REVIEW

Genotype–Phenotype Relations for Isolated Dystonia Genes: MDSGene Systematic Review

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ABSTRACT: This comprehensive MDSGene review is devoted to 7 genes — *TOR1A*, *THAP1*, *GNAL*, *ANO3*, *PRKRA*, *KMT2B*, and *HPCA* — mutations in which may cause isolated dystonia. It followed MDSGene's standardized data extraction protocol and screened a total of ~1200 citations. Phenotypic and genotypic data on ~1200 patients with 254 different mutations were curated and analyzed. There were differences regarding age at onset, site of onset, and distribution of symptoms across mutation carriers in all 7 genes. Although carriers of *TOR1A*, *THAP1*, *PRKRA*, *KMT2B*, or *HPCA* mutations mostly showed childhood and adolescent onset, patients with *GNAL* and *ANO3* mutations often developed first symptoms in adulthood. *GNAL* and *KMT2B* mutation carriers frequently have 1 predominant site of onset, that is, the neck (*GNAL*) or the lower limbs (*KMT2B*), whereas site of onset in DYT-*TOR1A*, DYT-*THAP1*, DYT-*ANO3*, DYT-*PRKRA*, and DYT-*HPCA* was broader. However, in most DYT-*THAP1* and DYT-*ANO3* patients, dystonia first manifested in the upper half of the body (upper limb, neck, and craniofacial/laryngeal), whereas onset in DYT-*TOR1A*, DYT-*PRKRA* and DYT-*HPCA* was frequently observed in an extremity, including both upper and lower ones. For *ANO3*, a segmental/multifocal distribution was typical, whereas *TOR1A*, *PRKRA*, *KMT2B*, and *HPCA* mutation carriers commonly developed generalized dystonia. *THAP1* mutation carriers presented with focal, segmental/multifocal, or generalized dystonia in almost equal proportions. *GNAL* mutation carriers rarely showed generalization. This review provides a comprehensive overview of the current knowledge of hereditary isolated dystonia. The data are also available in an online database (http://www.mdsgene.org), which additionally offers descriptive summary statistics. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: *TOR1A*; *THAP1*; *GNAL*; *ANO3*; *KMT2B*; *PRKRA*; *HPCA*; dystonia; movement disorder

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Dystonia is a rare movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both.[1] Nowadays, genetic testing gains an increasing awareness and importance to patients and doctors alike. Patients with an age at onset (AAO) in childhood and/or a positive family history often have a genetic cause, but also patients presenting with first symptoms in adulthood may carry a pathogenic variant (also referred to as "mutation"). However, major challenges for neurologists are to decide whom to test, for which gene, and how to interpret the result.[2]

The phenotypic spectrum in dystonic syndromes is wide, and distribution can be focal (1 affected body site), segmental/multifocal (>1 contiguous/noncontiguous sites), or generalized (trunk and ≥2 other sites affected). AAO can be grouped into 5 categories: infancy (0–2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40 years), and late adulthood (>40 years).[1] Furthermore, dystonia can be classified based on the accompanying clinical signs. When dystonia is the only presenting feature except for a possible tremor, it is referred to as isolated dystonia, for which genetic forms will be covered in this International Parkinson and Movement Disorder Society Genetic Mutation Database (MDSGene) review. Dystonia associated with another movement disorder is classified as combined dystonia, whereas dystonia as (a maybe less prominent) part of other neurological or systemic disorders is designated as complex dystonia.[1,3]

The first isolated dystonia gene, *TOR1A*, was found almost 25 years ago.[4] Since then, an increasing number of genetic forms has been identified, mainly by next-generation sequencing (NGS) approaches.[5,6] Of these ~200 dystonia genes,[7] 3 were listed as isolated dystonia genes by the MDS Task force on Genetic Nomenclature in Movement Disorders in 2016[3]: *TOR1A*, *THAP1*, and *GNAL*. Meanwhile, there is increasing evidence for a pathogenic role of *ANO3* variants, particularly because of the identification of de novo mutations.[7,8] Mutations in *PRKRA* were initially reported as a cause of a combined dystonia (dystonia-parkinsonism, DYT16).[9] However, the literature review revealed that parkinsonism is neither a predominant nor a consistent finding,[10] especially in more recent reports.[11] Thus, we now consider it a genetic form of isolated dystonia (DYT-*PRKRA*). Although mutations in these 5 genes usually lead to isolated dystonia, mutations in *KMT2B* and *HPCA* present as isolated dystonia only in a subset of patients. Mutations in *KMT2B* were first reported in 2016/2017[12,13] as a cause of dystonia and have been confirmed in a number of independent studies since then.[14,15] Biallelic mutations in *HPCA* were validated as a cause of dystonia in 2018.[16,17] Thus, a total of 7 genes (3 well established and 4 rather new/newly confirmed ones) are covered in this systematic MDSGene review on isolated dystonia. Of note, we did not include *CIZ1* and *COL6A3*, as the data regarding these genes are inconsistent, and their causative role for dystonia has yet to be confirmed.[3,18-20] The overarching goal is to assist movement disorder doctors in deciding on genetic testing and interpreting findings. This review has 3 objectives: (1) to provide an overview of genotypic and phenotypic data in affected mutation carriers, (2) to compare phenotypes across genes, and (3) to evaluate pathogenicity of variants.

Methods

The present MDSGene review follows a standardized data extraction protocol as described elsewhere.[21] Data have been posted on the MDSGene website (www.mdsgene.org) and were collected based on a systematic literature review with certain inclusion and exclusion criteria, and pathogenicity scoring of variants differentiating definitely, probably, and possibly pathogenic from benign variants (Supplementary Material).

Results

Relevant Articles and Overview of Included Patients and Mutations

The PubMed literature search yielded 1179 citations, among which 275 were used to extract clinical and genetic data for 1235 dystonia patients. Of these, 1167 mutation carriers from 246 publications were eligible for inclusion in MDSGene (Supplementary Figure S1 and Supplementary Material). An overview of relevant articles ordered by publication year is shown in Supplementary Figure S2. In total, 254 different variants have been included and scored as "definitely pathogenic" (n = 43, 16.9%), "probably pathogenic" (n = 136, 53.5%), or "possibly pathogenic" (n = 75, 29.5%); see Table 1. Sixty-eight patients did not fulfill inclusion criteria and were excluded (Supplementary Tables S3 and S4).

Phenotypic and Mutational Details by Gene

In the following paragraphs, we discuss the specific clinical and genetic findings for each gene individually. Detailed data are presented on www.mdsgene.org and summarized in Figures 1 (dystonia categories across genes), 2 (initial site of onset), and 3 (distribution of dystonia and signs and symptoms at examination). Because of the small number of *HPCA* mutations carriers, *HPCA* has not been included in Figures 1–3. A detailed overview of the locations of mutations alongside their pathogenicity status in all genes and proteins is given in Figure 4.

TABLE 1. Overview of publication numbers and demographic, clinical, and genetic findings related to carriers of mutations in genes linked to isolated dystonia

	TOR1A	*THAP1*	*GNAL*	*ANO3*	*PRKRA*	*KMT2B*	*HPCA*	Total
Publications								
Publications with search term (March 15, 2020)	678	178	61	33	183	27	19	1179
Extracted publications	141	64	22	18	9	19	2	275
Included publications	132	57	19	17	7	19	2	253[a]
Patients (mutation carriers)								
Extracted mutation carriers	706	289	91	57	27	77	6	1253[b]
Included mutation carriers	694	241	76	53	23	75	5	1167
Included genetic variants								
Total	11	97	38	31	6	68	3	254
Definitely pathogenic	1	4	3	0	1	34	0	43
Probably pathogenic	6	63	22	17	5	21	2	136
Possibly pathogenic	4	30	13	14	0	13	1	75
Type of variant								
Missense	8	56	20	29	6	24	1	144
Truncating (nonsense, frame shift, splice site)	1	29	9	1	0	30	2	72
In-frame deletions	2	1	1	0	0	2	0	6
Structural variants (large deletions)	0	1	0	0	0	12	0	13
Other (UTR, intronic, silent, start loss)	0	10	8	1	0	0	0	19
Ethnicity								
Most frequent (%)	White (17.4)	White (41.9)	White (65.8)	White (43.4)	Mixed (56.5% from Brazil)	White (38.7)	Sephardic Jewish (60.0)	White (28.6)
Second most frequent (%)	Asian (14.1)	Amish-Mennonite (12.0)	Asian (13.2)	Asian (26.4)	White (34.8)	Asian (14.7)	White (40.0)	Asian (13.6)
Demographic characteristics								
Male (%)	48.4	43.6	31.6	39.6	60.9	45.3	60.0	46.0
Family history positive (% of known pat)	24.2	57.7	64.5	49.1	56.5	12.0	na	na
Phenotypic characteristics across all mutation carriers								
Median AAO (IQR)	9 (7–12)	15 (9–29)	38 (25–47)	23 (9–42)	8 (4–14)	6 (4–8)	5 (0.5–12.5)	na
AAO range	1–70	2–69	2–68	1–69	1–53	0–43	0–17	0–70
Most common initial site (%)	Upper limb (31.7)	Upper limb (27.0)	Neck (65.8)	Neck (26.4)	Limb (65.2)	(Lower) limb (61.3)	Lower limb (80.0)	na
Second most common initial site (%)	Lower limb (23.3)	Neck (22.0)	Craniofacial/larynx (10.5)	Upper limb (18.9)	Larynx (17.4)	≥ 2 sites (10.7)	na	na
Most frequently involved site (%)	Limb (71.6)	Neck (63.5)	Neck (88.2)	Neck (64.2)	Limb (91.3)	Limb (94.7)	na	na
Second most frequently involved site (%)	Axial (41.2)	Limb (60.6)	Craniofacial (30.3)	Limb (56.6)	Larynx (69.6)	Larynx (72.0)	na	na
Additional features that occurred in several patients	Rare	Rare	Rare	Rare	Neurodevelopmental disorder, parkinsonism	Neurodevelopmental disorder	na	na
Phenotypic characteristics of only those mutation carriers with isolated dystonia								
Number of patients (%)	409 (58.9)	211 (87.6)	74 (97.4)	39 (73.6)	13 (56.5)	33 (44.0)	3 (60.0)	na
Median AAO (IQR)	9 (7–12)	15 (9–26)	38 (25–46)	30 (12–42.5)	7.5 (6–16)	6 (4–8)	5 (3–6.5)	na
Most common initial site (%)	Upper limb (29.3)	Upper limb (27.5)	Neck (66.2)	Neck (35.9)	Limb (61.5)	(Lower) limb (72.7)	Lower limb (66.7)	na
Most frequently involved site (%)	Limb (65.5)	Neck (62.1)	Neck (87.8)	Neck (61.5)	Limb (84.6)	Limb (100.0)	na	na

UTR, untranslated region; AAO, age at onset; IQR, interquartile range; na, not available.
[a]This number includes several articles that cover more than 1 genetic form. Data extraction was done from 246 individual articles.
[b]This number also includes patients that have been reported in more than 1 publication. Data extraction was done for 1235 individual patients.

