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Hereditary Dystonia Overview

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Summary

The purpose of this overview on hereditary dystonia is to help clinicians determine if an individual has a hereditary dystonia in order to provide information regarding recurrence risk and evaluation of relatives at risk.

Goal 1

Describe the clinical characteristics of dystonia.

Goal 2

Review the causes of hereditary dystonia.

Goal 3

Provide an evaluation strategy to determine the etiology of hereditary dystonia in a proband.

Goal 4

Review the differential diagnosis of hereditary dystonia (i.e., non-genetic causes of dystonia).

Goal 5

Provide information regarding recurrence risk and evaluation of relatives of a proband with hereditary dystonia who are at risk.

Clinical Characteristics of Dystonia

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements and/or postures. Dystonic movements are typically patterned and twisting, and may be associated with tremor. Dystonia is often initiated or worsened by voluntary action and

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associated with overflow muscle activation. Most forms of dystonia tend to worsen initially. Forms of dystonia without neurodegeneration usually reach a plateau with stable findings, whereas those associated with neuronal loss progressively worsen over time.

Dystonia can be classified clinically according to age of onset, body distribution (see Table 1), temporal pattern, and associated features.

Age of onset

- Infancy (neonatal – 2 years)
- Childhood (3-12 years)
- Adolescence (13-20 years)
- Early adulthood (21-40 years)
- Late adulthood (>40 years)

Body distribution. See Table 1.

Table 1. Classification of Dystonias by Affected Body Part

Type of Dystonia	# of Body Parts Affected	Detail
Focal [1]	1	Examples: • Eyelids (blepharospasm) • Mouth (oromandibular dystonia, musician's cramp) • Larynx (dystonic adductor dysphonia, "whispering dysphonia") • Neck (cervical dystonia, previously known as spasmodic torticollis) • Hand & arm (writer's cramp)
Segmental	≥2 contiguous body parts	Examples: • Axial (neck & trunk) • Brachial (1 arm & trunk; both arms ± neck ± trunk) • Crural (1 leg & trunk; both legs ± trunk)
Multifocal	≥2 non-contiguous body parts	Example: • Faciobrachial (blepharospasm & writer's cramp)
Hemidystonia	≥2	Ipsilateral arm & leg
Generalized	≥3	Trunk & ≥2 other sites; ± leg involvement

1. Some localized dystonias may spread and eventually generalize.

Temporal pattern

- Persistent. Dystonia persists to about the same extent throughout the day.
- Action-specific (e.g., musician's dystonia, writer's cramp)
- Diurnal fluctuations (e.g., dopa-responsive dystonia)
- Paroxysmal. Dystonia/dyskinesia appear suddenly and are self-limited, usually induced by a specific trigger.

Classification of dystonias by associated features

- Isolated dystonia. Dystonia is the only motor feature with the exception of possible tremor (see Table 3).
- Combined dystonia. Dystonia is combined with another movement disorder (e.g., myoclonus, parkinsonism) (see Table 3).

- Complex dystonia. Dystonia co-occurs with other neurologic or systemic manifestations; dystonia is not necessarily the most prominent disease manifestation and may even be an inconsistent feature (see Table 4).

When dystonic movements are the presenting or predominant sign, the class of dystonia (i.e., isolated, combined, or complex) may be difficult to identify. Whereas gradual-onset focal or segmental dystonia can be classified as isolated in the vast majority of adult-onset dystonia, this is true for fewer than half of those with childhood-onset dystonia [Fahn et al 1987]. Therefore, the presence of dystonia in a child must be considered a potential sign of complex and often severe disease, and warrants thorough assessment.

Causes of Hereditary Dystonia

Initially these monogenic disorders were designated DYT followed by a number that represented the chronologic order in which the description of the phenotype and/or genetic discovery first appeared in the literature; see Table 2 (pdf). Although some of the inherited dystonias have a distinct phenotype, considerable phenotypic overlap can occur, making classification based on phenotype alone problematic (for example, DYT-Tor1A and DYT-KMT2B can mimic each other).

Because of the inconsistencies in the "DYT nomenclature," a naming system that combines the "DYT" designation and the name of associated gene was proposed by Marras et al [2012] and now follows the recommendations for the Nomenclature of Genetic Movement Disorders by the International Parkinson's Disease and Movement Disorder Society Task Force [Marras et al 2016] (see Table 3). This naming system eliminates previously listed loci that were erroneous, duplicated, or unconfirmed as well as disorders that were not predominantly dystonic. Distinguishing paroxysmal movement disorders by replacing "DYT" with "PxMD" is recommended by Marras et al [2016]. Of note, genes associated with an increased risk for dystonia – but not meeting a threshold to be considered a gene in which pathogenic variants are causative – are not included.

