



Genetics in dystonia

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SUMMARY

While Hermann Oppenheim probably described the first cases of genetic (DYT1) dystonia in 1911, the 'modern history' of dystonia genetics dates back to 1994 when mutations in the *GTP cyclohydrolase I* gene were discovered to cause dopa-responsive dystonia. Due to the advent of next-generation sequencing, the field of dystonia genetics has been evolving very rapidly over the past two years, resulting in the reporting of 'DYT1-25' and, for the first time, in the identification of genes associated with adult-onset focal/segmental dystonia. However, three of these putative new genes still await independent confirmation (*TUBB4/DYT4*; *CIZ1/DYT23*; *ANO3/DYT24*) and only 11 'DYT' genes have been unequivocally demonstrated to cause different forms of dystonia. Based on a recent consensus approach, dystonias are subdivided on clinical grounds into isolated (with or without tremor) and combined (with other movement disorders) forms. Confirmed genes for isolated dystonias include *TOR1A/DYT1*; *THAP1/DYT6*; *GNAL/DYT25*. In the combined forms, dystonia is accompanied by parkinsonism (*GCH1/DYT5a*; *TH/DYT5b*; *ATP1A3/DYT12*; *TAF1/DYT3*) or myoclonus (*SGCE/DYT11*). Persistent and paroxysmal forms are distinguished according to their temporal pattern. The paroxysmal forms of dystonia/dyskinesias present with a mixed pattern of hyperkinetic movement disorders (*PRRT2/DYT10*; *MR-1/DYT8*; *SLC2A1/DYT18*).

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1. Introduction

It may have been Hermann Oppenheim who described the first case of genetic (DYT1) dystonia as early as 102 years ago in his landmark paper from 1911 entitled "Über eine eigenartige Krampfkrankheit des kindlichen und jugendlichen Alters [About a peculiar cramping sickness in children and adolescents] (Dysbasia lordotica progressiva, Dystonia musculorum deformans)" [1,2]. This article is remarkable not only for its insightful clinical description and for the coining of the term 'dystonia', but also for the fact that Oppenheim clearly recognized dystonia as an organic disorder, as opposed to 'hysteria'. Notably, he even pointed to a possible hereditary influence, as well as to the uniform ethnic (Ashkenazi Jewish) and geographic (Eastern European) origin of his patients [1,2].

The 'modern history' of dystonia genetics (Fig. 1) dates back to 1994 when the first 'DYT' gene was discovered, i.e. *GTP cyclohydrolase I*, mutations in which cause dopa-responsive dystonia [3]. This was followed by the identification of an additional eight dystonia genes over the next 15 years. Due to the advent of next-generation sequencing technology, the field of dystonia genetics has been evolving very rapidly over the past two years, leading to the reporting of another five genes since 2011.

Importantly, however, three of these putative new genes still await independent confirmation (Figs. 1 and 2).

Following an introductory paragraph on the recently revised definition and classification of dystonia, confirmed genetic forms will be reviewed in detail below.

2. Definition and classification of dystonia

From 2011 to 2013, an international panel of dystonia experts developed a consensus update of the definition and classification of dystonia suggesting the following revised definition: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation [4].

Several classification schemes have been employed to categorize the various forms of dystonia and are useful when trying to establish the diagnosis of a specific form of dystonia. The two main axes of classification currently considered most relevant are clinical and etiological [4]. On clinical grounds, the updated dystonia classification proposes characterization by age of onset (infancy, childhood, adolescence, early and late adulthood), body distribution (focal, segmental, multifocal and generalized), temporal pattern (static or progressive disease course; persistent, action-specific, diurnal or paroxysmal presentation), and association with