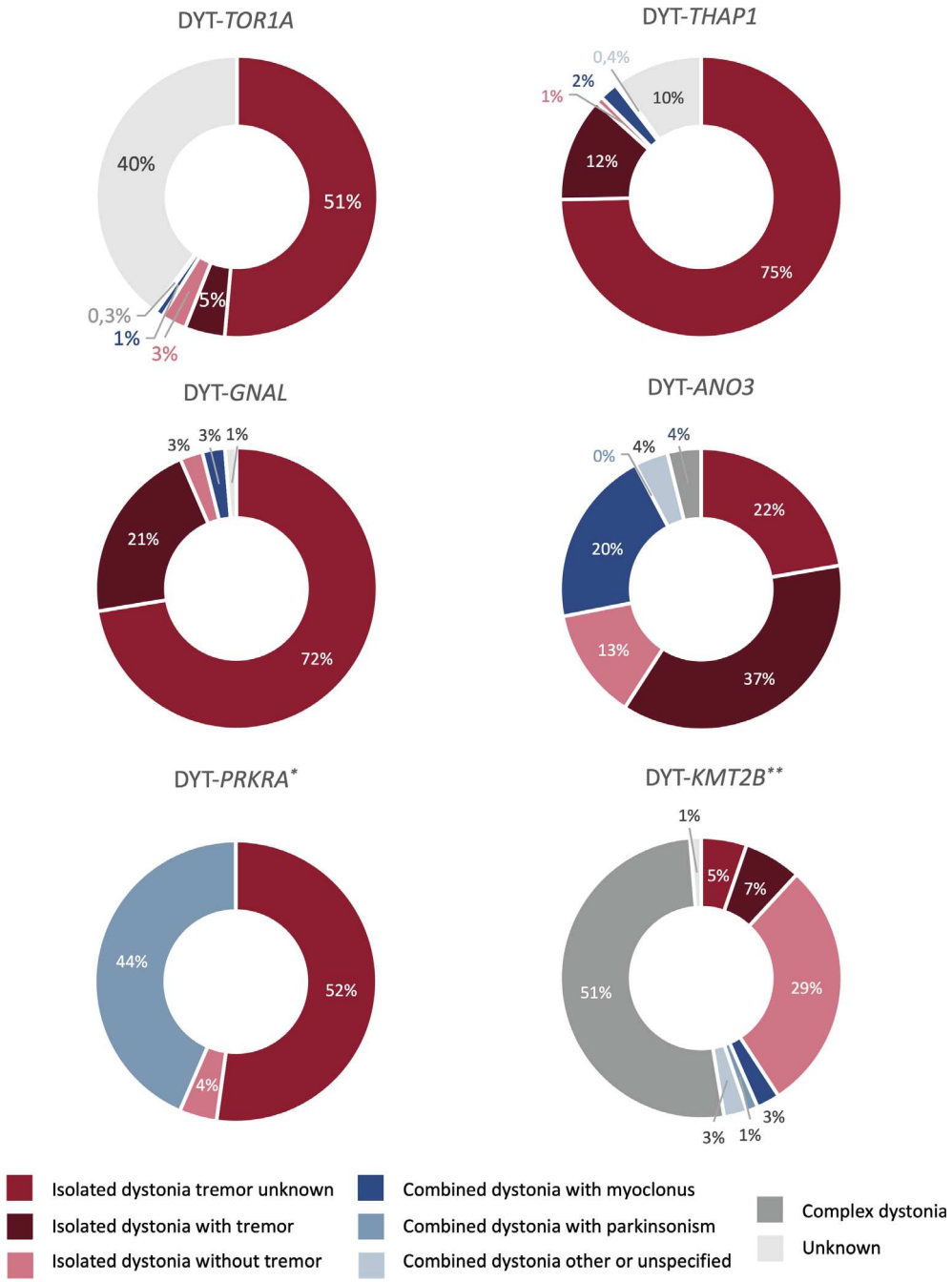


FIG. 1. Categories of dystonia across genes. The circles indicate the percentage of patients with isolated (red), combined (blue), and complex (gray) dystonia. The different subgroups of each category are displayed in lighter or darker color shades. *DYT-*PRKRA*: Several cases were reportedly diagnosed with Parkinson's disease and therefore classified as combined dystonia based on the presence of bradykinesiae but data missingness was high only. However, slow movements can also be caused by dystonia itself, making the occurrence of parkinsonism uncertain. **DYT-*KMT2B*: Additional features defining the complex phenotype are often mild, thus a clear categorization of cases into these categories (isolated vs complex) is often challenging and may have to be reevaluated over time.

TOR1A

We identified 694 *TOR1A* mutation carriers from 638 families, of whom 48.4% were male (11.0% missing). Ethnicity was not provided for 433 patients (62.4%); otherwise, they were white European (17.4%) or Asian (14.1%), Ashkenazi Jewish, or mixed/other ancestry (2.9% each). The median AAO was 9 years (IQR, 7–12 years), with 7.5% missing. The majority (68.1%) had childhood onset and 11.7% adolescence onset; only 5.2% of patients had an AAO > 30 years. Notably, an earlier AAO was associated with a more severe phenotype (for details, see Supplement). Family history was positive in 24.2% of mutation carriers, negative in 14.8%, and unknown in 61.0% of patients.

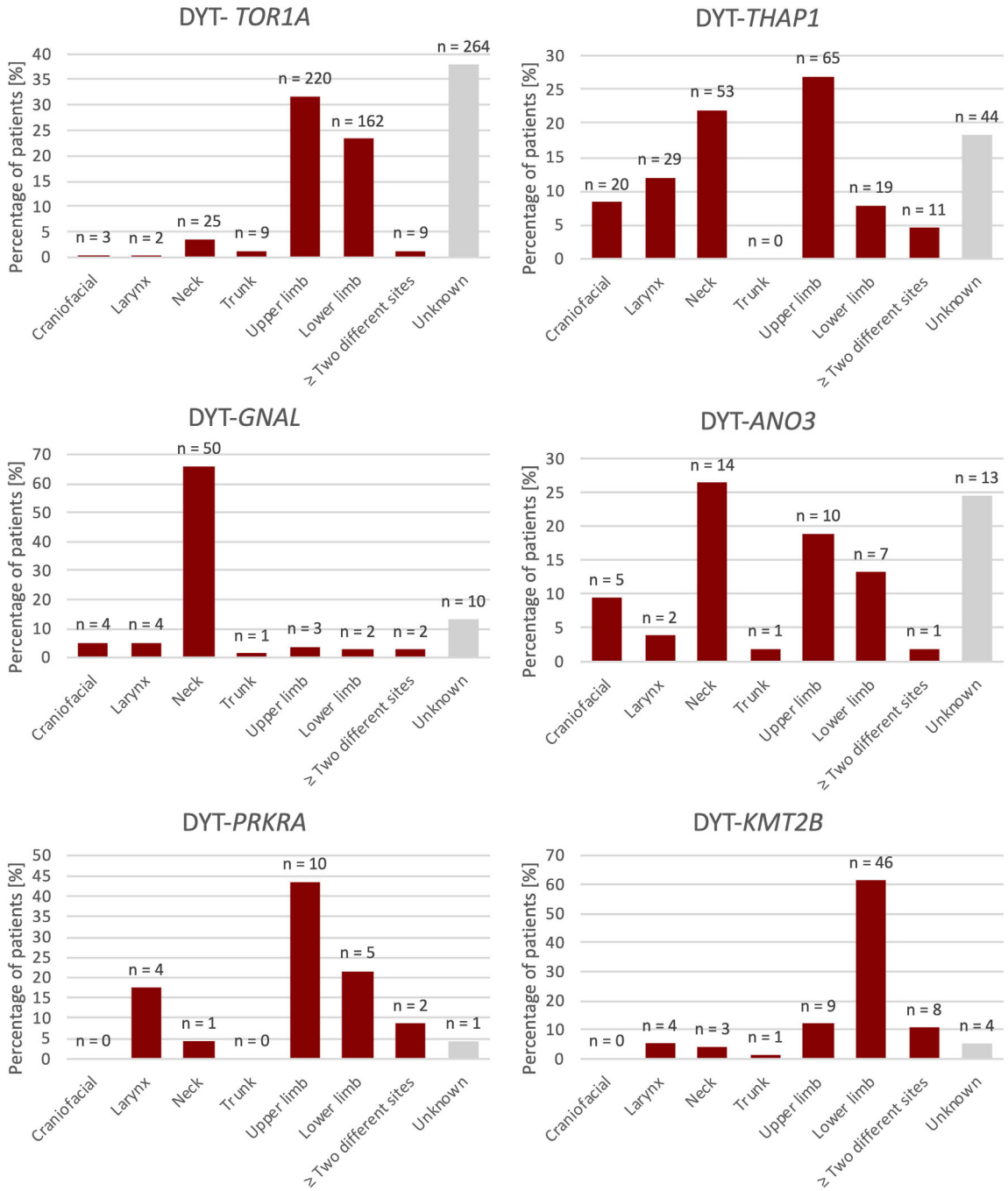


FIG. 2. Initial site of onset per gene. Each of the diagrams refers to findings for one of the genes. Because of the small number of reported *HPCA* patients, data for *HPCA* are not shown. The body site that was initially affected is given as 6 different groups. In addition, the number of patients with 2 or more reported initial sites or with no data on site at onset is also provided. [Color figure can be viewed at wileyonlinelibrary.com]

About 60% of patients had generalized dystonia; focal distribution was rather rare (~10%). The onset was mostly in the limbs (~60%). Interestingly, patients with focal dystonia had more often upper than lower limb onset, whereas for generalized dystonia, it was the other way around (for detailed statistics, see Supplement). Other onset sites were rare but data missingness was high (>35%). Over the course of the disease, limb involvement was characteristic, but also axial and cervical involvement was common, whereas only a small percentage had craniofacial or laryngeal involvement. A dystonic tremor was reported in 31 patients and myoclonus in six, and none had parkinsonism (Figs. 2 and 3). Nonmotor symptoms were rarely mentioned (>90% missing), and depression and psychosis were only reported in a single patient.[22]

