CLINICAL MANIFESTATIONS AND CLASSIFICATION OF DYSTONIA

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The term “dystonia” was coined by Oppenheim in 1911 for a disorder causing variable muscle tone and recurrent muscle spasm. Initially it was called dystonia musculorum deformans (1) and later primary generalized torsion dystonia (2). In modern times, dystonia has been defined as a movement disorder causing sustained muscle contractions, repetitive twisting movements, and abnormal postures of the trunk, neck, face, or extremities (3-5). A new, expanded consensus definition has stated the following: “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, twisting, and may be tremulous. Dystonia is often either initiated or worsened by voluntary action and associated with overflow muscle activation” (5). Unfortunately, most general physicians and many general neurologists are inexperienced with the dystonias. It is therefore frequently misunderstood, often confused with spasticity, rigidity, or other movement disorders and sometimes mistakenly attributed to psychological causes. Patients with dystonia often see several physicians in multiple specialties before a correct diagnosis is made. Common misdiagnoses, for example, include cerebral palsy in a child with genetically determined generalized dystonia, dry eyes in blepharospasm, neck strain in cervical dystonia, temporomandibular joint syndrome in oromandibular dystonia, carpal tunnel syndrome in writer’s cramp, and chronic laryngitis in spasmodic dysphonia. Recent advances concerning the causes and treatment of dystonia make it important that this disorder become more widely recognized.

CLINICAL FEATURES

Dystonia results from the involuntary co-contraction of agonist and antagonist muscles together with overflow of unwanted muscle contraction into adjacent muscles. Contrary to popular belief, muscular rigidity is not necessarily a clinical feature of dystonia as resistance to passive manipulation is variable depending on the patient’s level of activity or their posture and may be normal, increased, or even decreased, giving rise to Oppenheim’s original use of the term dystonia. Dystonic movements can be slow or rapid, may change during different activities or postures, may occur episodically, and in advanced cases sometimes become increasingly fixed. Tremor and myoclonic muscle jerks are sometimes associated with dystonia. Action dystonia refers to abnormal movements or postures which occur only during certain voluntary activities and which are sometimes task-specific. Some localized dystonias respond to simple sensory tricks such as lightly touching the affected body part, known as the “geste antagoniste.”

CLASSIFICATION OF DYSTONIA

Until recently dystonia was classified according to age of onset, topographic body distribution, etiology and genetics (6-8). New information concerning etiology and problems with the older terminology have led to a recently published consensus conference which has reclassified the dystonias (Table 1).

Axis I. Clinical Characteristics (Table 1). Because of their recognized importance, classification by age of onset and topographic distribution have been retained in the new classification. With regard to *age of onset*, it had been recognized that genetically determined dystonia with onset in childhood and even up to age 26 usually progresses from focal limb dystonia to more generalized dystonia while dystonia after age 26 usually begins in cranial-cervical muscles, nearly always remains localized or segmental, and is usually relatively non-progressive (6). However, as indicated in Table 2, considering the range of dystonias which occur in infancy, early and late childhood, adolescence, and in early or late adulthood, it is more useful to classify dystonias into narrower age ranges (5). Classification according to affected *body distribution* continues along traditional lines (Table 2) and includes focal (one affected body region), segmental (two or more contiguous body regions), multifocal (two or more separate body regions), generalized (trunk and at least two other sites with or without leg involvement), and hemidystonia (body regions limited to one side of body).

The new classification also recognizes the variety of *temporal patterns* which occur in dystonic syndromes. Disease course may be static or progressive while disease variability encompasses the persistent, action-specific, diurnal, and paroxysmal patterns which occur among the dystonias.

Associated features, listed within Axis 1, are a particularly important aspect of the new classification. This breaks down into isolated dystonias and dystonias which are combined with another movement disorder. Isolated dystonia includes forms of dystonia previously called "primary" in which dystonia is the only motor abnormality which is present with the exception of tremor or myoclonus. Combined dystonia includes dystonias associated with other movement disorders such as parkinsonism or myoclonus. Traditional classifications had often broadly divided dystonias into "primary" dystonias including both generalized and focal dystonia and "secondary" dystonias, such as those occurring in heredodegenerative disorders, following acquired structural brain lesions, due to drug-induced dystonias, and in so-called dystonia-plus syndromes (10,11).