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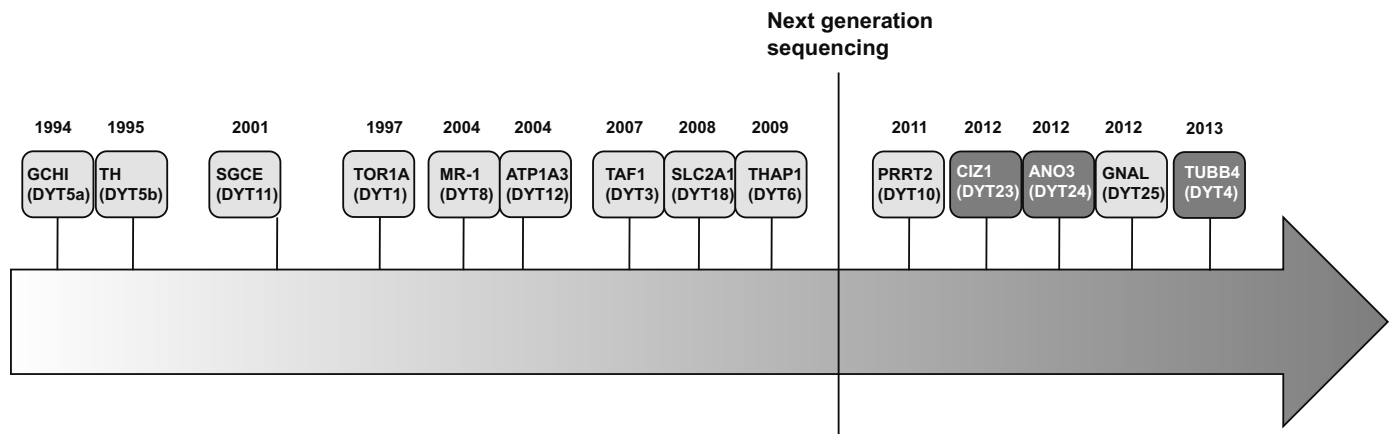


Fig. 1. Time line of gene discoveries for isolated and combined forms of dystonia. While the advent of next-generation sequencing has led to rapid advances in gene identification, three of these five novel genes (shaded in gray) have not yet been independently confirmed.

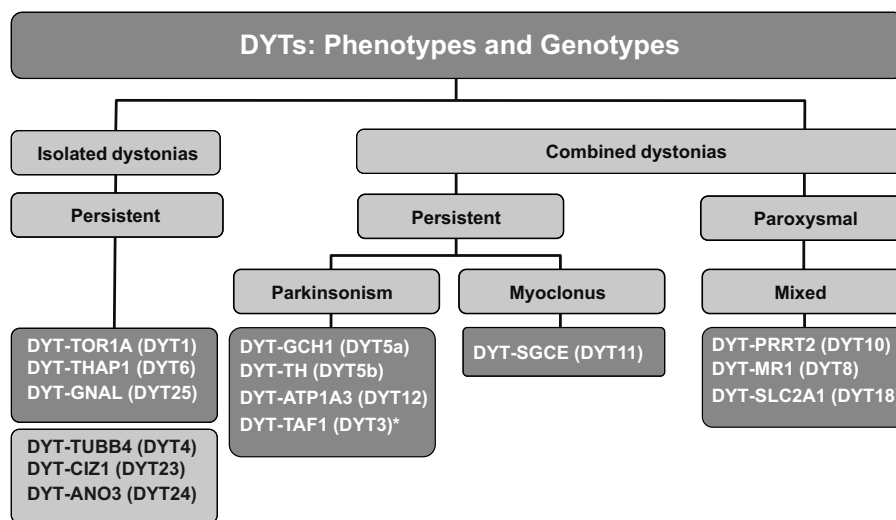


Fig. 2. Overview of phenotypes and corresponding genotypes of hereditary forms of isolated and combined dystonia. Based on distribution of symptoms, dystonias can be further subdivided into isolated and combined (with other movement disorders) forms. According to the temporal pattern of the dystonia/dyskinesia, the latter are further grouped into persistent and paroxysmal. In most of the persistent forms, dystonia is combined with parkinsonism. Another well-recognized form of dystonia is myoclonus-dystonia, in which dystonia and myoclonus coexist. The paroxysmal forms of dystonia/dyskinesias present with a mixed pattern of hyperkinetic movement disorders. Forms of dystonia with confirmed genes are shaded in dark gray; three recently reported new dystonia genes awaiting independent confirmation are shaded in light gray. *The genetic basis of DYT-TAF1 (DYT3) has not been unequivocally determined. However, it is linked to the X chromosome and can be tested for on the basis of a clearly established founder haplotype, and is thus included in the scheme.