There was considerable clinical heterogeneity, even within families regarding body distribution.[23-26]

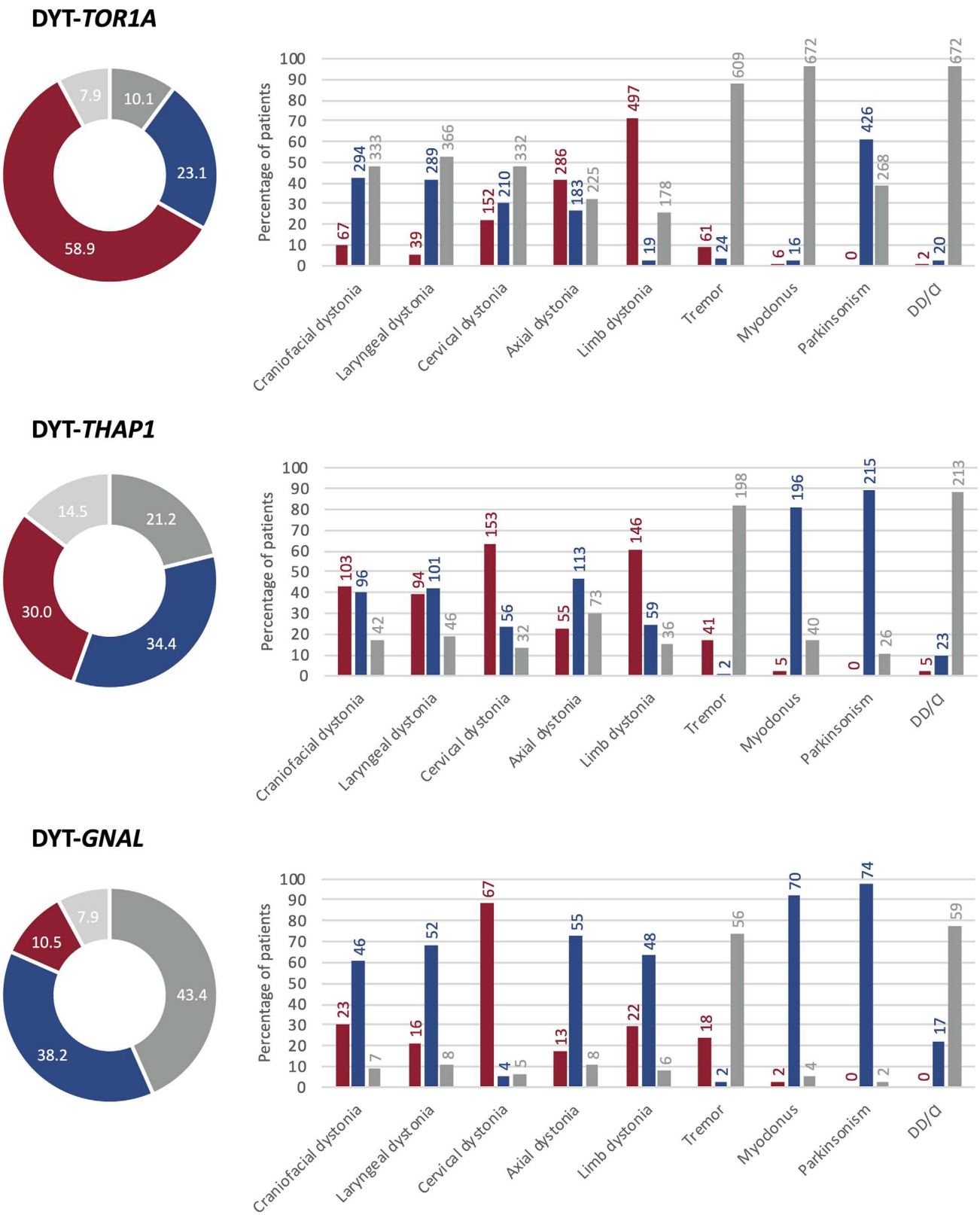


FIG. 3. Distribution of dystonia and signs and symptoms at examination across genes. The circles indicate the percentage of patients with generalized (red), segmental/multifocal (blue), focal (dark gray), and unknown (light gray) distribution of signs and symptoms. Of note, diagnoses from the original publications that were not in accordance with the current classification guidelines[1] have been reclassified accordingly (see Supplementary Methods). The diagrams indicate the presence (red), absence (blue), or missing data (gray) of dystonia and other main movement disorder phenotypes, as well as of developmental delay/cognitive impairment (DD/CI).

FIG. 3. (continued)

DYT-*TOR1A* is inherited in an autosomal-dominant fashion. Among the 694 heterozygous patients, 11 different variants were found. Almost all patients (98.0%) carried the same in-frame 3-base-pair (BP) deletion (c.907_909delGAG, aka GAG deletion [ΔGAG]) in *TOR1A*. Twelve patients carried 8 different rare missense variants. One patient harbored an in-frame 6-bp deletion and another one a frameshift mutation.

There are 4 documented de novo cases.[27-29] To estimate penetrance, we identified studies that performed mutational screenings in families with >10 individuals. In these families, penetrance varied from 18% to 55%.[23,26,28,30] These families included 135 individuals with genetic information. Of those, 48 were carriers of the GAG deletion, and 14 of them were affected, indicating a mean penetrance of 29%, thus confirming previous estimates.[31]

Commonly used oral treatments included anticholinergics and baclofen with a beneficial effect in some patients but based on small numbers. Benzodiazepine and dopamine were rather ineffective. Deep brain stimulation (GPi-DBS) was reported in >200 patients, often with good to excellent response. Other surgical methods (thalamotomy, pallidotomy) were effective in about half the patients (Supplement).

THAP1

We identified 241 *THAP1* mutation carriers from 169 families, of whom 43.6% were male (12.4% missing). Information on ethnicity was given in 176 of 241 patients (27.0% missing) and comprised white Europeans (41.9%) and Asians (10.4%). Furthermore, 29 patients (12.0%) from 8 families were of Amish-Mennonite decent. The median AAO was 15 years (IQR, 9–29 years) with 17.0% missing. Many patients (34.9%) had onset in childhood; onset during adolescence or early or late adulthood was less frequent (17.8%, 16.6%, and 14.5%, respectively). Family history was positive in 57.7% of mutation carriers, negative in 32.0%, and unknown in 10.4%.

Regarding type of dystonia, a segmental/multifocal or generalized distribution was more frequent than focal dystonia. Initial onset was variable including upper limb, neck, or craniofacial/laryngeal muscles. Lower limb or onset in 2 or more sites was rather unusual. Affected body regions over the course of the disease were mostly neck and limbs (upper > lower), but craniofacial and axial dystonia was also common. Importantly, laryngeal dystonia associated with dysarthria and/or dysphonia was typical. Tremor was reported in 41 patients, myoclonus in 5, and parkinsonism in none. Nonmotor symptoms were rarely mentioned (>88% missing); depression and cognitive impairment were reported in 5 patients each (Figs. 1–3).

There was considerable clinical heterogeneity, even within families regarding body distribution and AAO.[32-34] Nonetheless, there were also families with a quite similar phenotype.[35]

DYT-*THAP1* follows an autosomal-dominant mode of inheritance, and 97 variants were reported. Most patients carried missense variants (57.7%), followed by frameshift mutations (21.6%), variants with an unknown effect (variants in untranslated regions, intronic outside the canonical splice sites, or affecting