"Primary" dystonia previously referred to dystonia unaccompanied by other neurological abnormalities and with an absence of known causes or identifiable brain pathology. However, this term is problematic as it has been based on both phenomenology and etiology. So called primary dystonias are, in fact, not always isolated as they may be accompanied by tremor or myoclonus. Moreover, the absence of known brain pathology is based on only a small number of postmortem studies showing variable abnormalities and in many cases genetic causes have, in fact been identified (8). In the new consensus classification, "isolated" refers only to phenomenology and not etiology while in "combined" forms dystonia may not necessarily be the predominant movement disorder. The term "secondary" dystonia is also problematic as it groups together a broad range of unrelated heredodegenerative disorders as well as a number of metabolic disorders. Other secondary dystonias include acquired dystonias due to structural brain lesions, medications, toxins, trauma and other causes. Finally, to date the small group of genetically determined "dystonia-plus syndromes", sometimes placed within the category of secondary dystonia, has remained limited to dopa-responsive dystonia, myoclonus-dystonia, and rapid-onset dystonia-parkinsonism and has served largely as a place holder for a group of unrelated genetic disorders in which dystonia is associated with another significant extrapyramidal abnormality such as parkinsonism or myoclonus.

Axis II. Etiology (Table 1). This includes both inherited and acquired disorders in which there is degenerative brain pathology, the presence of structural brain lesions, or disorders without identifiable brain abnormalities. Inherited disorders included here include autosomal dominant, autosomal recessive, X-linked, and mitochondrial disorders. A well known genetic classification of dystonia is based on the DYT coding system and includes both proven and unproven gene locus abnormalities, often with uncertain relationships to causation and clinical phenotype. The DYT1 through DYT25 loci currently listed include a very mixed group of isolated dystonic syndromes some of which are very rare and, in some cases, have even been limited to a single family (Table 3). This classification is unavoidably incomplete as several well established genetic disorders in which dystonia is prominent such as Wilson's disease, Lesch-Nyhan disease, and deafness-dystonia syndrome do not have DYT assignments because they were described before the use of DYT designations (5). Moreover, the DYT disorders will necessarily have to be updated as new information accumulates concerning genetics, clinical features, pathology, and brain imaging associated with existing as well as new DYT disorders. Acquired disorders which cause dystonia include the usual list of traumatic, infectious, drug-induced, toxic, vascular, neoplastic, and psychogenic causes. Finally, also included in Axis 2 are idiopathic adult-onset focal or segmental dystonias with either sporadic or familial distribution. This practical clinical overview will follow the new consensus classification and concentrate mainly on the more common and better understood dystonias.

ISOLATED DYSTONIAS

For reasons already given, the term "primary" dystonia is problematic and has been discarded in favor of "isolated" in the new classification (5). However, as discussed by Bressman (12), until more information is acquired the term retains some utility as a practical construct and it is likely it will continue to be utilized. By definition, except for tremor, these dystonias are unaccompanied by other neurologic abnormalities and have no known cause except for identified genetic mutations in some cases. The prevalence of early-onset generalized dystonia is estimated to be as low as 0.7 per million or as high as 50 per million in population studies (13). Prevalence is 111 per million among Ashkenazi Jews (14). The prevalence of isolated dystonia is higher when late-onset cases are included, with estimates ranging from 30 per million in a survey in China (15) to 732 per 100,000 in a population-based study in Italy which focused on individuals over age 50 (16). Cervical dystonia is

the most common isolated dystonia. In an early epidemiological study, an estimated 88,000 persons in the United States were said to have primary focal dystonia (17) but this is well known to have been a major underestimate due to failure to recognize or diagnose dystonia in an era before useful treatment was available.