additional features (isolated or combined with other movement disorders [4]. Formerly, isolated dystonia was referred to as 'primary dystonia' and combined dystonia (e.g. with parkinsonism or myoclonus) as 'dystonia-plus'. Clinical description along these lines enables formulating dystonia syndromes, e.g. early-onset generalized isolated dystonia or focal isolated dystonia with onset in adulthood.

Genetic features used for classification include mode of inheritance and molecular genetic data, such as linkage to a known gene locus or identification of a specific genetic defect. This list of currently 25 'DYTs' (Table 1) represents an assortment of clinically and genetically heterogeneous disorders, which names monogenic forms of dystonia in chronologic order based on their first appearance in the literature. In response to the increasing number of inconsistencies of the 'DYT' designations, a new nomenclature system for genetic forms of movement disorders, including dystonia, has been proposed [5]. According to the new system, only confirmed genes are included in the list of 'DYTs' and are no longer numbered. Rather, the 'DYT' prefix is followed by the gene name or gene locus, for example, 'DYT-TOR1A' (previously known as DYT1) [5] (Table 2).

In the present article, the revised definition and categorization as well as the new nomenclature will be employed.

An accurate description of the dystonia phenotype is the first step when evaluating a patient for dystonia. Important hints for classification can also be derived from the disease course. For example, a sudden-onset dystonia disorder is compatible with rapid-onset dystonia-parkinsonism. While many dystonias can be triggered or exacerbated by non-specific factors, such as stress, fatigue, action or certain postures, other forms of dystonia/dyskinesia may be elicited by specific triggering factors, such as sudden movement in paroxysmal kinesigenic dyskinesia. Response to treatment may also aid in the confirmation of a diagnosis, as a 'therapeutic' response to alcohol is characteristic of myoclonus-dystonia, and improvement with L-dopa supports a diagnosis of dopa-responsive dystonia.

Finally, dystonia may occur in conjunction with a wide variety of other neurological and non-neurological symptoms and signs, which is then labeled 'complex dystonia'. Complex dystonia has previously often been referred to as 'secondary dystonia'; also, the term 'secondary dystonia' has been used to indicate a known cause

Table 1
Monogenic forms of dystonia/dyskinesias (DYTs)

