)</td>
<td>na</td>
<td>17 (34)</td>
<td>13 (76)</td>
<td>8 (89)</td>
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<tr>
<td>Mean mg/d (range)</td>
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<td>na</td>
<td>na</td>
<td>na</td>
<td>500 (500)</td>
<td>na</td>
</tr>
<tr>
<td>Mean mg/kg/d (range)</td>
<td>na</td>
<td>4.7 (2.8-8)</td>
<td>3.6 (1-5.5)</td>
<td>3.5 (0.5-16)</td>
<td>3.58 (0.9-10)</td>
<td>na</td>
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</tbody>
</table>

Positive response refers to the number of treated patients; the mean values are calculated from the data of patients; the values for positive response refer to the number of treated patients; the mean values are calculated from the data of patients with a positive response; na refers to not available for fewer than 3 patients with information. We excluded information on medications that were used in fewer than two subgroups, such as Rotigotine, used in autosomal dominant DYT/PARK-GCH1 in 4 patients (1%) with a positive response in all of them (mean dose: 16.5 mg/d, range: 4-22.5 mg/d); trihexyphenidyl, used in autosomal dominant DYT/PARK-GCH1 in 8 patients (4%) with a positive response in 6 (75%, mean dose: 11.75 mg/d, range: 6-20 mg/d); biperiden, used in DYT/PARK-TH in 6 patients (6%) with a positive response in 5 (83%, mean dose: 0.2 mg/kg/d, range: 0.04-0.44 mg/kg/d); folinic acid, used in DYT/PARK-QDPR in 8 patients (73%) with a positive response in 7 (88%, mean dose: 26.9 mg/d, range: 2.5-75 mg/d, or mean dose: 0.15 mg/kg/d, range: 0.07-0.23 mg/kg/d); intramuscular botulinum neurotoxin A, used in autosomal dominant DYT/PARK-GCH1 in 5 patients (1%) with a positive response in 4 (80%, no data on dosage).

 Abbreviation: 5-HTP, 5-hydroxytryptophan.
TABLE 3  Biochemical data in cerebrospinal fluid, blood and urine

<table>
<thead>
<tr>
<th>CSF</th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVA</td>
<td>5HIAA</td>
<td>Neo</td>
</tr>
<tr>
<td>DYT/PARK-GCH₁ Autosomal dominant</td>
<td>101 (4)</td>
<td>44 (5)</td>
</tr>
<tr>
<td>DYT/PARK-GCH₁ Autosomal recessive</td>
<td>144 (4)</td>
<td>94 (4)</td>
</tr>
<tr>
<td>DYT/PARK-TH</td>
<td>73 (35)</td>
<td>191 (32)</td>
</tr>
<tr>
<td>DYT/PARK-PTS</td>
<td>186 (18)</td>
<td>86 (19)</td>
</tr>
<tr>
<td>DYT/PARK-SPR</td>
<td>77 (21)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>DYT/PARK-QDPR</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Reference value (min–max)</td>
<td>324⁴</td>
<td>189ᵇ</td>
</tr>
</tbody>
</table>
| Mean values are shown. Number of patients are indicated in brackets. na refers to not available because of n < 3; unit of CSF: nmol/L, unit of blood: ng/mL, units of urine: neopterin and bipterin: nmol/mol creatine. Blue-labeled values are values lower than the reference value range; red-labeled values are values higher than the reference value range; gray-labeled values are those not available because of n < 3; reference values are marked in boldface with the lowest border in the upper and the highest border in the lower column; Superscript letters a, b, c, and d, Table S2 reference D9; superscript letter e, Table S2 reference E8; superscript letter f and i, Table S2 reference E8; superscript letter g, Table S2 reference E1; superscript letters h, j, and k, Table S2 reference D4. 

Phenotypic and Mutational Characteristics by Subgroups

Besides the aforementioned shared features that are important to differentiate DRDs from other movement disorders, the six different monogenic DRD subtypes showed characteristic within-group signs and symptoms.