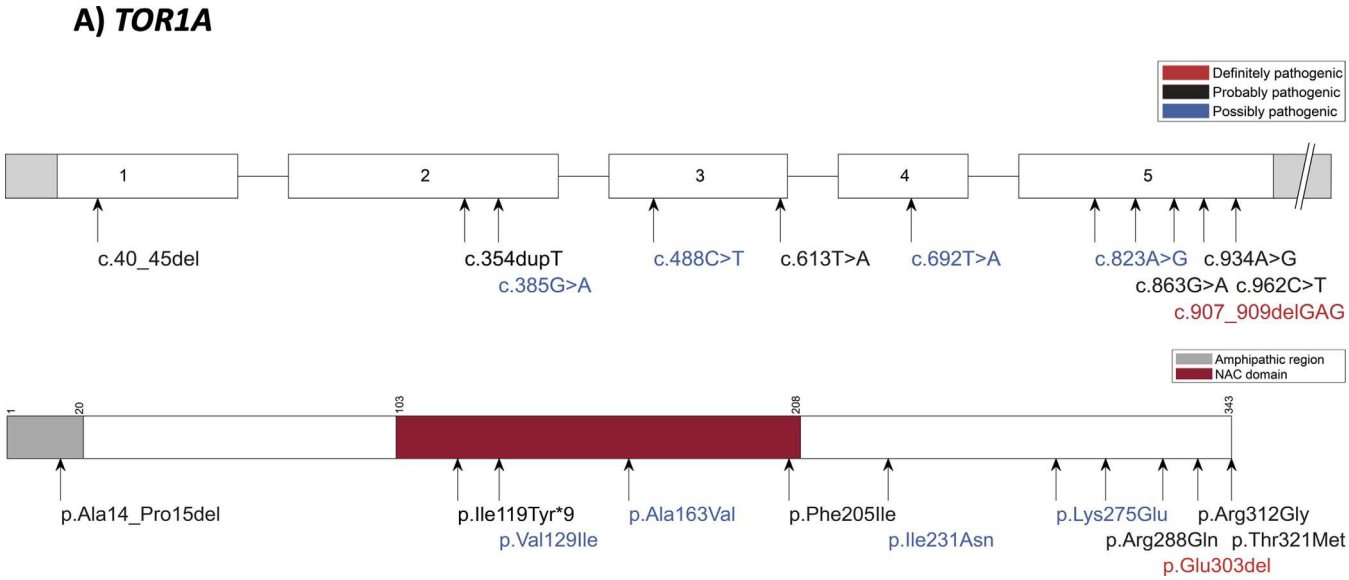
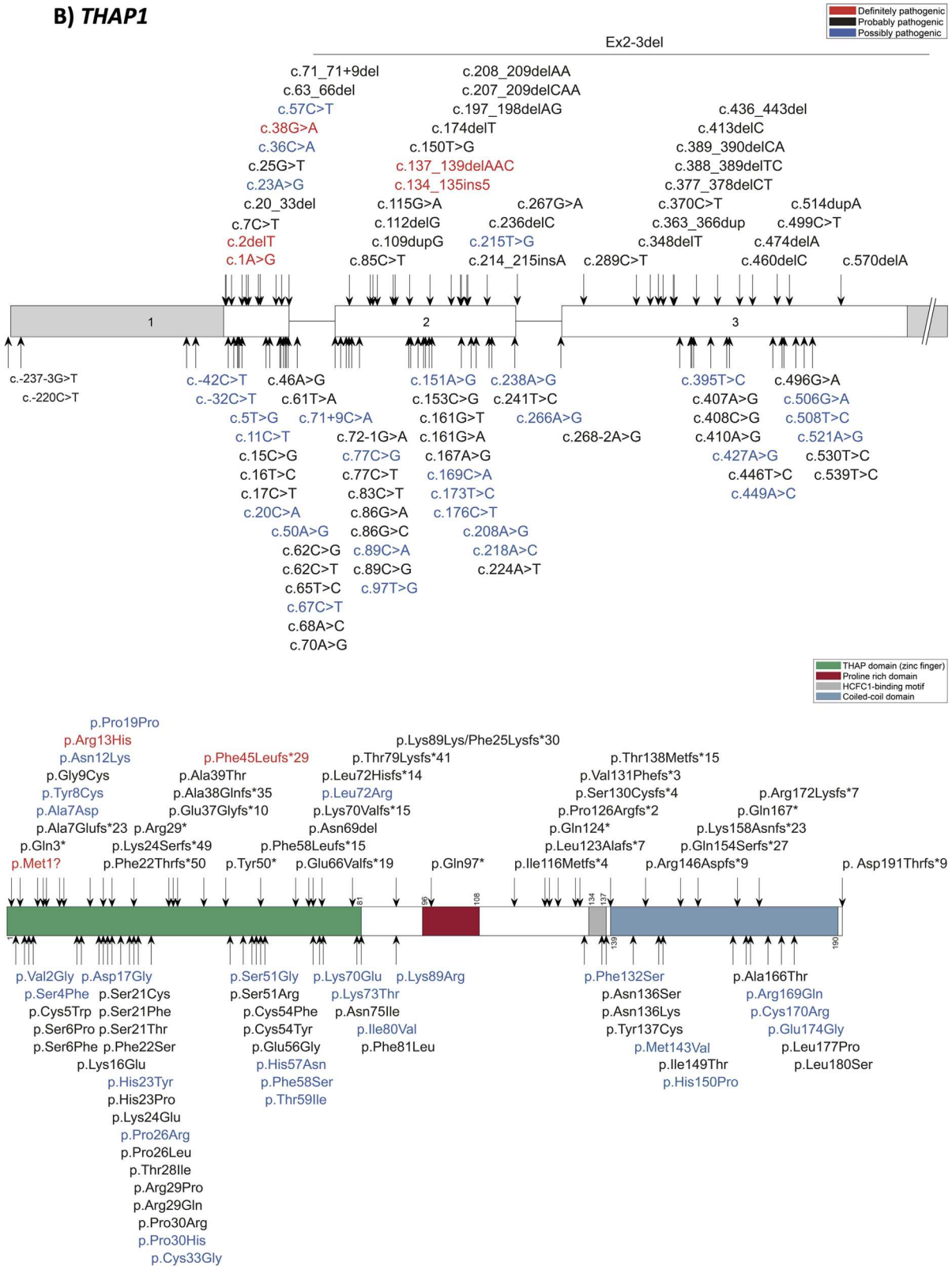


FIG. 4. Overview of mutations per gene/protein. The gene is shown with exons as boxes and introns as shortened lines. Exons are to scale. Untranslated regions are abbreviated and illustrated in gray. For proteins, functional domains are highlighted. Position of mutations is indicated by arrows, and predicted pathogenicity is provided by color (red, definitely pathogenic; black, probably pathogenic; blue, possibly pathogenic). Variants scored as benign are not included and are listed in Table S3.



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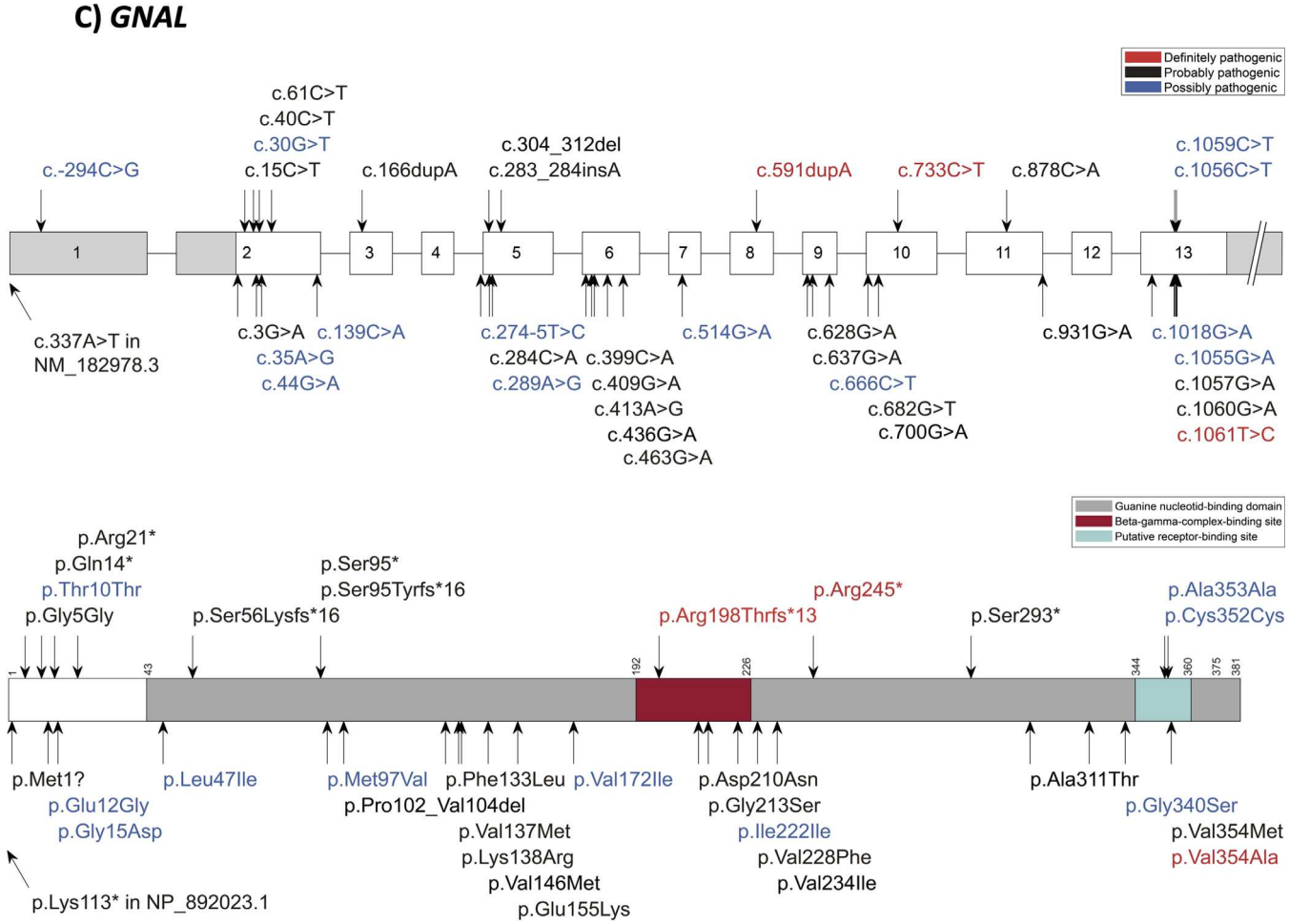


FIG. 4. (continued)

the start codon; 8.2%), and nonsense mutations (6.2%). Splice site (2.1%), silent (2.1%), and in-frame deletion variants (1.0%) were rare. In 3 patients, the mutation was shown to have arisen de novo.[36-38]

To estimate penetrance, we used all families with at least 1 described unaffected carrier (to ensure that healthy individuals also were genotyped). This revealed 25 families with a total of 93 mutation carriers, of whom 45 were affected; thus the estimated penetrance of *THAP1* mutations is 48.4%. Although this is an estimate in which only families with at least 1 unaffected mutation carrier were included, which may lead to underestimation of penetrance, we believe that it represents a valid and close approximation. The calculated penetrance would be higher when including all families (also the ones only reporting affected members), but there is always also a bias toward screening affected members, which would lead to an artificial increase of penetrance estimate. Because of small numbers, it was not possible to take predicted pathogenicity scores into account.

Information on medical treatment was scarce. Only botulinum toxin and anticholinergic medication showed a fairly good outcome. Dopaminergic drugs did not show any effect, and the outcome of GPi-DBS was variable.

GNAL

We identified 76 *GNAL* mutation carriers from 44 families, with 31.6% male (5.3% missing). The majority of patients were white European (65.8%), or Asian (13.2%), with 11.8% missing. The median AAO was 38 years (IQR, 25–47 years), with 11.8% missing. Most patients had onset of symptoms during adulthood (35.5% in early adulthood and 39.5% in late adulthood), with the latest AAO being 68 years. Only 12 patients (15.8%) had an AAO < 20 years (9.2% missing). Family history of dystonia was positive in 64.5% of mutation carriers, negative in 26.3%, and unknown in 9.2%.