Symbol ^a	Gene locus	Disorder	Inheritance	Gene symbol	Status and remarks
DYT1	9q32-q34	Early-onset generalized dystonia	ADom	TOR1A	Confirmed
DYT2	Missing	Autosomal recessive dystonia	AR	Unknown	Unconfirmed. Missing locus, cases are being lumped on the basis of inheritance pattern alone
DYT3^b	Xq13.1	X-linked dystonia parkinsonism; “Lubag”	XR	TAF1?	The pathogenicity of TAF1 gene mutations remains unconfirmed
DYT4	19p	“Non-DYT1” dystonia; whispering dysphonia	ADom	TUBB4	Independently found by two groups but in the same family; TUBB4 mutations may cause broader phenotype including leukoencephalopathy
DYT5a	14q22.1–22.2	Dopa-responsive dystonia, Segawa syndrome	ADom	GCH1	Confirmed
DYT5b	11p15.5	Dopa-responsive dystonia, Segawa syndrome	AR	TH	Confirmed
	2p14-p12	Dopa-responsive dystonia	AR	SPR	Not listed
DYT6	8p11.1	Adolescent-onset dystonia of mixed type	ADom	THAP1	Confirmed
DYT7	18p	Adult-onset focal dystonia	ADom	Unknown	Unconfirmed (not replicated since first described in 1996)
DYT8	2q35	Paroxysmal nonkinesigenic dyskinesia 1 (PKND1)	ADom	MR1	Confirmed
DYT9	1p31	Paroxysmal choreoathetosis with episodic ataxia and spasticity	ADom	SLC2A1	Removed because identical to DYT18
DYT10	16p11.2-q12.1	Paroxysmal kinesigenic choreoathetosis (PKD1) and infantile convulsions	ADom	PRRT2	Confirmed
DYT11	7q21.3	Myoclonus-dystonia	ADom	SGCE	Confirmed
DYT12	19q13.2	Rapid-onset dystonia-parkinsonism	ADom	ATP1A3	Confirmed
DYT13	1p36	Multifocal/segmental dystonia	ADom	Unknown	Unconfirmed (not replicated since first described in 2001)
DYT14	11p15.5	Dopa-responsive dystonia, Segawa syndrome	ADom	GCH1	Withdrawn. Erroneous locus (identical to DYT5a)
DYT15	18p11	Myoclonus-dystonia	ADom	Unknown	Unconfirmed (not replicated since first described in 2002)
DYT16	2q31.2	Young-onset dystonia-(parkinsonism)	AR	PRKRA	Unconfirmed (no additional homozygous/compound heterozygous mutation since first described in 2008)
DYT17	20p11.22-q13.12	Autosomal recessive primary dystonia	AR	Unknown	Unconfirmed (not replicated since symbol in 2008)
DYT18	1p34.2	Paroxysmal exertion-induced dyskinesia 2	ADom	SLC2A1	Confirmed
DYT19 ^c	16q	Episodic kinesigenic dyskinesia 2 (PKD2)	ADom	Unknown	Unconfirmed (clinical overlap with PKD1; locus very close to DYT10)
DYT20**	2q	Paroxysmal nonkinesigenic dyskinesia 2 (PKND2)	ADom	Unknown	Unconfirmed (clinical overlap with PKND1; locus very close to DYT8)
DYT21**	2q14.3-q21.3	Late-onset pure dystonia	ADom	Unknown	Unconfirmed
DYT22	Not listed in OMIM				
DYT23	9q34	Adult onset cranial-cervical dystonia	ADom	CIZ1	Unconfirmed
DYT24	11p	Adult onset cranial-cervical dystonia	ADom	ANO3	Unconfirmed
DYT25	18p	Adult onset cranial-cervical dystonia	ADom	GNAL	Confirmed

ADom, autosomal dominant; AR, autosomal recessive; XR; X-linked recessive.

^a Boldface type indicates confirmed ‘DYTs’.

^b The genetic cause for DYT3 has not been unequivocally identified, however, linkage to the X chromosome has been clearly demonstrated and Filipino mutation carriers can be indirectly identified based on testing for an established founder haplotype.

^c Not approved by HGNC.

of the dystonia. However, as a number of different etiologies have been identified for both isolated/combined and complex dystonia, usage of the terms ‘primary’ and ‘secondary’ dystonia has led to some confusion and is no longer recommended.

A description of the complex dystonias is beyond the scope of the present article, which will focus on clinical and genetic features of isolated and combined forms of dystonia. In accordance with Table 2, confirmed genetic forms of dystonia will be presented in the following order: (i) isolated and (ii) combined. Combined dystonias will be subdivided by temporal pattern as persistent vs. paroxysmal. The former group is then further categorized as dystonia with parkinsonism or dystonia with myoclonus (Fig. 2).

3. Isolated dystonias

In isolated forms of dystonia, dystonia is the only disease manifestation with the possible exception of tremor. Currently, three genes are known to cause isolated dystonia.

3.1. DYT-TOR1A: early-onset generalized dystonia; Oppenheim dystonia (DYT1)

First signs of TOR1A-associated dystonia typically begin in childhood (mean age 13 years, range 1–28 years) with twisting of an arm or leg, and progression to involve other limbs and torso, but usually not the face and neck [6]. There is a tendency for symptoms to move up the body, and for later- and arm-onset cases to be less severe. Almost all cases are caused by a specific mutation, a 3-base pair deletion (GAG) in the coding region of the