Table 3. Nomenclature System for Inherited (Monogenic) Forms of Isolated Dystonia and Combined Dystonia/Dyskinesia

Form of Dystonia		Gene	Locus Name	New Designation & Phenotypic Subgroup	Additional Distinguishing Features	MOI
Isolated		*TOR1A*	DYT1	DYT-TOR1A	Childhood or adolescent-onset, generalized	AD
		THAP1	DYT6	DYT-THAP1	Adolescent-onset, cranial or generalized	AD
		ANO3	DYT24	DYT-ANO3	Adult-onset, focal or segmental	AD
		GNAL	DYT25	DYT-GNAL	Mostly adult-onset, focal or segmental	AD
		KMT2B	DYT28	DYT-KMT2B	Early-onset, generalized, mild syndromic features	AD
Combined	**Dystonia plus parkinsonism**	*GCH1*	DYT5a	DYT-GCH1	Dopa-responsive	AD, AR
		TH	DYT5b	DYT-TH	Dopa-responsive	AR
		SPR	Not assigned	DYT-SPR	Dopa-responsive, cognitive impairment	AR
		TAF1 [1]	DYT3	DYT-TAF1	Neurodegeneration	XL
		PRKRA	DYT16	DYT-PRKRA	Dystonia w/mild parkinsonism	AR
		ATP1A3	DYT12	DYT-ATP1A3	Rapid-onset	AD
	Dystonia plus myoclonus	*SGCE*	DYT11	DYT-SGCE	Psychiatric disease	AD

Table 3. continued from previous page.

Form of Dystonia		Gene	Locus Name	New Designation & Phenotypic Subgroup	Additional Distinguishing Features	MOI
	Paroxysmal dystonia + other dyskinesia	*PNKD* [2]	DYT8	PxMD-PNKD	Paroxysmal nonkinesigenic dyskinesia	AD
		PRRT2	DYT10	PxMD-PRRT2	Paroxysmal kinesigenic dyskinesia	AD
		SLC2A1	DYT18	PxMD-SLC2A1	Paroxysmal exertion-induced dyskinesia	AD
		ECHS1	Not assigned	PxMD-ECHS1	Paroxysmal exertion induced dyskinesia	AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Pathogenicity of *TAF1* variants unconfirmed but molecular genetic testing for founder haplotype linked to disease is possible and can be used for diagnostic purposes.

2. Previously known as *MR-1*

Isolated Dystonias

DYT-TOR1A (early-onset generalized dystonia) typically first manifests in childhood (mean age 13 years, range 1-28 years) as twisting of an extremity. Symptoms tend to start in lower parts of the body, progressing to involve other limbs and the torso, but usually not the face or neck [Bressman et al 2000]. Penetrance is reduced; approximately 35% of persons heterozygous for a *TOR1A* pathogenic variant are affected. If manifestations are not evident in a person heterozygous for a *TOR1A* pathogenic variant by age 28 years, that individual will usually remain symptom-free for life. Expressivity varies with respect to age of onset, site of onset, and progression. Individuals with later onset or onset in the arms tend to be less severely affected. A specific *TOR1A* pathogenic variant, a three-base pair deletion (NM_000113.2:c.907_909delGAG) in the coding region, accounts for about 60% of generalized dystonia in the non-Jewish population and about 90% in the Ashkenazi Jewish population as a result of a founder effect [Ozelius et al 1997].

DYT-THAP1 (adolescent-onset segmental/generalized dystonia). Although some phenotypic overlap with DYT-TOR1A is observed, the onset of DYT-THAP1 is later (mean 19 years; range 5-38 years) and cranial involvement is more prominent especially in muscles of the tongue, larynx, and face, with dysphonia being a predominant feature. DYT-THAP1 was first identified in three Mennonite families who are related to a common ancestor [Fuchs et al 2009]. Currently more than 90 different pathogenic missense and truncating *THAP1* variants have been reported – mainly in people from Europe but also from China and Brazil [Blanchard et al 2011]. Penetrance is estimated at 50%.

DYT-ANO3 (adult-onset focal or segmental dystonia). Pathogenic variants in *ANO3* were initially reported in individuals with predominantly craniocervical dystonia with a widely variable age of onset [Charlesworth et al 2012]. Pathogenic variants were detected in about 1% of individuals with dystonia and shown to cosegregate with the disease phenotype in small family pedigrees. Notably, a large number of missense variants can be found in variant databases and in healthy individuals, however, the presence of a *de novo* variant in *ANO3* supports pathogenicity of the variant [Zech et al 2017].