ISOLATED GENERALIZED DYSTONIA

These would be classified as isolated dystonias in Axis I and as either inherited or idiopathic dystonias in Axis 2. Isolated generalized dystonia, known formerly as dystonia musculorum deformans, is a progressive and very disabling disorder which usually begins in childhood or adolescence. Many cases are inherited as autosomal dominant traits caused by a guanine-adenine-guanine (GAG) deletion in the DYT1 gene, resulting in a glutamate deletion in torsin A (18), a brain protein with uncertain function highly concentrated in the substantia nigra. This gene defect accounts for 80% of early limb-onset cases in Ashkenazi Jewish populations and less than 50% of cases in non-Jewish populations (4). Penetrance is estimated at 30% and clinical expression varies from generalized dystonia to occasional adult-onset focal dystonia (19-21). It begins as a focal action dystonia before age 26 with most cases beginning in childhood or adolescence (22). Because of its rarity and unfamiliar features, in early stages it is sometimes misdiagnosed as a psychogenic disorder. About 65% progress to a generalized or multifocal distribution, 10% become segmental, and 25% remain focal (4). Childhood-onset cases commonly evolve to generalized dystonia (23) which produces a major and disfiguring disability due to severe abnormalities of gait and posture.

ISOLATED FOCAL DYSTONIA

These would be classified as isolated dystonias in Axis I and, in most cases, as idiopathic, sporadic dystonias in Axis 2. These disorders are estimated to be ten times more common than isolated generalized dystonia and are usually first encountered by primary care physicians and non-neurologist subspecialists. Isolated focal dystonias nearly always occur in adults and may involve the neck, eyelids, face, jaw, or arm while the leg is only rarely involved (Table 4). These typically begin in middle adult life or later and, with the exception of writer's cramp, are more common in women than in men. They typically progress for 1-2 years followed by a relatively static course. They may occasionally spread to adjacent muscle groups to become segmental in distribution. Rare remissions have been reported. Special features characterize some of these dystonias such as task specificity in writer's cramp or musician's dystonia of the hand in piano or string instrument musicians and of the perioral region in wind instrument musicians (embouchure dystonia). Sensory tricks often ameliorate symptoms in cervical dystonia and blepharospasm. Certain activities may aggravate symptoms such as walking in foot dystonia or improve symptoms such as the effect of speaking out loud on blepharospasm. When carefully investigated, a family history of focal dystonia may be identified but the genetics of these disorders has not been defined (24). A small number of incompletely penetrant, autosomal dominant focal and segmental dystonias have been genetically mapped including DYT6, DYT7, and DYT23-25 (Table 3). DYT6 is due to a defect in the THAP (thanatos-associated protein domain-containing, apoptosis-associated protein 1 gene) gene originally identified in Amish-Mennonite families but later identified in individuals with other ancestries. The clinical phenotype is that of young adult-onset focal or segmental dystonias including laryngeal, limb, orofacial and oromandibular involvement (25,26). DYT1 mutations have also been identified in occasional patients with adult-onset focal dystonia (19-21)

Cervical dystonia Cervical dystonia, also known as spasmodic torticollis, is the most common adult-onset focal dystonia. It presents with several different abnormal postures including rotational torticollis, laterocollis, retrocollis, and anterocollis. Mixed forms of these postures are very common. Onset usually occurs between ages 30 and 50 and is more common in women than in men. Because of frequent neck pain and stiffness and restricted head mobility it is often misdiagnosed at first as muscle strain, cervical spondylosis, or cervical disc herniation. Abnormal head postures appear early and are often associated with an irregular and sometimes jerky head tremor, called dystonic tremor, which may vary with head position. Pain is typically present in posterior cervical and shoulder muscles in 75% of cases while pain in the sternomastoid muscles is very uncommon (27). Sensory tricks such as lightly contacting the face or chin with a finger or hand are helpful in many patients. Differential diagnosis includes essential tremor predominantly involving the head, tardive dystonia in which retrocollis is particularly common, anterocollis due to a cervical myopathy, and secondary forms of more fixed torticollis due to neck injury, atlanto-axial dislocation, spinal cord neoplasm, or soft tissue infections of the neck.

Cranial dystonia Cranial dystonia may involve the eyelids, jaw, vocal cords, face, tongue, platysma, or pharynx. Onset usually occurs after age 40. Blepharospasm is the most common cranial dystonia and produces increased blink frequency, episodic forced eye closure, and/or difficulty opening the eyes. Symptoms are typically aggravated by bright light, reading, watching television, or driving and rarely are severe enough to cause functional blindness. Blepharospasm is often confused with simple tic disorders or eyelid ptosis due to

myasthenia gravis. Secondary blepharospasm occurs in tardive dyskinesia, following deep brain stimulation in Parkinson's disease, and rarely has been associated with structural brainstem lesions. Although subjective dry eyes is often an early symptom, significant dry eyes due to eyelid or lacrimal disorders is very infrequent and is often an initial incorrect diagnosis in blepharospasm.