Autosomal Dominant DYT/PARK-GCH₁

The vast majority of all included monogenic DRD patients (66%, n = 488) suffered from autosomal dominant DYT/PARK-GCH₁. Patients descended from 278 families. They were mostly of white European (39%, n = 188) or Asian (26%, n = 127) ethnicity. Family history was positive in 69% (n = 336). In comparison to the other DRD subtypes, patients showed the highest median AAO with 8 years (range: 0–68 years), with the majority of patients (56%, n = 274) developing symptoms in childhood (3–12 years) and only 11% (n = 54) starting after the age of 40 years. Dystonia without parkinsonism was the most prominent motor sign (70%, n = 340) (Fig. 1) and, in contrast to most of the other DRDs, dystonia, in general, was the initial sign in the majority of patients (35%, n = 171; 58% missing data), with onset mostly in the foot (19%, n = 91) or leg (7%, n = 34) (Table 1). The body distribution was mostly multifocal (24%, n = 116) or generalized (16%, n = 78) (Figure S3). In contrast to all other non-GCH₁ DRD subtypes, dystonia was more frequently isolated (67%, n = 327) and combined (16%, n = 80) than complex. It was located in the lower limbs (67%, n = 327), upper limbs (25%, n = 120; 66% missing data), trunk (18%, n = 86; 71% missing data), and neck (12%, n = 60; 79% missing data). Parkinsonism without dystonia was present in 11% (n = 53, 63% missing data) and combined with dystonia in 17% (n = 81, 63% missing data). In terms of treatment, 89% (n = 436) of patients received L-dopa, with 87% (n = 379) having a positive response (mean dose: 236 mg/d, range: 25–1800 mg/d, or mean dose: 5.5 mg/kg/d, range: 0.4–20 mg/kg/d) and 1% (n = 5) having a lack of response (no data on dosage reported). Residual motor signs (mostly dystonia n = 22 or tremor n = 2, 78% missing data) after L-dopa treatment were reported in 36 patients (mean dose: 270 mg/d, range: 125–800 or 5.2 mg/kg/d, range: 2–10 mg/kg/d) (Tables 1 and 2).

Deep brain stimulation was used in 4 patients (bilateral subthalamic nucleus in 3 and missing data on stimulation target in 1). All 4 patients were reported to suffer from wearing off and L-dopa-induced dyskinesia despite frequent dopaminergic medication and therefore required deep brain stimulation. When studying all included autosomal dominant DYT/PARK-GCH₁ patients, we identified 14 patients with reported abnormal dopamine transporter density

homovanillic and/or 5-hydroxyindoleacetic acid in the cerebrospinal fluid (CSF) (Table 3). We recognized a high amount of missing data, especially in studies reporting mutational screening results (41% missing data) in comparison to case reports (25% missing data) or family studies (34% missing data).
Autosomal dominant DYT/PARK-GCH1

Autosomal recessive DYT/PARK-GCH1

DYT/PARK-TH

FIG. 1. Categories of dystonia and motor and nonmotor signs and symptoms across genes. The circles (left) indicate the percentage of patients with isolated (light blue), combined (blue), complex (dark blue) dystonia, parkinsonism without dystonia (red), and no/unknown dystonia (gray). The diagrams indicate the presence (red), absence (blue), or missing data (gray) of motor (middle) and nonmotor signs and symptoms (right). Absolute numbers are stated above the bars. Signs and symptoms with a frequency above 10% are shown in the figure. For DYT/PARK-GCH1, all nonmotor signs and symptoms with a frequency equal to or above 2% are shown. Other demographic and clinical information is presented in Table 1 and Table S6. [Color figure can be viewed at wileyonlinelibrary.com]
parkinsonism. Twenty-five patients were reported to have undergone a DaTSan without a reported pathology, and for 446 patients no information was available (Table S3).