DYT-GNAL (adult-onset segmental dystonia) is characterized by cervical or cranial dystonia that often begins in the fourth decade (range 7-54 years) [Fuchs et al 2013]. About 30 different *GNAL* pathogenic variants, mostly in the heterozygous state, have been reported in individuals with dystonia and are spread over the entire gene. *GNAL* pathogenic variants appear to be highly but not fully penetrant [Vemula et al 2013].

DYT-KMT2B (early-onset, generalized dystonia with mild syndromic features) is characterized by early-onset, generalized dystonia, which may be clinically indistinguishable from DYT-TOR1A and may be the most

common cause of early-onset generalized dystonia, at least outside the Askenazi Jewish population [Zech et al 2016, Meyer et al 2017].

As *KMT2B* has only very recently been described in conjunction with dystonia and mild syndromic features, it remains to be determined whether DYT-KMT2B falls under the "isolated" or "complex" category of inherited dystonias. Given the broad phenotypic overlap with DYT-TOR1A and only mild and inconsistent expression of microcephaly, intellectual disability, developmental delay, seizures, spasticity, eye movement abnormalities, and facial dysmorphism, it has been tentatively grouped in the "isolated dystonias" category.

Combined Dystonias

Dystonia Plus Parkinsonism

DYT-GCH1 (GTP cyclohydrolase 1-deficient dopa-responsive dystonia) is characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of oral administration of levodopa. The average age of onset is approximately six years. This disorder typically presents with gait disturbance caused by foot dystonia, later development of parkinsonism, and diurnal fluctuation of symptoms. Non-motor features including sleep disturbances, mood disorders, and migraine are present in a considerable subset of affected individuals [Tadic et al 2012]. In general, gradual progression to generalized dystonia is observed. Intellectual, cerebellar, sensory, and autonomic disturbances generally do not occur. Inheritance is autosomal dominant with reduced penetrance – particularly in males. Both inter- and intrafamilial phenotypic variability is reported.

DYT-TH is an incompletely dopa-responsive infancy-onset dystonia caused by tyrosine hydroxylase deficiency. Onset is between age 12 months and six years; initial symptoms are typically lower-limb dystonia and/or difficulty in walking. Diurnal fluctuation of symptoms (worsening of the symptoms toward the evening and their alleviation in the morning after sleep) may be present. Other typical clinical features include bradykinesia and hypotonia (both of which can be severe), autonomic disturbances (particularly facial flushing), ptosis, and oculogyric crises.

DYT-SPR is a rare cause of partially dopa-responsive childhood-onset dystonia characterized by axial hypotonia, motor and speech delay, weakness, and oculogyric crises; symptoms show diurnal fluctuation and sleep benefit. Other common features include parkinsonian signs, limb hypertonia, hyperreflexia, intellectual disability, psychiatric and/or behavioral abnormalities, autonomic dysfunction, and sleep disturbances.

DYT-TAF1 is endemic on Panay Island in the Philippines [Lee et al 2011], where it is known as "lubag" in the local Filipino dialect, meaning "twisted." DYT-TAF1 is characterized by a combination of dystonia and parkinsonism, and is the only known "DYT" with documented neurodegeneration. Penetrance is complete in men. Although almost all women who are obligate heterozygotes are unaffected, 14 affected females with phenotypes of variable severity have been reported. The exact *TAF1* pathogenic variant remains a matter of debate since several variants (disease haplotype) segregate with the phenotype. A disease-specific change (DSC) within *TAF1* [Herzfeld et al 2013] or a retrotransposon (SVA) insertion [Kawarai et al 2013] are under discussion as potential disease-causing mechanisms [Domingo et al 2015].

DYT-PRKRA is characterized by dystonia with prominent oromandibular involvement, dysphagia, and retrocollis. Parkinsonian features are mild (or even absent) and do not respond to levodopa therapy [Camargos et al 2008]. Recently, a number of reports described single families with the homozygous NM_003690.4:c.665C>T (NP_003681.1:p.Pro222Leu) variant in *PRKRA* and thus confirmed pathogenicity of this change [Quadri et al 2016] in the context of dystonia.