Table 2

The proposed new list of genetically determined dystonias

New designation and phenotypic subgroup	Additional phenotypic notes	Inheritance pattern	Locus symbol
Isolated dystonias			
DYT-TOR1A	Early-onset generalized dystonia	AD	<i>DYT1</i>
DYT-THAP1	Adolescent-onset dystonia of mixed type	AD	<i>DYT6</i>
DYT-GNAL	Adult onset cranial-cervical dystonia	AD	<i>DYT25</i>
Combined dystonias			
<i>Dystonia plus parkinsonism</i>			
DYT-GCH1	Dopa-responsive dystonia	AD	<i>DYT5a</i>
DYT-TH	Dopa-responsive dystonia	AR	<i>DYT5b</i>
DYT-ATP1A3	Rapid-onset dystonia-parkinsonism	AD	<i>DYT12</i>
DYT-TAF1 ^a	Dystonia-parkinsonism	X-linked	<i>DYT3</i>
<i>Dystonia plus myoclonus</i>			
DYT-SGCE	Myoclonus-dystonia	AD	<i>DYT11</i>
<i>Paroxysmal dystonia plus other dyskinesia</i>			
DYT-PRRT2	Paroxysmal kinesigenic dyskinesia	AD	<i>DYT10</i>
DYT-MR-1	Paroxysmal non-kinesigenic dyskinesia	AD	<i>DYT8</i>
DYT-SLC2A1	Paroxysmal exertion-induced dyskinesia	AD	<i>DYT18</i>

^a Due to a founder effect, genetic testing is possible. The pathogenicity of the TAF1 gene is not absolutely confirmed, however testing of selected variants within the XDP-linked haplotype is sufficient for the diagnosis.

TOR1A gene that accounts for about 60% of cases with generalized dystonia in the non-Jewish population and about 90% of cases in the Ashkenazi Jewish population due to a founder effect [7]. *TOR1A*-associated dystonia is inherited in an autosomal dominant fashion with reduced penetrance (only about 30% of mutant gene carriers are affected) and variable expressivity with respect to age and site of onset and progression. If symptoms do not occur prior to 28 years of age in mutation carriers, they usually remain unaffected for the rest of their life. Symptoms can be as mild as writer's cramp.

3.2. *DYT-THAP1: adolescent-onset dystonia with mixed phenotype (DYT6)*

THAP1-associated dystonia has features of focal and generalized primary dystonia and was first identified in three Mennonite families who are related by a common ancestor dating to the mid-1700s. It is inherited in an autosomal dominant manner with penetrance estimated at 40%. Some phenotypic features overlap with *TOR1A*-associated dystonia, but the onset is later (mean 19 years; range 5–38 years) and there is more prominent cranial involvement, especially in muscles of the lung, larynx and face, with dysphonia being a predominant feature. Mutations in the *THAP1* (*THAP domain containing, apoptosis associated protein 1*) gene were identified to underlie this form of dystonia [8–10]. *THAP1* shows significant mutational heterogeneity with currently over 60 different missense and truncating *THAP1* mutations reported mainly in European patients, but also in patients of other ethnicities [11].

3.3. *DYT-GNAL: adult-onset segmental dystonia (DYT25)*

Mutations in the *guanine nucleotide-binding protein (G protein), alpha activating activity polypeptide, olfactory type* gene cause cervical or cranial dystonia with onset often in the thirties, however with a broad range from 7 to 54 years [8]. *GNAL* mutations have been identified in 6 of 39 (19%) dystonia families [8], and independently confirmed in a large African-American dystonia pedigree [12] and a number of familial and singleton cases [12,13]. Although additional

studies in larger samples are clearly needed, *GNAL* mutations probably account for about 1% of all cases of focal or segmental dystonia involving the cranio-cervical region [13, unpublished observation].

In addition to *GNAL*, three other genes have recently been implicated in adult-onset segmental dystonia, namely *CIZ1* [14], *ANO3* [15], and *TUBB4* [16,17]. As mutations in the former two genes have not yet independently been confirmed and appear to also occur in controls at considerable frequencies, these two genes are not discussed in detail in the present article. The latter gene, *TUBB4*, was found independently by two different groups, albeit in the same Australian family with dystonia and prominent whispering dysphonia [16,17]. The phenotype is characterized by cranio-cervical dystonia with prominent spasmodic dysphonia and shows variable expressivity within the family. The dystonia frequently generalizes and is at least partially responsive to alcohol and propranolol [18]. A second missense mutation was found in an unrelated patient with familial craniocervical dystonia [16].