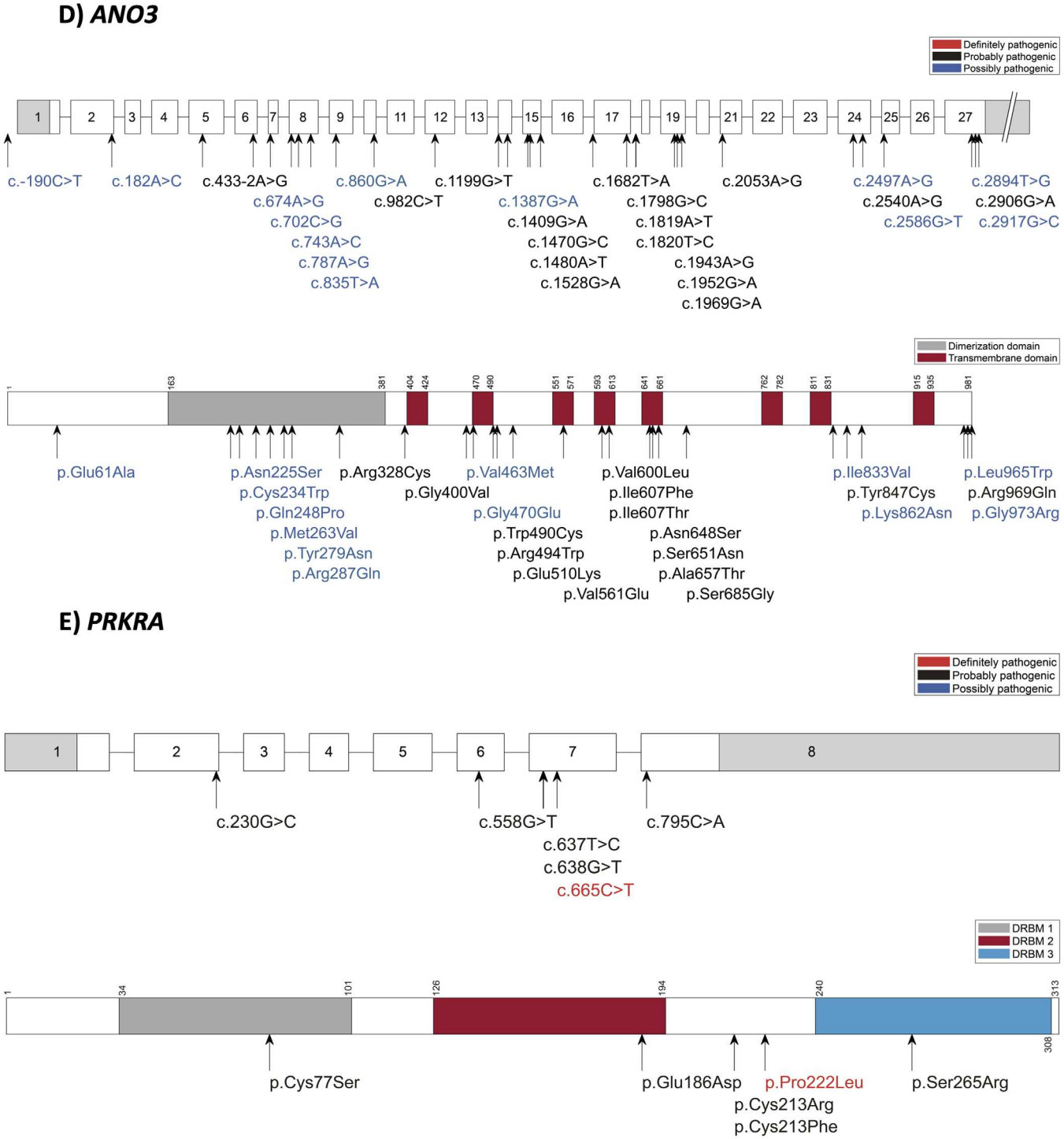
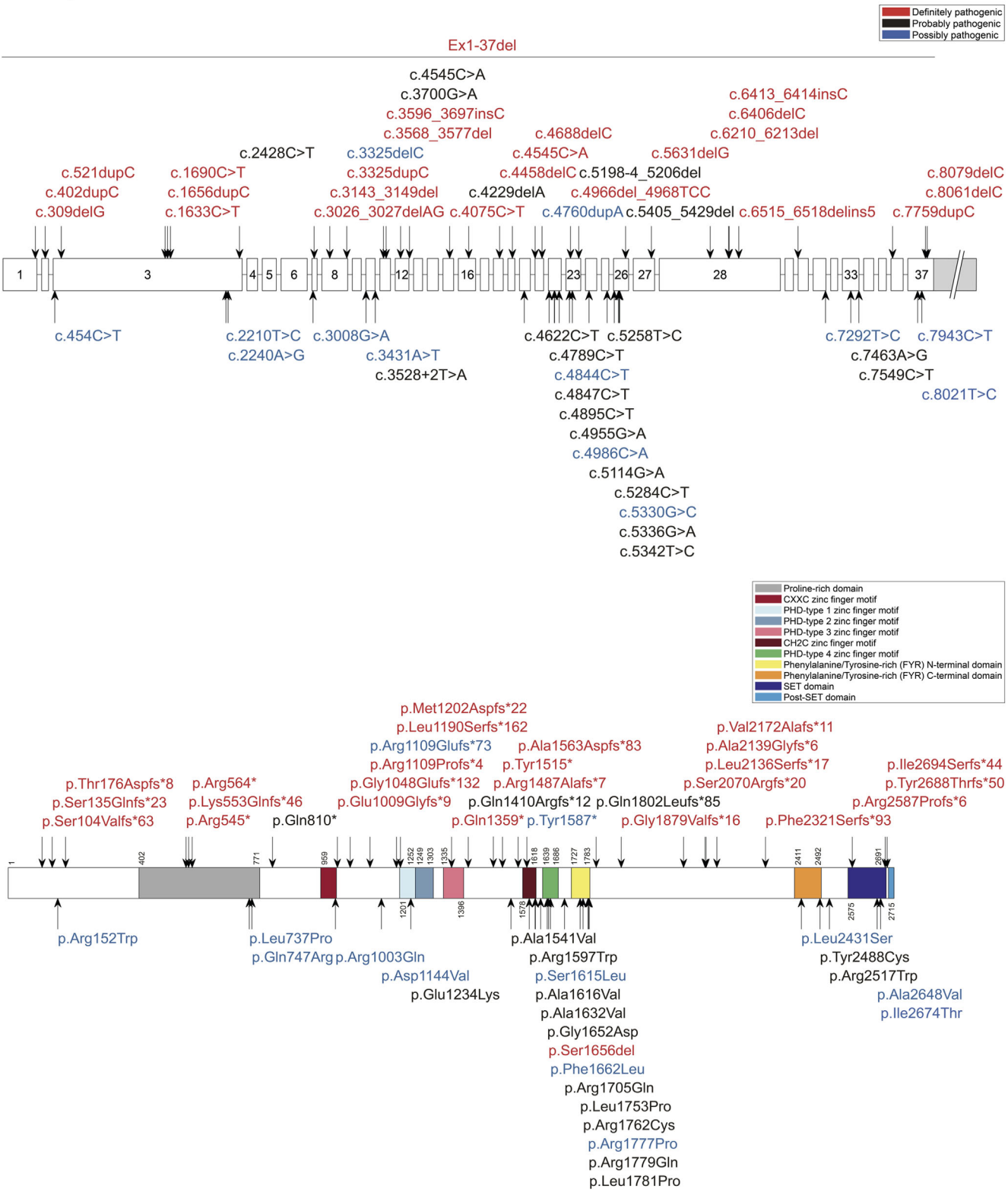


FIG. 4. (continued)

Most patients had focal dystonia, followed by multifocal/segmental dystonia, and only a small proportion had generalized dystonia. Initial onset was mostly cervical and sometimes craniofacial/laryngeal, axial, or in an extremity. Cervical involvement was characteristic. Involvement of other body regions including craniofacial, limb (upper > lower), laryngeal, and axial dystonia was rarer. Tremor, mostly as dystonic head tremor, was reported in 18 patients and myoclonus in 2.[39,40] Nonmotor signs and symptoms were rarely reported (>76.7% missing).

DYT-*GNAL* follows an autosomal-dominant mode of inheritance. A total of 38 variants were published. Most



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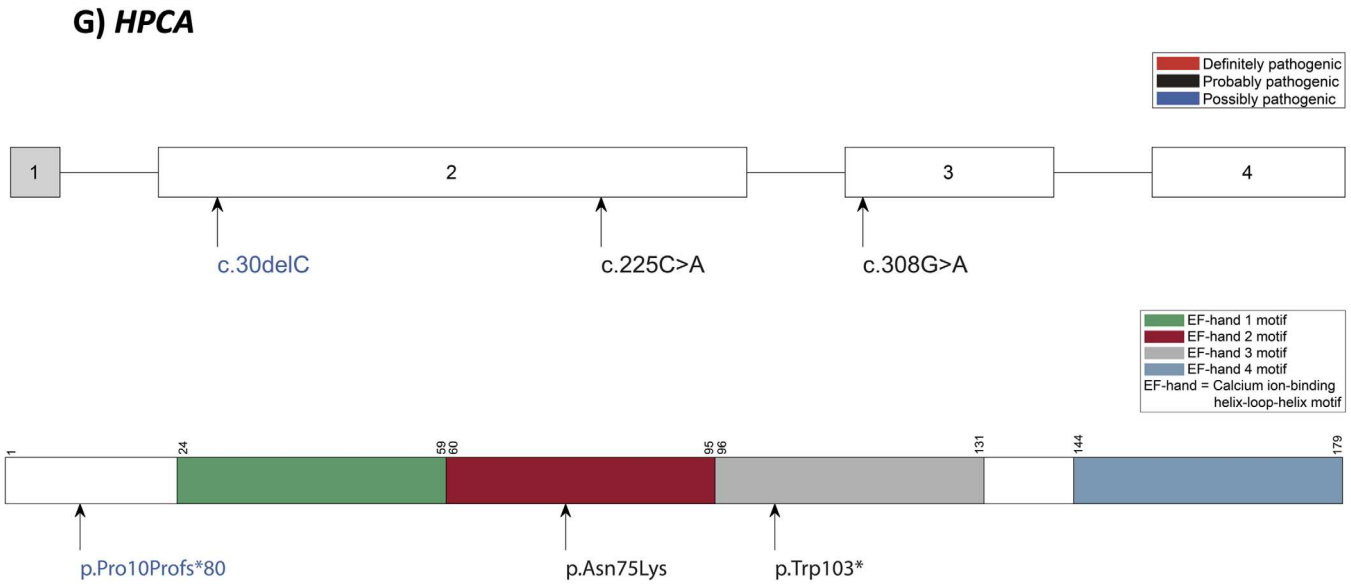

FIG. 4. (continued)

of them were missense variants (n = 20), followed by nonsense (n = 6) and frameshift (n = 3) mutations. In addition, 5 silent variants, 3 variants with an unknown effect (2 potential recurrent splice region variants and a stop codon loss), and 1 in-frame deletion were reported.

Information on medical treatment was available for <10% of patients. It comprised botulinum toxin injections with variable outcome and dopaminergic drugs with no effect. GPi-DBS seemed to be effective.

ANO3

We identified 53 *ANO3* mutation carriers from 36 families, of whom 39.6% were male (3.8% missing). Most patients were white Europeans (43.4%) or Asians (26.4%), with 30.2% missing. The median AAO was 23 years (IQR, 9–42 years), with 3.8% missing. Interestingly, there were 2 peaks in the AAO distribution, 1 in infancy/childhood (≤12 years; 32.1%) and 1 in early and late adulthood (24.5% each). Onset in adolescence (17.0%) was rarer (1.9% missing). Family history of dystonia was positive in 49.1% of mutation carriers, negative in 39.6%, and unknown in 11.3%.