DYT-ATP1A3 is characterized by rapid onset of dystonia with parkinsonism (primarily bradykinesia and postural instability); a rostra-caudal (face>arm>leg) gradient of involvement including bulbar regions; and no response to an adequate trial of L-dopa therapy [Brashear et al 2007]. Anxiety, depression, and seizures have

been reported. The age of onset ranges from four to 55 years. Fever, physiologic stress, or alcoholic binges often trigger the onset of symptoms. After their initial appearance, findings commonly stabilize, but with little improvement. Occasionally, subsequent episodes cause abrupt worsening. Penetrance is incomplete. *ATP1A3* pathogenic variants can also cause alternating hemiplegia of childhood presenting with episodes of weakness and/or dystonia, seizures, and gradual cognitive decline [Heinzen et al 2014].

Dystonia with Myoclonus

DYT-SGCE is characterized by a combination of myoclonus and (in most individuals) dystonia [Zimprich et al 2001]. Many heterozygotes for an *SGCE* pathogenic variant develop psychiatric features in addition to or instead of the movement disorder [Weissbach et al 2013]. Maternal imprinting of *SGCE* explains the observation that the vast majority of affected individuals inherit their pathogenic variant from their fathers; in contrast, those inheriting the variant from their mothers will likely remain unaffected throughout their lives [Müller et al 2002].

Paroxysmal Dystonia with Other Dyskinesia

PxMD-PNKD (Paroxysmal nonkinesigenic dyskinesia) attacks are usually a combination of dystonia, chorea, athetosis, and ballismus; last from minutes to hours; and in the most severely affected individuals may occur several times a week. Attacks can be precipitated by alcohol and caffeine as well as by stress, hunger, fatigue, and tobacco. Two *PNKD* (formerly *MR-1*) pathogenic missense variants (NM_015488.4:c.20C>T (p.Ala7Val) and NM_015488.4:c.26C>T p.Ala9Val) are causative [Lee et al 2004]. Other likely pathogenic variants were found in single families [Ghezzi et al 2009, Gardiner et al 2015].

PxMD-PRRT2 (paroxysmal kinesigenic dyskinesia) attacks are mostly dystonia, choreoathetosis, and ballism triggered by sudden movement. Attacks usually last several minutes and may occur up to 100 times per day. Onset is usually in childhood or adolescence [Bhatia 2011]. Heterozygous missense and truncating *PRRT2* variants were identified as the cause of DYT-PRRT2 [Chen et al 2011] as well as the allelic disorders benign familial infantile seizures (BFIS) and the syndrome of rolandic epilepsy, paroxysmal exercise-induced dyskinesia, and writer's cramp [Schmidt et al 2012, Heron & Dibbens 2013]. In addition, phenotypes associated with pathogenic variants in *PRRT2* included a high frequency of migraines and hemiplegic migraine [Gardiner et al 2015].

PxMD-SLC2A1 (paroxysmal exertion-induced dyskinesia). The attacks are characterized by the combination of chorea, athetosis, and dystonia in 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. Of note, *SLC2A1* pathogenic variants can be associated with variable phenotypes also including paroxysmal kinesigenic dyskinesia, paroxysmal nonkinesigenic dyskinesia, episodic ataxia, and myotonia [Gardiner et al 2015]. In addition to the movement disorder, other disease manifestations can include epilepsy, hemolytic anemia, and migraine.

***ECHS1*-related paroxysmal dyskinesia** (see Mitochondrial Short-Chain Enoyl-CoA Hydratase 1 Deficiency). Biallelic *ECHS1* pathogenic variants are typically associated with severe infantile Leigh-like syndromes. Biallelic *ECHS1* pathogenic variants have recently been reported in individuals with milder phenotypes characterized by paroxysmal exertion-induced dystonia with prominent axial involvement, particularly opisthotonus. Onset is typically between age two and four years. Interictally, some affected children are asymptomatic, others have a mild-to-moderate Leigh-like syndrome with speech problems, dysphagia, pyramidal involvement, and cognitive impairment. Pallidal hyperintensities on brain MRI are very characteristic [Olgiati et al 2016, Mahajan et al 2017].

Complex Dystonias

Although complex dystonias share dystonia as a manifestation, atypical features and additional neurologic signs are often observed. These may include:

- Sustained dystonia at rest (whereas isolated or combined dystonia is usually action- or posture-dependent)
- Prominent tongue and perioral involvement leading to a *risus sardonicus* (i.e., fixed, exaggerated, or distorted smiling)
- Pyramidal or cerebellar signs
- Ataxia
- Oculomotor abnormalities
- Cognitive disturbances
- Hearing loss
- Intellectual disability / developmental delay
- Seizures

Although the list of complex dystonias is long and unwieldy, certain rules and patterns help to make an accurate diagnosis and tailor management. Grouping the complex dystonias into those that are hereditary neurodegenerative or metabolic disorders (see Table 4) and those that are acquired due to brain lesions, drugs, or psychological causes (see Table 5) has proven useful.