Oromandibular dystonia Oromandibular dystonia involves the medial and lateral pterygoid muscles and causes involuntary closing, opening, or deviation of the jaw. Muscles of the mouth, tongue or neck are also frequently involved. Severe cases may cause jaw pain, dysarthria, difficulty chewing, dysphagia, and dental trauma. Differential diagnosis includes temporomandibular joint disorders, bruxism, edentulous mouth movements, and tardive dyskinesia.

Spasmodic dysphonia Spasmodic or laryngeal dysphonia is an action dystonia in which speaking precipitates inappropriate adduction or abduction of the vocal cords. Adductor dysphonia accounts for 90% of cases and is due to overcontraction of the thyroarytenoid muscles causing strained speech and voice breaks. In abductor dysphonia, posterior cricoarytenoid overcontraction separates the vocal cords causing an intermittent breathy voice, particularly when vowels follow voiceless consonants such as p, k, h, t, s, and f. Mixed forms of these two forms of spasmodic dysphonia also occur. Initially, spasmodic dysphonia is often misdiagnosed as a psychogenic disorder. Differential diagnosis includes voice tremor, more diffuse pharyngeal dystonias which affect the voice, and structural or inflammatory vocal cord disorders.

Limb dystonia Limb dystonia in adults is less frequent than the other adult onset focal dystonias. It involves the arm or hand much more frequently than the leg or foot. It causes involuntary twisting, flexion, or extension postures of the extremities or digits. In the upper extremity these are often task-specific and are referred to as occupational cramp disorders. The most common of these occur while writing or playing a musical instrument. In writer's cramp, involuntary hand and finger postures cause slow, effortful handwriting. Similar problems occur in pianists and string musicians (28). Unlike painful orthopedic overuse syndromes with which they are frequently confused, limb dystonia does not respond to prolonged rest or splinting. Limb dystonia affecting the foot or toes is typically an action dystonia which is absent at rest and is precipitated by walking or running. It may occur in isolation but can be a presenting sign of young-onset Parkinson's disease and may also occur in more established Parkinson's disease. Focal limb dystonia is not infrequently caused by structural basal ganglia lesions and often occurs in corticobasal degeneration, progressive supranuclear palsy, and focal lesions of the basal ganglia although nearly always in association with other major neurological findings.

SECONDARY DYSTONIA

These would be classified as combined dystonias in Axis I and as inherited or acquired dystonias in Axis 2. This is a large and diverse group of disorders with many etiologies previously labeled as "heredodegenerative diseases" with known neuropathology, drug-induced dystonias, and dystonias caused by acquired structural abnormalities.

Heredodegenerative disorders

These would be classified as combined dystonias with other neurological or systemic abnormalities in Axis 1 and as inherited disorders with or without evidence of degeneration in Axis 2. This is a very heterogeneous group of degenerative and metabolic disorders, many of which are genetic and usually associated with other prominent neurologic abnormalities (Table 5). The term is not very useful as the list contains a grab-bag of hereditary, degenerative, and developmental disorders in which dystonia is a highly variable component (5). Those disorders associated with distinctive pathologic abnormalities in the basal ganglia are typically associated with parkinsonism and other extrapyramidal signs.

Drug-induced dystonias

Acute and more chronic drug-induced dystonia would be classified as an acquired disorder in Axis 2. This occurs during treatment with levodopa, antipsychotic drugs, anticonvulsants, serotonin reuptake inhibitors, and rarely after other miscellaneous drugs. Persistent tardive dystonia may occur following chronic use of dopamine receptor blocking antipsychotic drugs and metoclopramide (29). Dystonia may also be due to manganese, carbon monoxide, carbon disulfide, and other intoxications.

Acquired structural brain lesions
Acquired structural brain lesions causing dystonia would be classified as either an isolated or combined dystonia with or without other neurologic abnormalities and as an acquired disorder in Axis 2. These may produce either hemidystonia or focal limb dystonia and brain imaging is frequently abnormal. Basal ganglia lesions involving the putamen and thalamus are particularly common (30) and occur following perinatal injury, kernicterus, brain infarcts, hemorrhage, infection, trauma, anoxia, multiple sclerosis, and brain tumors (31).