4. Combined dystonias

In combined dystonias, the clinical features of dystonia are combined with another movement disorder, most commonly parkinsonism or myoclonus. In rare cases, parkinsonism or myoclonus may even be the sole disease manifestation.

4.1. *Dystonia combined with parkinsonism*

4.1.1. *DYT-GCH1 and DYT-TH: dopa-responsive dystonia; Segawa syndrome (DYT5a and DYT5b)*

Dopa-responsive dystonia (DRD) is characterized by childhood onset of dystonia, diurnal fluctuation of symptoms, and a dramatic response to L-dopa therapy [3]. Later in the course of the disease, parkinsonian features may occur and may, in rare cases, be the only sign of the condition. In addition, a variety of atypical presentations of DRD have been described including onset in the first week of life, generalized hypotonia and proximal weakness, or psychiatric

abnormalities. While rare autosomal recessive forms of DRD are associated with mutations in the tyrosine hydroxylase (*TH*) gene, the more frequent form of DRD (*DYT5a*) is dominantly inherited and usually caused by mutations in the *GTP cyclohydrolase 1 (GCHI)* gene. Importantly, mutations in *TH* cause a much more severe clinical phenotype than dopa-responsive dystonia due to *GCHI* mutations and resemble the phenotype observed in the rare carriers of homozygous *GCHI* mutations [19]. To date, more than 100 different mutations, spread across the entire *GCHI* coding region, have been reported and include missense, nonsense, and splice-site mutations, small and large (whole-exon or whole-gene) deletions, and mutations in the untranslated regions.

GCHI mutation carriers show a high degree of both inter- and intrafamilial phenotypic variability and reduced penetrance. While penetrance is lower among men than women, the underlying mechanisms affecting penetrance are not yet resolved. Although the *GCHI* gene was the first gene to be discovered for a monogenic form of dystonia almost 20 years ago and the disorder is exquisitely treatable, there is still considerable diagnostic delay of about 13 years. Of further note, many mutation carriers display some residual (dystonic and/or parkinsonian) features. Likewise, non-motor features (sleep disturbances, mood disorders, migraine) are present in a considerable subset of patients and are probably due to involvement of the serotonergic system [20].

4.1.2. *DYT-ATP1A3: rapid-onset dystonia-parkinsonism (DYT12)*

ATP1A3-associated dystonia has a characteristic sudden onset within hours to weeks, typically in adolescence or young adulthood (but as late as 55 years), in response to physical or mental stress, with persistence of symptoms throughout life. It is inherited in an autosomal dominant manner with reduced penetrance. Symptoms include dystonic spasms predominantly in the upper limbs, orofacial dystonia, dysarthria, and dysphagia, slowness of movement, sometimes along with symptoms of parkinsonism, including bradykinesia, rigidity and postural instability. Stressful events precipitating onset include fever, prolonged exercise or childbirth [21]. Although some individuals show reduced levels of the dopamine metabolite homovanillic acid in the CSF, there is no evidence for a decrease in the density of dopaminergic terminals or clinical response to L-dopa treatment.

Several different missense mutations were identified in the gene *ATP1A3* on chromosome 19q13, (23 exons) which encodes Na⁺/K⁺ATPase alpha 3 [22].

Notably, the spectrum of phenotypes associated with mutations in *ATP1A3* has recently been expanded, as it has been shown that the *ATP1A3* mutations are the cause of 74% of alternating hemiplegia of childhood (AHC) cases. AHC is a severe neurodevelopmental syndrome characterized by recurrent hemiplegic episodes and distinct neurological manifestations [23].

Another well-described form of dystonia-parkinsonism is X-linked dystonia-parkinsonism [24]. This condition is endemic to the Philippines and inherited in an X-linked recessive fashion. As the underlying genetic cause has not yet been unequivocally identified, this form of dystonia is not discussed in detail in the present article. Of note, however, patients of Filipino origin can be tested for this condition based on a founder haplotype.