Misdiagnoses were found in 41 patients (8%, 91% missing data), with cerebral palsy (n = 15) and orthopedic conditions (n = 9) being the most prominent ones. Twenty patients were reported to have undergone unnecessary operations in most of the lower extremities (n = 15). The median diagnostic delay was 8 years with a wide range from 0 to 61 years (71% missing data) (Table 1). The biochemical profile was characterized by a reduction in homovanillic acid and 5-hydroxyindoleacetic acid, as well as neopterin,
bioppterin, and BH4 in CSF (Table 3). We identified 173 different pathogenic variants, including missense (46%, n = 79), frameshift (15%, n = 26), nonsense (11%, n = 19), and structural variation variants (10%, n = 16). Of these variants, 106 were scored probably, 53 possibly, and 14 definitely pathogenic. De novo variants were reported in 5 patients (85% missing data) (Fig. 2A). Information on benign variants or excluded variants of all DRD subtypes is presented in Tables S4 and S5.

In addition to the 488 heterozygous DYT/PARK-GCH1 patients (symptomatic mutation carriers [SMC]), we extracted data (eg, current age and sex) of 151 asymptomatic, heterozygous GCH1 mutation carriers (AMC). All AMC had a positive family history. Information on AAO or age at examination and sex was available for 397 SMC (276 female and 121 male) and 59 AMC (21 female and 38 male) and was plotted in a Kaplan–Meier curve to illustrate and estimate the probability of disease manifestation. Interestingly, whereas only 33% (n = 154) of SMC were male, 64% of the AMC were of male sex and beyond the median AAO of autosomal dominant DYT/PARK-GCH1 (8 years). When all AMC were evaluated, including carriers of pathogenic variants aged 0 to 8 years, there was an equal distribution among sexes (49%, n = 74 males). The median AAO in women (8 years, range: 0–66 years, confidence interval [CI]: 6.9–9.0) was lower than that in men (19 years, 0–68 years, CI: 3.4–34.6). Figure S4 shows that the 25th/75th percent rank (eg, the time when 25% or 75% of all included subjects carrying a heterozygous pathogenic GCH1 variant develop the disease) was 5 (25%) or 15 years (75%) in women and 6 (25%) or 52 years (75%) in men. At the age of 30 years, 53% of males but already 85% of females developed the disease.

When comparing AMC versus SMC regarding the frequency of truncating (eg, frameshift, nonsense, splice site, or structural variations) and nontruncating variants (eg, missense variants and in-frame deletions), there was a higher frequency of truncating variants compared to nontruncating variants among the SMCs (SMC: truncating variants = 61% [n = 299] and nontruncating variants = 36% [n = 177] vs. AMC: truncating variants = 51% [n = 77] and nontruncating = 47% [n = 71]; P = 0.02, Fisher’s exact test). This might indicate that the penetrance of truncating mutations is higher as that of nontruncating variants in SMC compared to AMC. However, the publication bias should be considered and conclusions drawn with caution.

When analyzing SMC regarding sex and clinical signs and symptoms, 58% (n = 281) of all DYT/PARK-GCH1 patients were females and suffered from dystonia and 14% (n = 67) from parkinsonism, whereas 24% (n = 119) of all patients were male carriers with dystonia and 10% (n = 50) with parkinsonism (Figure S5). In general, patients who initially developed parkinsonism without dystonia had a much higher median AAO of 43 years in comparison to those who showed dystonia as initial symptom with an AAO of 8 years.