Peripheral trauma of the neck or extremities is sometimes followed by local signs resembling focal dystonia but is not specifically classified as a dystonia in Axis I or 2. The relationship between these postures and true dystonia is uncertain and somewhat controversial (32,33). This disorder should probably be classified as a pseudodystonia (5). In these disorders peripheral trauma is followed by abnormal, fixed postures that differ from dystonia by their acute appearance following injury, absence of involuntary movements, absence of sensory tricks, often features of complex regional pain syndrome, and a limited response to treatment with botulinum toxin (34,35). Although isolated forms of dystonia are often mistakenly attributed to psychological causes, psychogenic dystonia has also been documented as a cause of dystonia, often occurring abruptly following peripheral or psychological trauma (36).

Other rare but important dystonia syndromes
There are several rare genetic disorders which, in previous classifications, were distinguished from the heredodegenerative disorders because, to date at least, they do not appear associated with known neuropathological findings. In previous classifications these were arbitrarily referred to as "Dystonia-plus syndromes". They include dopa-responsive dystonia (DRD), myoclonus-dystonia, and rapid onset dystonia-parkinsonism (37-40). They would be classified in Axis 1 as combined dystonias and in Axis 2 as inherited disorders without evidence of degeneration. These disorders are associated with other neurological signs such as parkinsonism in dopa-responsive dystonia (DRD) or rapid onset dystonia-parkinsonism and myoclonus in myoclonus-dystonia.

DRD is a rare disorder presenting in early childhood with foot dystonia, gait abnormality, and hyperreflexia followed by progressive generalized dystonia (38). Diurnal fluctuation with worsening of symptoms late in the day is sometimes a unique feature. Normal early childhood development distinguishes it from spastic cerebral palsy with which it is often confused. Symptoms may sometimes be limited to a focal or multifocal dystonia which persists into adult life. Parkinsonism often predominates in adult-onset forms of DRD. The major hallmark of DRD is its very complete and sustained response to levodopa. DRD is an autosomal dominant disorder due to a point mutation in the gene for guanosine triphosphate cyclohydrolase 1 which is necessary for synthesis of tetrahydrobiopterin, a cofactor in dopamine synthesis. There are no known neuropathologic changes in dopamine-containing neurons of the substantia nigra and fluorodopa positron emission tomography is normal. Differential diagnosis includes dystonic forms of cerebral palsy, juvenile parkinsonism in which dystonia is often prominent early in the disease, and DYT1 dystonia which shows no response to levodopa.

Myoclonus-dystonia is a rare autosomal dominant disorder due to a mutation in the gene coding for ε-sarcoglycan (39,40). It begins in childhood or adolescence producing brief multifocal myoclonic muscle jerks associated with relatively mild dystonic features which improve following alcohol (39). Rapid onset dystonia parkinsonism is a very rare autosomal dominant disorder which begins in adolescence or young adulthood with the relatively abrupt appearance of dystonia, pseudobulbar palsy, and/or parkinsonism followed by a plateau in symptoms followed later by further acute exacerbations over a period of many years There is no apparent nigrostriatal neuronal loss or clinical response to L-dopa (41).

PAROXYSMAL DYSTONIA
Paroxysmal dystonias are rare disorders beginning in childhood or young adulthood characterized by episodic dystonia and other involuntary movements without symptoms or neurological findings between episodes. It would be classified in Axis 1 as a paroxysmal dystonia and in Axis 2 as either an inherited or acquired dystonia. Their relationship to other dystonias is uncertain as they overlap clinically with other episodic disorders such as epilepsy and episodic ataxia and some are ion channel disorders. They are broadly divided into brief kinesigenic dystonias precipitated by sudden movement which respond to anticonvulsants, more prolonged spontaneous dystonias

which are much more treatment resistant, exercise-induced dystonia, and mixed forms (42). A gene locus has been found in several families with paroxysmal dystonia (Table 3) but other genetic types with unknown loci exist and secondary cases due to acquired brain lesions such as in multiple sclerosis also occur. Paroxysmal dystonia must be distinguished from seizures, nonepileptic events, and psychogenic symptoms.