Most patients had multifocal/segmental dystonia, focal or generalized distribution was less common. Cervical dystonia was the most common onset, followed by upper limb. Lower limb onset has also been reported for some patients and seems to be associated with a younger AAO (all patients < 20 years). In 4 patients, a head tremor was the initial symptom. Cervical involvement was a characteristic clinical feature. Other commonly involved sites were the limbs (upper > lower) and the craniofacial and laryngeal regions. Axial dystonia was rather rare. Tremor was a frequent finding (29 patients) at examination, myoclonus was described in 13 patients with mostly young onset, and parkinsonism was found in 2 patients. Nonmotor signs and symptoms were rarely reported (≥79.6% missing). There were 2 patients with cognitive impairment, one of them in the context of a (neuro)developmental disorder.[41]

DYT-*ANO3* follows an autosomal-dominant mode of inheritance, and only heterozygous mutations have been reported to date. The description of multiplex families with *ANO3* mutations is rare, and 5 different de novo mutations in 6 patients have been reported.[7,8,41-44]

A total of 31 variants have been described. Because of the rarity of truncating or recurrent mutations and functional studies, none of the variants has yet been scored as definitely pathogenic based on MDSGene criteria. The majority of *ANO3* variants were missense mutations (n = 29), whereas a splice site change and a substitution of unknown effect in the 5′-untranslated region were reported in 1 patient each.

Treatment information was limited. There might be a good response to dopaminergic treatment in a subset of patients, and anticholinergics and antiepileptics might also be beneficial. Several patients also responded to GPi-DBS.

PRKRA

We identified 23 *PRKRA* mutation carriers from 15 families (including 5 consanguineous families),[9,11] of whom 60.9% were male (8.7% missing). Patients were mostly of mixed/other ethnicity (56.5%, all originating from Brazil); 34.8% were white Europeans (4.3% missing). The median AAO was 8 years (IQR, 4–14 years), with 4.3% missing. Most patients had onset of symptoms at <13 years (69.6%), and only a

few had onset during adolescence (21.7%) or adulthood (1 patient each in early and late adulthood, 4.3% each). Family history of dystonia was positive in 56.5% of mutation carriers, negative in 34.8%, and unknown in 8.7%.

The vast majority of *PRKRA* mutation carriers showed generalized dystonia, 2 patients had segmental/multifocal dystonia and 1 patient had focal dystonia. DYT-*PRKRA* most often started in the limbs (upper > lower) but also in the larynx or rarely in the neck. Two patients showed first symptoms in the neck and upper limb at the same time. All patients with available information had limb dystonia and also laryngeal, craniofacial, and axial involvement. Cervical dystonia was also common. Laryngeal dystonia was often associated with dysphonia and/or dysarthria. Two patients presented with an opisthotonic posture.[9] Tremor was reported in 2 patients, myoclonus in none. Parkinsonism was described in about half the patients, however, diagnosis was based on slowed movements in body regions affected by dystonia, and thus diagnostic criteria for Parkinson's disease were not fulfilled.[45] There was no information on psychiatric signs. Other nonmotor symptoms were rarely indicated and included cognitive impairment (6 patients) and global developmental delay (4 patients, all from consanguineous families).

DYT-*PRKRA* follows an autosomal-recessive mode of inheritance. The majority of patients carried a homozygous *PRKRA* mutation (82.6%), whereas 4 patients from 3 families were carriers of compound-heterozygous variants.[11,46,47] Six variants (all missense) were reported. Almost all patients carried the same homozygous (n = 18) mutation (c.665C > T, p.Pro222Leu), which was also present in 2 patients with compound-heterozygous changes.

GPi-DBS may be the only helpful intervention in DYT-*PRKRA*. Symptomatic treatment with botulinum toxin injections, baclofen, and benzodiazepines was not shown to be beneficial.

KMT2B

We identified 75 *KMT2B* mutation carriers from 72 families, of whom 45.3% were male (2.7% missing). The majority of patients were white Europeans (38.7%); others were of Asian (14.7%) or Hispanic (1.3%) ethnicity (45.3% missing). The median AAO was 6 years (IQR, 4–8 years), with 5.3% missing. The majority (86.7%) showed first dystonic symptoms in infancy or childhood, and only 4.0% each had onset in adolescence and adulthood. Family history of dystonia was positive in only 12.0% of patients, negative in 77.3%, and unknown in 10.7%.

Most patients showed generalized dystonia, only 4 patients each had a multifocal/segmental or focal distribution. Onset was usually in the limbs, with the lower limbs being affected about 4 times more often than the upper limbs. Other onset sites (neck, larynx, trunk) were rare. Over the course of the disease limb dystonia was characteristic. Many patients also had laryngeal dystonia associated with dysphonia (35 patients), dysarthria (41 patients), or even anarthria (9 patients). Axial, cervical, and craniofacial dystonia was also common. Myoclonus (8 patients), tremor (7 patients), and parkinsonism (1 patient)[14] were rather rare. Other neurological or psychiatric features such as seizures, depression, anxiety, spasticity, and muscular hypotonia (1–2 patients each) were rare.

Nonmotor signs are characteristic for DYT-*KMT2B* and were reported in 80.3% of patients. About half the *KMT2B* mutation carriers had been diagnosed with a rather complex type of dystonia including features of a (neuro)developmental disorder, with 47 patients showing at least mild dysmorphic features. Cognitive impairment (37 patients), developmental delay (21 patients), short stature (24 patients), and microcephaly (17 patients) were also reported (3.9%–53.9% missing). Even within families, strikingly different phenotypes could occur, including unaffected mutation carriers, members with severe dystonia, and patients with developmental delay.[48] Interestingly, in some *KMT2B* mutation carriers, brain MRI abnormalities have been described.

All reported *KMT2B* mutations occurred in the heterozygous state (autosomal-dominant). Most mutations arose de novo (n = 51), 10 were inherited including 6 transmissions from an unaffected parent (4 maternal and 2 paternal), and 4 transmissions from an affected parent (2 maternal and 2 paternal). For 12 patients, parents were not available for testing.

A total of 68 different variants were reported. Truncating and protein-loss mutations were the most frequent consequence of mutations (frameshift variants 30.7%, whole-gene deletions 17.3%, nonsense mutations 10.7%, splice-site changes 4.0%). Missense variants (34.7%) and in-frame mutations (2.7%) were found in the remaining patients.

While the outcome of anticholinergic treatment was positive in about half of the treated patients, dopaminergic supplementation was reported to be mostly ineffective in DYT-*KMT2B*. Treatment with botulinum toxin injections, benzodiazepines, baclofen, neuroleptics and antiepileptics yielded variable effects. GPi-DBS was reported in many patients, often with good benefit.[13,15,49]

HPCA

We identified 5 *HPCA* mutation carriers (3 male, 2 female) from 3 families. Three patients were from Iran (Sephardic Jewish family), and 2 unrelated patients were from Turkey. Median AAO was 5 years (IQR,

0.5–12.5 years), and onset was in infancy (n = 2), childhood (n = 2), or adolescence (n = 1).

All patients had generalized dystonia. Lower limb onset was reported for 3 patients, 1 had the lower limb and face as onset sites, and 1 patient initially presented with cervical dystonia. At examination, all patients had limb (including lower limbs) and axial involvement. Four patients had cervical, craniofacial, and laryngeal dystonia, which was associated with dysphonia in 1 patient and dysarthria in 3 patients.

A dystonic tremor was reported in 3 patients, and myoclonus and parkinsonism in none. Psychiatric features were described for 3 patients, all had anxiety and 2 had additional depression (40.0% missing). For 3 patients, possible cognitive impairment was reported, and 2 of them showed learning difficulties.

While the affected members of the initially reported family had progressive, but relatively mild isolated dystonia, pronounced in the upper body parts (upper limb, cervical, and cranial areas) and were well functioning in daily life,[17] the 2 more recently reported mutation carriers presented with severe, rather complex dystonia including cognitive difficulties, jerking of the trunk and limbs or attacks with muscle cramps, involuntary movements, and speaking difficulties.[16]

DYT-*HPCA* follows an autosomal-recessive mode of inheritance. Three homozygous variants were reported. This included a missense variant in the Sephardic Jewish family and truncating mutations in the 2 more severely affected sporadic patients (a frameshift and a nonsense change).

A positive response to anticholinergic drugs was reported in 1 patient,[16] whereas other drugs (benzodiazepines, dopaminergics, antiepileptics) had no effect. Pallidotomy in 1 patient resulted in partial transient improvement.[16]

Discussion

This is the first systematic review on dystonia providing a comprehensive and up-to-date review in the English language of the published peer-reviewed literature on *TOR1A*, *THAP1*, *GNAL*, *ANO3*, *PRKRA*, *KMT2B* and *HPCA* mutation carriers. This review is based on data from ~1200 dystonia patients carrying ~250 different disease-causing mutations in these 7 genes.

All genes have a broad phenotypic spectrum, and there is overlap between the different genes. Thus, defining clinical "red flags" that allow diagnosing a specific genetic cause on an individual patient level is challenging. However, on the group level, there are differences regarding AAO ($P < 0.001$, Kruskal-Wallis test) and site of onset ($P < 0.001$, chi-square test) in all mutation carriers, but also when focusing on mutation carriers with isolated dystonia only (for detailed statistics, see Supplement). Furthermore, the occurrence rate of additional features such as developmental delay differs among the groups. *ANO3* and *GNAL* mutation carriers share a rather late median AAO (>20 years) and typically remain focal with predominant craniocervical involvement, making it clinically difficult to distinguish them from one another and from idiopathic dystonia. A clinical hint may arise from the presence of myoclonus, a recurrent feature of DYT-*ANO3* that is rare in DYT-*GNAL* and idiopathic dystonia. Notably, the presence of myoclonus also points toward other possible differential diagnoses including genetic forms of combined dystonia such as DYT-*SGCE*, which are not covered in this review. A specific combination pointing toward DYT-*KMT2B* in a subset of patients is dystonia and developmental delay/cognitive impairment.[13,15] Notably, these additional signs can be mild.[49,50] The differential diagnosis of complex dystonia (especially dystonia plus a neurodevelopmental disorder) is broad and a multitude of genes have to be considered. This is beyond the scope of this review. Laryngeal dystonia is found in almost all patients with *PRKRA* or *KMT2B* mutations but rare in DYT-*TOR1A*. The phenotype resulting from *THAP1* mutations is broad. All genetic forms targeted in this review except DYT-*GNAL* frequently also affect the limbs.