**Autosomal Recessive DYT/PARK-GCH1**

We analyzed the data of 25 biallelic autosomal recessive DYT/PARK-GCH1 patients, comprising 12 homozygous and 13 compound-heterozygous mutation carriers from 19 different families. Asian and white European ethnicity were most frequent (each 16%, n = 4) (68% missing data). Most patients had an infantile AAO at a median below 1 year (range: 0–8 years) (Table 1). Positive family history was observed in 54% (n = 13). Some of the most frequent motor signs were dystonia without parkinsonism (60%, n = 15) and dystonia-parkinsonism (24%, n = 6; 76% missing data), dyskinesia (24%, n = 6), and muscular hypotonia (20%, n = 5; 52% missing data) (Table 1; Fig. 1). Parkinsonism without dystonia was very rare in this DRD subgroup and observed only in 8% (n = 2, 68% missing data) (Table 1). Dystonia was isolated (40%, n = 10) or complex (32%, n = 8) and rarely combined (12%, n = 3). The majority of patients showed dystonia in the lower limbs (52%, n = 13), trunk (40%, n = 10; 60% missing data), or upper limbs (20%, n = 5; 80% missing data) (Fig. 1). Dystonia was generalized in 40% (n = 10, 56% missing data) (Figure S3). Nonmotor features were common: global developmental delay was found in 36% (n = 9, 52% missing data), motor delay in 48% (n = 12), and cognitive impairment in 8% (n = 2, 68% missing data) of patients (Fig. 1). At the start of the disease, dystonia (24%, n = 6), tremor (of any kind 20%, n = 5), and motor delay (12%, n = 3) were most commonly present (Table 1). L-Dopa treatment was used in 92% (n = 23) of patients. All of them showed a positive response (Tables 1 and 2) with a mean L-dopa dose of 208 mg/d (range: 80–625 mg/d) or 8.4 mg/kg/d (range: 1.5–20 mg/kg/d). Dyskinesias were observed in 24% (n = 6) and residual motor signs in 16% (n = 4, 72% missing data) of patients, with 3 of them suffering from residual dystonia. Misdiagnoses were reported in 5 patients (20%, 72% missing data), with cerebral palsy being most frequent (n = 3). The median diagnostic delay was 1 year (range: 0–6 years, 80% missing data). Biallelic DYT/PARK-GCH1 patients showed reduced neopterin, biopterin, BH4, 5-hydroxyindoleacetic acid, and homovanillic acid in CSF, as well as mildly reduced neopterin and biopterin values in urine and hyperphenylalaninemia in blood (Table 3). Hyperphenylalaninemia can also be absent in this subgroup of DRDs.

In this autosomal recessive form of DYT/PARK-GCH1, we identified 25 different biallelic pathogenic
variants, 10 of which were also carried by heterozygous patients. All variants were missense variants except for two frameshift deletions and one variant of unknown effect. Of these variants, 18 were classified as probably pathogenic, 5 as possibly, and 2 as definitely pathogenic (Fig. 2A).
MDS Gene REVIEW: GCH1, TH, SPR, PTS, AND QDPR

FIG. 2. (continued)
We included 104 patients with DYT/PARK-TH descending from 89 different families. Patients were mostly of Asian (57%, n = 59) and white European (19%, n = 20) ethnicity with an infantile AAO (median: <1 year, range: 0–38 years; 90% missing data).
and cognitive impairment (27%, n = 22) or multifocal (19%, n = 20) (Figure S3) and localized in the limbs, with lower limbs (40%, n = 42; 59% missing data) being more often affected than upper limbs (28%, n = 29; 70% missing data), and trunk (38%, n = 39; 62% missing data). Dystonia was more frequently complex (69%, n = 72) than isolated (5%, n = 5) or combined (5%, n = 5). Nonmotor signs such as motor developmental delay (67%, n = 70), global developmental delay (63%, n = 66), and cognitive impairment (27%, n = 28; 60% missing data) were frequent. Autonomic symptoms were present in 24% (n = 25, 75% missing data) and a decreased body weight in 15% (n = 16, 77% missing data) (Table 1). Most patients showed muscular hypotonia (22%, n = 23), dystonia (21%, n = 22), or a developmental delay (12%, n = 12) at the start of the disease.