PATIENT EVALUATION

Evaluation begins with a careful history and examination to exclude secondary forms of dystonia (43). Birth, developmental, medication, toxin, trauma, and family histories are important. When other neurological findings are present, brain magnetic resonance imaging (MRI) and laboratory testing for an underlying structural, degenerative or metabolic disorder should be carried out. Wilson's disease should always be excluded with serum ceruloplasmin, 24-hour urinary copper and slit lamp examination. DRD may be excluded by lack of a response to a 4 week trial of levodopa/carbidopa at a dose of 25/100 mg three times daily. In adults, when dystonia is the only neurological abnormality, a search for rare degenerative or metabolic disorders is unlikely to be fruitful. A family history of isolated focal or generalized dystonia suggests a genetically determined dystonia. DYT1 genetic testing is commercially available and should be carried out in patients with generalized or focal dystonia with onset before age 26, when limb dystonia appears even if after age 26, and if there is dystonia in a family member beginning before age 26. Because DYT1 has only 30% penetrance it should be tested for even in the absence of a positive family history. Hemidystonia suggests a structural brain lesion, which warrants brain imaging, while cervical spine imaging is indicated for atypical or post-traumatic forms of cervical dystonia. Following complete investigation an attempt should be made to classify the patient's dystonia according to the new classification system described in this review.

TABLES

Table 1. Proposed classification of dystonia

Axis I. Clinical characteristics	**Axis II. Etiology**

Clinical characteristics of dystonia
Age at onset
• Infancy (birth to 2 years)
• Childhood (3-12 years)
• Adolescence (13-20 years)
• Early adulthood (21-40 years)
• Late adulthood (>40 years)
Body distribution
• Focal
• Segmental
• Multifocal
• Generalized (with or without leg involvement)
• Hemidystonia
Temporal pattern
• Disease course
  ○ Static
  ○ Progressive
• Variability
  ○ Persistent
  ○ Action-specific
  ○ Diurnal
  ○ Paroxysmal
Associated features
Isolated dystonia or combined with another movement disorder
• Isolated dystonia
• Combined dystonia
Occurrence of other neurological or systemic manifestations
• List of co-occurring neurological manifestations
	Nervous system pathology
	Evidence of degeneration
	Evidence of structural (often static) lesions
	No evidence of degeneration or structural lesion
	Inherited or acquired
	Inherited
	• Autosomal dominant
	• Autosomal recessive
	• X-linked recessive
	• Mitochondrial
	Acquired
	• Perinatal brain injury
	• Infection
	• Drug
	• Toxic
	• Vascular
	• Neoplastic
	• Brain injury
	• Psychogenic
	Idiopathic
	• Sporadic
	• Familial

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Table 2. Topographic classification of dystonia.

Type of dystonia	***Affected body parts***
Focal	Single body region
Segmental	Two or more adjacent body regions
Multifocal	Two or more non-adjacent body regions
Generalized	Leg or legs, trunk, and one other body region
Hemidystonia	Ipsilateral arm and leg

Adapted from Bressman SB (5)