4.2. Dystonia combined with myoclonus

4.2.1. *DYT-SGCE: myoclonus-dystonia (DYT11)*

Myoclonus-dystonia (M-D) is characterized by a combination of myoclonus and dystonia. Symptom onset is usually in childhood or early adolescence. The disease is inherited as an autosomal dominant trait with reduced penetrance. Loss-of-function mutations in the *epsilon-sarcoglycan* gene (*SGCE*) on chromosome 7q21 have

been implicated in numerous M-D families [25]. The myoclonic jerks typical of M-D are brief, lightning-like movements most often affecting the neck, trunk, and upper limbs, with legs affected less prominently. In most affected individuals myoclonic jerks are dramatically but transiently ameliorated by intake of alcohol. Approximately half of the affected individuals have focal or segmental dystonia that presents as cervical dystonia and/or writer's cramp. In contrast to primary torsion dystonia, involvement of lower limbs is rare and usually does not occur at onset. Reduced penetrance on maternal transmission of the disease allele is caused by maternal genomic imprinting of the *SGCE* gene [26]. Interestingly, large deletions of the entire *SGCE* gene are frequently accompanied by a deletion of the neighboring gene *COL1A2* (collagen type I alpha 2) coding for the fibrillar collagen found in cartilage. Thus, MD patients carrying large deletions within the *DYT11* locus may have associated phenotypes such as delayed skeletal development and severe osteoporosis.

4.3. Dystonia combined with other dyskinesia (paroxysmal)

4.3.1. *DYT-PRRT2: paroxysmal kinesigenic dyskinesia (DYT10)*

Paroxysmal kinesigenic dyskinesia (PKD) usually starts in childhood or adolescence and is triggered by sudden movements. Attacks usually last several minutes and may appear up to 100 times per day. They mostly consist of dystonic and choreoathetotic movements. PKD has been clinically and genetically linked to a variety of conditions including benign familial infantile seizures (BFIS), the syndrome of rolandic epilepsy, paroxysmal exercise-induced dyskinesia, and writer's cramp. Missense and truncating mutations in the *Proline-rich transmembrane protein 2 (PRRT2)* gene were identified as the cause of PKD [27].

4.3.2. *DYT-MR-1: paroxysmal non-kinesigenic dyskinesia (DYT8)*

In addition to alcohol and caffeine, attacks of paroxysmal nonkinesigenic dyskinesia can be precipitated by stress, hunger, fatigue, and tobacco. They usually consist of a combination of dystonia, chorea, athetosis or ballismus, last from minutes to hours and in the most severe cases may occur several times daily. Two missense mutations (p.A7V and p.A9V) in the myofibrillogenesis regulator 1 (*MR-1*) gene are the cause of the disease [28].

4.3.3. *DYT-SLC2A1: paroxysmal exertion-induced dyskinesia (DYT18)*

The *SLC2A1* gene, previously linked to GLUT1 (glucose transporter of the blood-brain barrier) deficiency syndrome, was identified to also cause paroxysmal exertion-induced dyskinesia [29]. The attacks in this disorder are clinically characterized by a combination of chorea, athetosis and dystonia in excessively exercised body regions. The legs are most frequently affected. A single attack lasts from a few minutes to an hour and occurs after prolonged physical exercise. In addition to the movement disorder, several patients have other disease manifestations such as epilepsy, hemolytic anemia, and migraine. A ketogenic diet is an effective therapeutic option. Of note, paroxysmal choreoathetosis with episodic ataxia and spasticity (*DYT9*) has also been linked to *SLC2A1* mutations [30].

Diagnostic genetic testing is available for all of the aforementioned forms of genetic dystonia (for an overview, see www.genetests.org). Several companies now offer gene panels for hereditary forms of dystonia with similar phenotypes, such as isolated dystonias or dopa-responsive dystonias.

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Conflict of interests

The author has no conflict of interest to declare.

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