1-Dopa treatment was used in 98% of patients (n = 102), with 94% (n = 96) having a positive response with a mean dose of 208 mg/d (range: 40–800 mg/d) or 5.0 mg/kg/d (range: 0.6–34.7 mg/kg/d), whereas 7% (n = 7) showed a lack of response (mean dose: 1.6 mg/kg/d, range: 0.2–2.4) (Tables 1 and 2). Residual motor signs were reported in 35% (n = 36) of patients who mostly suffered from residual dystonia (n = 6). The median diagnostic delay was 4 years (range: 0–32 years, 51% missing data). Misdiagnoses were reported in 33 patients (32%, 68% missing data), with cerebral palsy being most frequent (n = 20). Our literature-based analysis of biochemical variables revealed a decrease in neopterin and homovanillic acid and an increase in 3-O-methyl-dopa in the CSF. Elevation of 3-O-methyl-dopa is a result of 1-dopa therapy. We identified increased prolactin blood levels, with only 1 patient reporting clinical signs of hyperprolactinemia (galactorrhea) (Table 3). DYT/PARK-TH is an autosomal recessive disease. We identified 30 homozygous and 74 compound-heterozygous mutation carriers and found 69 different pathogenic variants, mostly missense (74%, n = 51), intronic (13%, n = 9), and nonsense (6%, n = 4). Of these, 55 variants were scored as probably, 8 possibly, and 6 definitely pathogenic (Fig. 2B).

DYT/PARK-PTS

We included 64 patients with DYT/PARK-PTS from 58 different families, mostly of Asian (22, n = 14), Arab (16%, n = 10), and Hispanic (8%, n = 5) ethnicity (52% missing data). Patients showed a median AAO in infancy below 1 year with a range from 0 to 11 years (Table 1). Positive family history was reported in 22% (n = 14, 72% missing data). Muscular hypotonia (69%, n = 44), seizures (55%, n = 35), and spasticity (48%, n = 31) were the most prominent clinical signs (Fig. 1). Of all subgroups, dystonia without parkinsonism was the rarest in DYT/PARK-PTS (31%, n = 20; 61% missing data) and combined with parkinsonism in only 4 patients (6%, 92% missing data). Parkinsonism without dystonia was reported in 16% (n = 10, 77% missing data). Dystonia was complex in 36% (n = 23, 63% missing data). Frequent nonmotor signs and symptoms were cognitive impairment (78%, n = 50), global developmental delay (77%, n = 49), and microcephaly (28%, n = 18) and autonomic symptoms (28%, n = 18; 61% missing data). Muscular hypotonia was the most common initial sign (27%, n = 17), followed by global developmental delay (13%, n = 9), dystonia (11%, n = 7), and seizures (8%, n = 5) (55% missing data). Of all DRD subtypes, DYT/PARK-PTS patients showed the lowest l-dopa responsiveness. From 83% (n = 53) of patients who were treated with l-Dopa, only 51% (n = 27) showed a positive response with a mean dose of 5.5 mg/kg/d (range: 1–10 mg/kg/d), and 6% of patients (n = 3) reported a lack of response with a mean dose of 2.8 mg/kg/d (range: 2–3.3 mg/kg/d) (Tables 1 and 2). 5-Hydroxytryptophan was used in 50 patients, with a positive response in 17 of them (mean dose: 3.6 mg/kg/d, range: 1–5.5 mg/kg/d). A lack of response was reported in 12 patients (mean dose: 1.9 mg/kg/d, range: 1.5–2.3 mg/kg/d). Treatment with BH4 was reported in 45, with a positive response in 31 patients (mean dose: 6.7 mg/kg/d, range: 1.2–21 mg/kg/d) and a lack of response in 1 patient (dose: 8.8 mg/kg/d). Residual motor signs were reported in only 2 patients who received l-dopa and BH4 and showed gait difficulties. There was hardly any diagnostic delay with a median below 1 year and a small range of 0 to 6 years. Biochemically, DYT/PARK-PTS was characterized by an increase in neopterin and a decrease in biotinidase, homovanillic acid, and 5-hydroxyindoleacetic acid in CSF. Neopterin was increased and biotinidase was decreased in urine. Prolactin and phenylalanine were elevated in blood, without clinical signs of hyperprolactinemia (Table 3). DYT/PARK-PTS follows an autosomal recessive mode of inheritance. We identified 29 homozygous and 35 compound-heterozygous mutation carriers. We found 31 different pathogenic variants, with the majority being missense variants (74%, n = 23). Most variants were considered probably pathogenic (n = 25), three possibly, and three definitely pathogenic variants (Fig. 2C).
DYT/PARK-SPR