For most genes, the majority of the reported mutation carriers in the considered English literature were of white European ethnicity. An exception were *PRKRA* mutation carriers, the majority of whom originated from Brazil (because of a founder mutation[52]; Table 1). The number of DYT-*HPCA* cases is too small to draw meaningful conclusions.

The sex ratio was balanced for most genes. There was a seemingly female predominance for *GNAL* and a male predominance for *PRKRA*. Although the deviation for *PRKRA* should be interpreted with caution given the small number of only 21 mutation carriers (95% confidence interval [CI] for males, 44.7%–88.7%), the finding for *GNAL* is more robust (95% CI for males, 22.2%–44.5%). Of note, we could not detect any sex-related phenotypic differences in *GNAL* mutation carriers (Supplementary Material).

Family history was often positive for *THAP1*, *ANO3*, *GNAL*, and *PRKRA* (range, 49.1%–57.7%). In contrast, family history for *KMT2B* and *TOR1A* was typically negative. Mutations in *TOR1A*, *THAP1*, and *GNAL* are usually inherited from an affected or unaffected (because of reduced penetrance) parent, and de-novo mutations in these 3 genes are rare. In contrast, the often sporadic occurrence of DYT-*KMT2B* is due to the high rate of de-novo mutations. *PRKRA* and *HPCA* mutations follow an autosomal-recessive mode of inheritance with usually unaffected but often consanguineous parents in DYT-*PRKRA*.

Treatment of genetic dystonia included pharmacological and surgical interventions. Regarding pharmacological

treatment, only anticholinergic medication was reported to show a fairly good outcome (*TOR1A*, *THAP1*, *KMT2B*, and partly *PRKRA*). Botulinum toxin injections seem to be a therapeutic option in focal dystonias independent of the genetic cause. Oral drugs (dopamine, muscle relaxants, etc.) did not show satisfactory responses across genes. DBS is often an excellent treatment choice in DYT-*TOR1A* and DYT-*KMT2B*,[13,53-55] and it also seems to be beneficial for *GNAL*, *ANO3*, and *PRKRA* cases. The effect in DYT-*THAP1* is more variable.[56] A detailed systematic literature review on DBS is available elsewhere.[57]

Because of the phenotypic overlap, the only way to arrive at a definite conclusion about the underlying genetic cause is genetic testing. The easiest and most cost-effective option is testing for the most frequent dystonia-causing mutation (GAG deletion in *TOR1A*) and, if negative, to perform NGS-based screening of many genes, either as a gene panel or exome/genome sequencing depending on the respective setting and availability. In contrast to a predefined panel, exome/genome sequencing will also cover newly identified dystonia genes but requires more sophisticated data interpretation and is more expensive.[58-60]

So far, the most recent guidelines of the European Federation of Neurological Societies (EFNS) on diagnosis of primary/isolated dystonia[61] only comment on genetic testing for *TOR1A* and *THAP1*. Genetic testing for *TOR1A* mutations is recommended in patients with early-onset (AAO ≤ 30 years) isolated dystonia with limb onset. Regarding the data from this review, 85.6% of *TOR1A* mutation carriers (344 of 402, missing data: 42.1%) met these criteria. Testing is also recommended in patients with limb onset dystonia and AAO > 30 years if there is an affected relative with early-onset dystonia. We identified 20 mutation-positive patients with limb-onset dystonia and an AAO > 30 years, 7 of whom did not have a relative with early-onset dystonia (information missing for 7 cases). Thus, the sensitivity of the EFNS criteria can be estimated to be 83%. Of note, several studies included in this analysis set the upper age limit to 30 years, hence, sensitivity might be lower. Genetic testing for *THAP1* is recommended in early-onset (AAO ≤ 30 years) dystonia or familial cases with craniocervical predominance. Based on our data, 8 mutation carriers (3.3%; 6 of them with variants of unknown effect and only possible pathogenicity) did not fulfill either of the proposed criteria. Otherwise, 45 patients (18.8%) fulfilled all 3 criteria, 153 (63.5%) met the AAO, 139 (57.9%) the family history, and 78 (32.5%) the distribution (craniocervical) criterion.

Comparing results of this review with previously published reviews, we could verify the commonly reported phenotypes. For instance, DYT-*TOR1A* was initially described as "early-onset torsion dystonia" (EOTD, DYT1) with a mean AAO of 12.5 years and mostly limb but rarely cervical or laryngeal onset.[62] This review confirms that limb onset is typical, and the median AAO is 9 years. Similarly, DYT-*THAP1* was initially summarized as "adolescent-onset dystonia of mixed type." In an early clinical review, the phenotype was described as childhood or adolescent onset, typically starting in an arm, spreading particularly to cranial muscles with speech involvement.[63] Regarding MDSGene data, this view still holds true, with a median AAO of 15 years and most often affected onset sites being upper limbs, neck, and larynx. In addition, the cranial muscles and/or speech are affected in most patients at examination.

As described for the Parkinson's disease genes[21,64] and also true for the dystonia genes reviewed here, there is an alarmingly high proportion of missing data, resulting in an inadequate description of patients. This problem is especially pronounced for the clinical symptom of tremor (26.5%–87.0% missing data), which, by definition, can be the only additional feature of isolated dystonia besides dystonia itself. It is unknown whether tremor was not evaluated during neurological examination or just not mentioned in the publication.

We applied the relatively simple MDSGene pathoscoring[21] to classify the pathogenicity of reported mutations based on 4 criteria (segregation, variant frequency in controls, in silico prediction, and available functional evidence). Of note, this approach (but also other classification schemes) yields results that are not cut in stone and are subject to change. This is because the necessary information is often limited by small family size, sometimes erroneous in silico predictions, and lack of comprehensive functional studies. Functional studies are often challenging, especially when a meaningful readout is missing, as it is the case for *PRKRA* and *KMT2B*. For *TOR1A*, *THAP1*, and *GNAL* functional assays have been established[65-69] but with focus on selected functions only. Furthermore, the use of in vitro models with overexpression may result in misinterpretation of functional impact that is driven by the artificial system rather than the genetic variant. Establishing functional tests is often time and labor-intensive and sometimes unsuccessful. Therefore, testing for *ANO3* and *HPCA* related alterations in calcium signaling is available but hardly carried out.[70,71] As a result of the limitations of our pathoscoring approach some scores may be rather conservative. For instance, many *THAP1* variants are only scored as probably pathogenic including truncating mutations because they were only reported in single individuals without information on segregation. Although truncating mutations usually result in a loss of function, they do not always relate to disease, as is the case for *LRRK2* mutations.[72] Similarly, the only well-established, "definitely pathogenic" variant in *TOR1A* is the GAG deletion; the pathogenicity of several missense variants is still under debate (here scored as "possibly pathogenic" or "benign"; Table S3). It is also conceivable that a few "benign"-scored variants actually contribute to the pathogenesis.

With increasing evidence, interpretation of genetic variants may change and will be reevaluated on a regular basis while updating the MDSGene database.

A noteworthy limitation of the MDSGene database is that it is based on published literature only. It is well known that shortly after gene identification, unselected mutation carriers may be reported, whereas in later years there is a bias toward unusual presentations.[73,74] As long as the initial number of mutation carriers is high enough, unusual cases only have a minor influence on the overall analysis and are an important addition to the literature, as is the case for *TOR1A* and *THAP1*.

Taken together, this first systematic review on genetic forms of isolated dystonia provides a comprehensive overview of demographic, clinical, and genetic findings in reported mutation carriers. The detection of red flags for specific forms of isolated dystonia is hampered by the overall overlapping and broad phenotype but also by relatively low numbers of reported mutation carriers of this rare disease. NGS-based genetic testing seems to be a straightforward approach to determine the subtype of (isolated) dystonia in patients. Furthermore, new publication formats (table-based, online case reports rather than print-journal publications) might enable collecting information on additional mutation carriers, as well as more detailed clinical descriptions. Knowing the genetic basis of a dystonia has translational importance in terms of prognosis, family planning, treatment, and, in the future, also prioritization for clinical trials.