Table 3. Monogenic forms of dystonia with a DYT designation

Designation	Dystonia type	Inheritance	Gene locus	Gene	OMIM number
DYT1	Early-onset generalized torsion dystonia (TD)	Autosomal dominant	9q	GAG deletion in *DYT1*	128100
DYT2	Autosomal recessive TD	Autosomal recessive	Unknown	Unknown	224500
DYT3	X-linked dystonia parkinsonism; "lubag"	X-chromo-somal recessive	Xq	*TAF1/DYT3*	314250
DYT4	"Non-DYT1" TD; whispering dysphonia	Autosomal dominant	Unknown	Unknown	128101
DYT5a/ DYT14 **DYT5b**	Dopa-responsive dystonia;Segawa syndrome	Autosomal dominant Autosomal recessive	14q 11p	*GTP-cyclohydrolase* *Tyrosine hydroxylase*	128230
DYT6	Adolescent-onset TD of mixed type	Autosomal dominant	8p	*THAP1*	602629
DYT7	Adult-onset focal TD	Autosomal dominant	18p	Unknown	602124
DYT8	Paroxysmal nonkinesigenic dyskinesia	Autosomal dominant	2q	*Myofibrillo-genesis regulator 1*	118800
DYT9	Paroxysmal choreoathetosis with episodic ataxia and spasticity	Autosomal dominant	1p	Unknown	601042
DYT10	Paroxysmal kinesigenic choreoathetosis	Autosomal dominant	16p-q	Unknown	128200
DYT11	Myoclonus-dystonia	Autosomal dominant	7q	*epsilon-sarcoglycan*	159900
DYT12	Rapid-onset dystonia-parkinsonism	Autosomal dominant	19q	*Na/K ATPase alpha 3*	128235
DYT13	Multifocal/segmental dystonia	Autosomal dominant	1p	unknown	607671
DYT14/ DYT5a	Dopa-responsive dystonia	Autosomal dominant	14q	*GTP-cyclohydrolase*	607195
DYT15	Myoclonus-dystonia	Autosomal dominant	18p	unknown	607488
DYT16	Young-onset dystonia-parkinsonism	Autosomal recessive	2p	*PRKRA*	603424
DYT17	Autosomal recessive primary torsion dystonia	Autosomal recessive	20pq	unknown	612406
DYT18	Paroxysmal exertion-induced dyskinesia 2	Autosomal dominant	1p	*SLC2A1*	612126
DYT19	Episodic kinesigenic dyskinesia 2	Autosomal dominant	16q	unknown	611031
DYT20	Paroxysmal nonkinesigenic dyskinesia 2	Autosomal dominant	2q	unknown	607488
DYT21	Adult-onset generalized/multifocal dystonia	Autosomal dominant	2q	unknown	614588
DYT23	Adult-onset cervical dystonia	Autosomal dominant	9q	*CIZ1*	614860
DYT24	Adult-onset craniocervical dystonia	Autosomal dominant	11p	*ANO3*	615034
DYT25	Adult-onset cervical dystonia	Autosomal dominant	18p	*GNAL*	615073

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Table 4. Isolated adult-onset focal dystonia

Type of dystonia	*Main clinical features*	*Common misdiagnosis*
Cervical dystonia (spasmodic torticollis)	Abnormal head postures Head tremor Neck pain	Muscle strain Cervical disk disease Osteoarthritis
Blepharospasm	Increased blink rate Forced eye closure Difficulty opening eyes	Myasthenia gravis Dry eyes
Oromandibular	Jaw clenching (bruxism) Jaw in open position Lateral jaw shift	TMJ syndrome Myasthenia gravis Dental malocclusion Edentulous movements
Orofacial	Action dystonias involving face, lips, tongue, or pharynx	Tic disorders
Spasmodic dysphonia		
Adductor type	Voice breaks and strain	Chronic laryngitis
Abductor type	Breathy voice	Vocal cord polyps
Mixed type	Features of both	Voice tremor Psychogenic causes
Limb dystonia	Action dystonias affecting writing, playing a musical instrument, handling tools, walking	Nerve entrapment Overuse syndromes Muscle cramps
Axial dystonia	Movements and postures of shoulders, back, or abdomen	Myoclonus Motor tics Psychogenic causes

Table 5. Degenerative and metabolic disorders that sometimes cause dystonia

Wilson's disease
Parkinsonian syndromes
- Parkinson's disease
- Juvenile parkinsonism (PARKIN mutations)
- Multiple system atrophy
- Corticobasal degeneration
- Progressive supranuclear palsy

Globus pallidus degenerations
Pantothenate kinase deficiency due to PANK2 mutations∗
Familial basal ganglia calcifications
Huntington's disease
Spinocerebellar degenerations
Lysosomal storage disorders
- Dystonic lipidosis
- Ceroid lipofuscinosis
- Metachromatic leukodystrophy
- GM1 and GM2 gangliosidosis
- Neiman Pick type C
- Krabbe disease
- Perlizaeus-Merzbacher disease

Organic aminoacidurias
- Glutaric academia
- Homocysteinuria
- Hartnup's disease
- Methylmalonic aciduria

Mitochondrial genetic disorders
- Leigh's disease
- Leber's plus dystonia disease

X-linked Dystonia-deafness
Neuroacanthocytosis
Lesch-Nyhan syndrome
Ataxia telangiectasia

Adapted from Fahn S, Bressman SB, Marsden CD (4); Friedman and Standaert (44)
∗Formerly known as Hallervorden Spatz syndrome

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