Our review comprised 42 patients with DYT/PARK-SPR from 30 different families, and 64% (n = 27) reported a positive family history. Patients were either white Europeans (33%, n = 14), Asians (10%, n = 4), or Arabs (2%, n = 1) (55% missing data). The disease started in infancy with a median AAO of 1 year (range from 0 to 7 years). Muscular hypotonia (76%, n = 32), oculogyric crises (62%, n = 26), dystonia without parkinsonism (60%, n = 25), and spasticity (29%, n = 12; 67% missing data) were some of the most prominent motor signs (Fig. 1). Parkinsonism without dystonia was reported only in 10% (n = 4, 76% missing data) and combined with dystonia in 14% (n = 6, 76% missing data). Dystonia was mostly localized in the upper extremities (29%, n = 12), lower extremities (17%, n = 7; 57% missing data), trunk (14%, n = 6; 55% missing data), and neck (12%, n = 5; 62% missing data). It was more frequently complex (69%, n = 29) than isolated (3%, n = 1) or combined (2%, n = 1). Prominent nonmotor signs and symptoms included global developmental delay (83%, n = 35), motor delay (81%, n = 34), cognitive impairment (52%, n = 22), sleep disorder (26%, n = 11; 71% missing data), and autonomic symptoms (17%, n = 7; 83% missing data) (Fig. 1). The three most common initial features were muscular hypotonia (36%, n = 15), global developmental delay (17%, n = 7), and oculogyric crises (12%, n = 5). L-Dopa treatment was reported in 93% (n = 39) of patients, all having a positive response (mean dose: 96 mg/d, range: 25–150 mg/d, or mean dose: 4.5 mg/kg/d, range: 0.65–20). 5-Hydroxytryptophan was used in 40% (n = 17) of patients, of whom 76% (n = 13) reported a positive response (mean dose: 3.5 mg/kg/d, range: 0.5–16 mg/kg/d) (Tables 1 and 2). A lack of response was reported in 16% (n = 3), with no data on dosage. Dyskinesias were observed in 29% (n = 12, 62% missing data) of patients. Residual motor signs were present in 24% (n = 12, 67% missing data), mostly as dystonia (n = 9). The diagnostic delay of DYT/PARK-SPR showed a median of 7 years, with a range of 0 to 24 years (50% missing data) (Table 1). Misdiagnoses were reported in 13 patients (33%, 67% missing data), with cerebral palsy being the most frequent one (n = 8). The biochemical profile of DYT/PARK-SPR was characterized by an increase in sepiapterin and biotinidase and a decrease in homovanillic acid, 5-hydroxyindoleacetic acid, and BH4 in the CSF. Prolactin was increased (without clinical signs of hyperprolactinemia), whereas phenylalanine was normal in blood, explaining the insensitivity of newborn screening (Table 3). DYT/PARK-SPR is inherited in an autosomal recessive fashion. We identified 33 homozygous and 9 compound-heterozygous mutation carriers harboring 20 different pathogenic variants. We found most frequently missense (55%, n = 11) but also nonsense (20%, n = 4), splice site (10%, n = 2), and frameshift variants (10%, n = 2). Of these variants, 17 were considered probably pathogenic, 2 definitely, and 1 possibly pathogenic (Fig. 2D).