References

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28(7):863–873.
2. Di Fonzo A, Monfrini E, Erro R. Genetics of movement disorders and the practicing clinician; who and what to test for? Curr Neurol Neurosci Rep 2018;18(7):37.
3. Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: recommendations of the international Parkinson and movement disorder society task force. Mov Disord 2016;31(4):436–457.
4. Ozelius LJ, Hewett JW, Page CE, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997;17(1):40–48.
5. Domingo A, Erro R, Lohmann K. Novel dystonia genes: clues on disease mechanisms and the complexities of high-throughput sequencing. Mov Disord 2016;31(4):471–477.
6. Lohmann K, Klein C. Update on the genetics of dystonia. Curr Neurol Neurosci Rep 2017;17(3):26.
7. Zech M, Boesch S, Jochim A, et al. Clinical exome sequencing in early-onset generalized dystonia and large-scale resequencing follow-up. Mov Disord 2017;32(4):549–559.
8. Olschewski L, Jesus S, Kim HJ, et al. Role of ANO3 mutations in dystonia: a large-scale mutational screening study. Parkinsonism Relat Disord 2019;62:196–200.
9. Camargos S, Scholz S, Simon-Sanchez J, et al. DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. Lancet Neurol 2008;7(3):207–215.
10. Lohmann K, Klein C. Dystonia. In: Rosenberg RN, Pascual JM, eds. Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease. Cambridge, MA: Academic Press; 2020:117–134.
11. Dos Santos CO, da Silva-Junior FP, Puga RD, et al. The prevalence of PRKRA mutations in idiopathic dystonia. Parkinsonism Relat Disord 2018;48:93–96.
12. Zech M, Boesch S, Maier EM, et al. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. Am J Hum Genet 2016;99(6):1377–1387.
13. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49(2):223–237.
14. Carecchio M, Invernizzi F, Gonzalez-Latapi P, et al. Frequency and phenotypic spectrum of KMT2B dystonia in childhood: a single-center cohort study. Mov Disord 2019;34(10):1516–1527.
15. Kawarai T, Miyamoto R, Nakagawa E, et al. Phenotype variability and allelic heterogeneity in KMT2B-associated disease. Parkinsonism Relat Disord 2018;52:55–61.
16. Atasu B, Hanagasi H, Bilgic B, et al. HPCA confirmed as a genetic cause of DYT2-like dystonia phenotype. Mov Disord 2018;33(8):1354–1358.
17. Charlesworth G, Angelova PR, Bartolome-Robledo F, et al. Mutations in HPCA cause autosomal-recessive primary isolated dystonia. Am J Hum Genet 2015;96(4):657–665.
18. Jinnah HA, Sun YV. Dystonia genes and their biological pathways. Neurobiol Dis 2019;129:159–168.
19. Lohmann K, Schlicht F, Svetel M, et al. The role of mutations in COL6A3 in isolated dystonia. J Neurol 2016;263(4):730–734.
20. Dufke C, Hauser AK, Sturm M, et al. Mutations in CIZ1 are not a major cause for dystonia in Germany. Mov Disord 2015;30(5):740–743.
21. Kasten M, Hartmann C, Hampf J, et al. Genotype-phenotype relations for the Parkinson's disease genes Parkin, PINK1, DJ1: MDSGene systematic review. Mov Disord 2018;33(5):730–741.
22. Edwards M, Wood N, Bhatia K. Unusual phenotypes in DYT1 dystonia: a report of five cases and a review of the literature. Mov Disord 2003;18(6):706–711.
23. Opal P, Tintner R, Jankovic J, et al. Intrafamilial phenotypic variability of the DYT1 dystonia: from asymptomatic TOR1A gene carrier status to dystonic storm. Mov Disord 2002;17(2):339–345.
24. Gajos A, Piaskowski S, Slawek J, et al. Phenotype of the DYT1 mutation in the TOR1A gene in a polish population of patients with dystonia. A preliminary report. Neurol Neurochir Pol 2007;41(6):487–494.
25. Szczaluba K, Jurek M, Milewski M, et al. Clinical characteristics of carriers of a GAG deletion in the DYT1 gene amongst polish patients with primary dystonia. Eur J Neurol 2007;14(6):659–662.
26. Gambarin M, Valente EM, Liberini P, et al. Atypical phenotypes and clinical variability in a large Italian family with DYT1-primary torsion dystonia. Mov Disord 2006;21(10):1782–1784.
27. Klein C, Brin MF, de Leon D, et al. De novo mutations (GAG deletion) in the DYT1 gene in two non-Jewish patients with early-onset dystonia. Hum Mol Genet 1998;7(7):1133–1136.
28. Hjermind LE, Werdelin LM, Sorensen SA. Inherited and de novo mutations in sporadic cases of DYT1-dystonia. Eur J Hum Genet 2002;10(3):213–216.
29. de Carvalho Aguiar P, Fuchs T, Borges V, et al. Screening of Brazilian families with primary dystonia reveals a novel THAP1 mutation and a de novo TOR1A GAG deletion. Mov Disord 2010;25(16):2854–2857.
30. Kostic VS, Svetel M, Kabakci K, et al. Intrafamilial phenotypic and genetic heterogeneity of dystonia. J Neurol Sci 2006;250(1–2):92–96.
31. Bressman SB, de Leon D, Brin MF, et al. Idiopathic dystonia among Ashkenazi Jews: evidence for autosomal dominant inheritance. Ann Neurol 1989;26(5):612–620.
32. Miyamoto R, Ohta E, Kawarai T, et al. Broad spectrum of dystonia associated with a novel thanatosis-associated protein domain-containing apoptosis-associated protein 1 mutation in a Japanese family with dystonia 6, torsion. Mov Disord 2012;27(10):1324–1325.
33. Krause P, Bruggemann N, Volzmann S, et al. Long-term effect on dystonia after pallidal deep brain stimulation (DBS) in three members of a family with a THAP1 mutation. J Neurol 2015;262(12):2739–2744.
34. Fuchs T, Gavarini S, Saunders-Pullman R, et al. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. Nat Genet 2009;41(3):286–288.

35. Xiao J, Thompson MM, Vemula SR, LeDoux MS. Blepharospasm in a multiplex African-American pedigree. J Neurol Sci 2016;362:299–303.
36. Sohn AS, Glockle N, Doetzer AD, et al. Prevalence of THAP1 sequence variants in German patients with primary dystonia. Mov Disord 2010;25(12):1982–1986.
37. Giri S, Naiya T, Equbal Z, et al. Genetic screening of THAP1 in primary dystonia patients of India. Neurosci Lett 2017;637:31–37.
38. LeDoux MS, Vemula SR, Xiao J, et al. Clinical and genetic features of cervical dystonia in a large multicenter cohort. Neurol Genet 2016;2(3):e69.
39. Carecchio M, Panteghini C, Reale C, et al. Novel GNAL mutation with intra-familial clinical heterogeneity: expanding the phenotype. Parkinsonism Relat Disord 2016;23:66–71.
40. Geoghegan AR, Al Hussona M, Beauchamp NJ, et al. A novel GNAL mutation in familial dystonia presenting with childhood tremor and myoclonus. Mov Disord 2019;34(6):923–924.
41. Nelin S, Hussey R, Faux BM, Rohena L. Youngest presenting patient with dystonia 24 and review of the literature. Clin Case Rep 2018;6(11):2070–2074.
42. Tunc S, Denecke J, Olschewski L, et al. A recurrent de-novo ANO3 mutation causes early-onset generalized dystonia. J Neurol Sci 2019; 396:199–201.
43. Yoo D, Kim HJ, Lee JS, et al. Early-onset generalized dystonia starting in the lower extremities in a patient with a novel ANO3 variant. Parkinsonism Relat Disord 2018;50:124–125.
44. Delamarre A, Chelly J, Guehl D, et al. Novel anoctamin-3 missense mutation responsible for early-onset myoclonic dystonia. Parkinsonism Relat Disord 2019;64:346–348.
45. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1591–1601.
46. Lemmon ME, Lavenstein B, Applegate CD, Hamosh A, Tekes A, Singer HS. A novel presentation of DYT 16: acute onset in infancy and association with MRI abnormalities. Mov Disord 2013;28(14): 1937–1938.
47. de Carvalho Aguiar P, Borges V, Ferraz HB, Ozelius LJ. Novel compound heterozygous mutations in PRKRA cause pure dystonia. Mov Disord 2015;30(6):877–878.
48. Dai L, Ding C, Fang F. An inherited KMT2B duplication variant in a Chinese family with dystonia and/or development delay. Parkinsonism Relat Disord 2019;63:227–228.
49. Zech M, Jech R, Havrankova P, et al. KMT2B rare missense variants in generalized dystonia. Mov Disord 2017;32(7):1087–1091.
50. Lange LM, Tunc S, Tennstedt S, et al. A novel, in-frame KMT2B deletion in a patient with apparently isolated, generalized dystonia. Mov Disord 2017;32(10):1495–1497.
51. Klein C, Lohmann K, Marras C, Munchau A. Hereditary dystonia overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle, WA: University of Washington; 1993.
52. Quadri M, Olgiati S, Sensi M, et al. PRKRA mutation causing early-onset generalized dystonia-parkinsonism (DYT16) in an Italian family. Mov Disord 2016;31(5):765–767.
53. Albanese A, di Giovanni M, Lalli S. Dystonia: diagnosis and management. Eur J Neurol 2019;26(1):5–17.
54. Gorman KM, Meyer E, Kurian MA. Review of the phenotype of early-onset generalised progressive dystonia due to mutations in KMT2B. Eur J Paediatr Neurol 2018;22(2):245–256.
55. Li XY, Dai LF, Wan XH, et al. Clinical phenotypes, genotypes and treatment in Chinese dystonia patients with KMT2B variants. Parkinsonism Relat Disord 2020;77:76–82.
56. Danielsson A, Carecchio M, Cif L, et al. Pallidal deep brain stimulation in DYT6 dystonia: clinical outcome and predictive factors for motor improvement. J Clin Med 2019;8(12):2163.
57. Tsuboi T, Cauraugh JH, Wong JK, Okun MS, Ramirez-Zamora A. Quality of life outcomes after globus pallidus internus deep brain stimulation in idiopathic or inherited isolated dystonia: a meta-analysis. J Neurol Neurosurg Psychiatry 2020;91(9):938–944.
58. Gorcenco S, Ilinca A, Almasoudi W, Kafantari E, Lindgren AG, Puschmann A. New generation genetic testing entering the clinic. Parkinsonism Relat Disord 2020;73:72–84.
59. van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. Mov Disord 2017;32(4):569–575.
60. Kumar KR, Davis RL, Tchan MC, et al. Whole genome sequencing for the genetic diagnosis of heterogenous dystonia phenotypes. Parkinsonism Relat Disord 2019;69:111–118.
61. Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol 2011;18(1):5–18.
62. Bressman SB, de Leon D, Kramer PL, et al. Dystonia in Ashkenazi Jews: clinical characterization of a founder mutation. Ann Neurol 1994;36(5):771–777.
63. Bressman SB, Raymond D, Fuchs T, Heiman GA, Ozelius LJ, Saunders-Pullman R. Mutations in THAP1 (DYT6) in early-onset dystonia: a genetic screening study. Lancet Neurol 2009;8(5): 441–446.
64. Trinh J, Zeldenrust FMJ, Huang J, et al. Genotype-phenotype relations for the Parkinson's disease genes SNCA, LRRK2, VPS35: MDSGene systematic review. Mov Disord 2018;33(12): 1857–1870.
65. Hettich J, Ryan SD, de Souza ON, et al. Biochemical and cellular analysis of human variants of the DYT1 dystonia protein, TorsinA/TOR1A. Hum Mutat 2014;35(9):1101–1113.
66. Vulinovic F, Lohmann K, Rakovic A, et al. Unraveling cellular phenotypes of novel TorsinA/TOR1A mutations. Hum Mutat 2014;35 (9):1114–1122.
67. Lohmann K, Uflacker N, Erogullari A, et al. Identification and functional analysis of novel THAP1 mutations. Eur J Hum Genet 2012; 20(2):171–175.
68. Kumar KR, Lohmann K, Masuho I, et al. Mutations in GNAL: a novel cause of craniocervical dystonia. JAMA Neurol 2014;71(4): 490–494.
69. Fuchs T, Saunders-Pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2013;45(1):88–92.
70. Charlesworth G, Plagnol V, Holmstrom KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet 2012;91(6):1041–1050.
71. Helassa N, Antonyuk SV, Lian LY, Haynes LP, Burgoyne RD. Biophysical and functional characterization of hippocalcin mutants responsible for human dystonia. Hum Mol Genet 2017;26(13): 2426–2435.
72. Whiffin N, Armean IM, Kleinman A, et al. The effect of LRRK2 loss-of-function variants in humans. Nat Med 2020;26(6):869–877.
73. Gatto EM, Pardal MM, Micheli FE. Unusual phenotypic expression of the DYT1 mutation. Parkinsonism Relat Disord 2003;9(5): 277–279.
74. Kabakci K, Hedrich K, Leung JC, et al. Mutations in DYT1: extension of the phenotypic and mutational spectrum. Neurology 2004; 62(3):395–400.

Supporting Data

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