DYT/PARK-QDPR

DYT/PARK-QDPR was the rarest group of monogenic DRDs in the literature, and our review could identify 11 patients from 10 different families only. Ethnicity was reported for 2 patients as Asian. A positive family history was indicated in 2 patients. All mutation carriers developed the disease within their first year of life. Dystonia without parkinsonism (45%, n = 5), muscular hypotonia (45%, n = 5; 55% missing data), seizures (27%, n = 3; 64% missing data), and spasticity (27%, n = 3; 73% missing data) were some of the most frequent motor signs (Fig. 1). In general, data on motor and nonmotor signs and symptoms were limited, with a high number of missing data, and can be found in detail in Figure 1, Table 1, and Table S6. L-Dopa treatment was used in 10 of all 11 patients (91%). A positive response was reported in 8 patients (80%) (mean dose: 600 mg/d, range: 500–700 mg/d, or mean dose: 5.8 mg/kg/d, range: 1–15 mg/kg/d). No response was indicated in 2 patients (20%) (mean dose: 1.6 mg/kg/d, range: 0–3.1 mg/kg/d) (Tables 1 and 2). There was no diagnostic delay. DYT/PARK-QDPR was the only of our subgroups in which more than 50% of patients (n = 6) were detected by newborn screening. Biochemically, patients showed an increase in prolactin and phenylalanine in blood. Only 1 patient was reported with signs of hyperprolactinemia (gynecomastia). Biotinidase and neopterin in urine were normal. Only 1 patient was reported with a decrease in 5-hydroxyindoleacetic acid and normal pterins in CSF (Table 3). The disease has an autosomal recessive mode of inheritance. We identified 6 homozygous and 5 compound-heterozygous mutation carriers, and 15 different pathogenic variants, mostly missense (80%, n = 12), but also 2 nonsense variants (13%) and 1 frameshift insertion were detected (7%). We found 14 probably pathogenic and 1 possibly pathogenic variant (Fig. 2E).

Automated Classification of Monogenic DRD Subtypes

Our automated classification approach revealed high accuracy for our extracted variables (Table S7) to distinguish between the different forms of monogenic DRDs. With the prior class probabilities set to “uniform” (ie, without prior knowledge of class probabilities/frequency of diagnoses), the classification resulted in a total accuracy of 89.2% (95% CI: 89.1%–89.3%) and a balanced accuracy of 72.6% (95% CI: 72.2%–
Discussion

This is the first comprehensive review on monogenic DRDs caused by mutations in five different genes that are all related to dopamine biosynthesis or recycling. Abstracted data combine individual genetic, clinical, treatment, and biochemical data in 734 patients with 333 different pathogenic variants, extracted by screening of over 3000 scientific articles in English.

We identified dystonia, l-dopa responsiveness, early AAO, and diurnal fluctuations as red flags for DRD. In comparison, isolated monogenic dystonia forms showed an overall later AAO, a mostly poor response to l-dopa, and no diurnal fluctuations. Importantly, in all DRD subgroups of our review, parkinsonian without dystonia was rarely reported (11%) and was combined with dystonia in only 18% of all included DRD subtypes. Thus, parkinsonian features are rather a minor presentation occurring in only 29% of patients questioning the recommendation of the prefix “DYT/PARK” to abbreviate monogenic DRDs.

Importantly, the overall very good response of symptoms to l-dopa warrants an l-dopa treatment trial in every patient with early-onset dystonia. However, the definition of “good response” varies greatly across studies and is incompletely defined. Moreover, in the non-
GCH1 DRDs, dystonia appeared later in the disease course, and hypotonia and developmental delay were the most frequent initial signs. Moreover, dystonia in these subtypes was mostly complex, for example, associated with developmental delay and cognitive impairment. In addition, we were able to identify specific signs and symptoms for certain DRD subgroups. Our automated classification approach revealed that our extracted variables reached a high accuracy to distinguish between groups. On a descriptive level, seizures and microcephaly were mostly observed in DYT/PARK-PTS. Autonomic symptoms appeared commonly in DYT/PARK-TH and DYT/PARK-PTS and sleep disorders and oculogyric crises in DYT/PARK-SPR. Such indicators can help to specify the diagnosis and accelerate the start of replacement therapy. Importantly, we found that besides l-dopa, BH4 and/or 5-hydroxytryptophan are of particular relevance in the treatment of autosomal recessive DRDs. For this, Table 2 provides detailed information on effective dosages and the number of treatment responses. This is of practical relevance for clinicians when starting or adjusting treatment in monogenic DRD patients.

Importantly, we highlight an often long diagnostic delay in DRD subgroups without available newborn screening. Surprisingly, in the era of advanced genetic screening methods and availability, there was no improvement in the diagnostic delay when comparing previously and recently published papers. Of note, in DYT/PARK-PTS and DYT/PARK-QDPR, the diagnosis was usually established within <1 year. Half of the DYT/PARK-QDPR patients were even identified on newborn screening, emphasizing the necessity of further development and application of such early diagnostic screening tools, as well as the further widespread application of next-generation sequencing techniques. Therefore, in this review, we provide detailed genetic information and metabolite levels in blood, CSF, and urine of all subgroups.

Across all included DRD forms, psychiatric symptoms such as depression, anxiety, sleep disorder, and behavioral abnormalities were rarely reported. This is of particular interest, as BH4 is also a cofactor for the enzyme tryptophan hydroxylase catalyzing the synthesis of serotonin (Figure S1), decreased levels of which were associated with psychiatric comorbidities such as depression. Among the published mutation carriers, all DRD patients with psychiatric comorbidities (except for 2 with behavioral abnormalities) received l-dopa or 5-hydroxytryptophan, but only 1 patient was reported to be treated with citalopram, illustrating the lack of diagnosing these psychiatric comorbidities and adequate psychotropic drug treatment.

Based on the systematic analysis of all published mutation carriers with autosomal dominant DYT/PARK-GCH1, we were able to narrow the rate of asymptomatic mutation carriers to approximately 25% (151 of 639), i.e., penetrance of 75%. Using studies on single or a few individual families, the penetrance has previously been estimated to be in the broad range of 38% to 85%. Because there is a bias toward identifying (and reporting) SMC, the population penetrance cannot directly be calculated from these numbers and is probably even lower. Notably, although sex was equally distributed across all other DRD subtypes, in autosomal dominant DYT/PARK-GCH1 only 33% of patients were male, and males showed a later AAO and less dystonia. Importantly, in the AMC group, sex was initially equally distributed but increased to 64% males among carriers older than the median AAO. The sex- and age-dependent reduced penetrance in autosomal dominant DYT/PARK-GCH1 and the less common
occurrence of the disease in male than in female mutation carriers imply sex-specific factors in the regulation of the GCH1 enzyme activity or compensatory mechanisms, such as physiologically lower levels of the GCH1 enzyme in female mutation carriers or reduced GCH1 mRNA levels, as found in brains from female mice.\textsuperscript{21,22} However, the mechanisms causing reduced GCH1 penetrance require further investigation.

We identified 15 autosomal dominant DYT/PARK-GCH1 patients, with pathologic DaTScans as a sign for nigrostriatal neurodegeneration. Importantly, the lack of longitudinal clinical and imaging studies in DRD limits the ability to more objectively investigate the existence of neurodegeneration in DRD.\textsuperscript{23}

In summary, we here provide a comprehensive review of 734 monogenic DRD patients. An important strength of our review is that, for the first time, individual genetic, clinical, biochemical, and treatment response data have been systematically analyzed. In conjunction with the identified red flags and subgroup-specific characteristics, our review can facilitate diagnosis and treatment. This is of particular relevance, as our data expand the current knowledge on DRDs that was so far limited to very small numbers of patients reported in multiple different single case reports of small case series. Our results have also been implemented in the MDSGene database (www.mdsgene.org) for online assistance with clinical diagnosis and treatment. A limitation for interpretation is the high number of missing data for many of the variables requiring caution when drawing conclusions. We would like to encourage the clinical-scientific community to more comprehensively report on detailed clinical, genetic, treatment response, and biochemical characteristics of their patients, as this lays the ground for the development of new and expansion of already-existing diagnostic screening tools and treatment strategies.\textsuperscript{5}

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Data Availability Statement

The data that support the findings of this study are openly available at www.mdsgene.org.

References


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.
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