Table 4. Complex Dystonias: Inherited Neurodegenerative/Metabolic Disorders

Disorder	MOI	Gene(s)	Clues to the Diagnosis
Neurodegenerative diseases			
DRPLA (dentatorubral-pallidolysian atrophy)	AD	*ATN1*	Huntington disease like; prominent myoclonus
Huntington disease (Westphal variant juvenile- or childhood-onset HD)	AD	*HTT*	Family history; caudate atrophy on MRI
Huntington disease-like 2	AD	*JPH3*	African ancestry
Rett or Rett-like syndrome	XL, AD	*MECP2, FOXG1, GNB1*	Unusual stereotypies; autism
Parkin type of early-onset Parkinson disease	AR	*PARK2*	Abnormal DaTscan
Chorea-acanthocytosis	AR (& possible AD)	*VPS13A*	Acanthocytes in blood smear
McLeod neuroacanthocytosis syndrome	XL	*XK*	Weak expression of Kell antigens; acanthocytes in blood smear
Neuronal intranuclear inclusion disease	AD or sporadic	Unknown	MRI: high-intensity signal in cortico-medullary junction on DWI images; intranuclear inclusions on skin biopsies
Disorders leading to brain calcification			
Primary familial brain calcification	AD	*PDGFB*, *PDGFRB*, *SLC20A2, XPR1*	MRI/CT: calcifications in basal ganglia, white matter & cerebellum
Disorders of heavy metal metabolism			
Wilson disease	AR	*ATP7B*	↓ plasma ceruloplasmin; Kaiser-Fleischer corneal ring; face of the giant panda sign on MRI
Hypermanganesemia with dystonia, polycythemia, and cirrhosis	AR	*SLC30A10*	T_1-weighted hyperintensities in basal ganglia & cerebellum on MRI
	AR	*SLC39A14*	
Neurodegeneration with brain iron accumulation (NBIA)			

Table 4. continued from previous page.

Disorder	MOI	Gene(s)	Clues to the Diagnosis
Mitochondrial membrane protein-associated neurodegeneration	AR	*C19orf12*	T_2-weighted hypointensities in substantia nigra & globus pallidus on MRI; T_2-weighted hyperintense streaking between hypointense internal globus pallidus & external globus pallidus
Aceruloplasminemia	AR	*CP*	MRI: hypointensity of basal ganglia, thalamus, red nucleus, occipital cortex, & cerebellar dentate nuclei on T_2-weighted images
Woodhouse-Sakati syndrome	AR	*DCAF17*	Dystonia deafness syndrome; hypogonadism; alopecia
Fatty acid hydroxylase-associated neurodegeneration	AR	*FA2H*	MRI: hypointensity of the globus pallidus, confluent hyperintensities of white matter on T_2-weighted images, pontocerebellar atrophy, thin corpus callosum
Neuroferritinopathy	AD	*FTL*	MRI: cystic lesions in the basal ganglia, bilateral pallidal necrosis; hypointensity of caudate, globus pallidus, putamen, substantia nigra, & red nuclei on T_2-weighted images
Pantothenate kinase-associated neurodegeneration	AR	*PANK2*	Eye of the tiger sign on MRI
PLA2G6-associated neurodegeneration	AR	*PLA2G6*	Cerebellar hypoplasia & T_2-weighted high signal in the cerebellum on MRI
Beta-propeller protein-associated neurodegeneration	XL	*WDR45*	MRI: hypointense globus pallidus & substantia nigra on T_2-weighted images
Lipid storage disorders			
Neuronal ceroid-lipofuscinoses	AR; adult-onset AD or AR	*ATP13A2*, *CLN3*, *CLN5*, *CLN6*, *CLN8*, *CTSD*, *CTSF*, *DNAJC5*, *GRN*, *KCTD7, MFSD8*, *PPT1*, *TPP1*	Dementia; epilepsy; visual loss in children
Fucosidosis	AR	*FUCA1*	MRI: hypointensity of globus pallidus & substantia nigra on T_2-weighted images; dysostosis multiplex
Niemann-Pick disease type C	AR	*NPC1*, *NPC2*	Supranuclear gaze palsy, splenomegaly, ↑ oxysterol blood levels
Sphingolipidosis			
Arylsulfatase A deficiency	AR	*ARSA*	Progressive demyelination
Lysosomal storage diseases			
Krabbe disease	AR	*GALC*	Progressive demyelination, enlargement of optic nerve & chiasm
GM1-gangliosidosis	AR	*GLB1*	MRI: hyperintensity of caudate nucleus & putamen w/signs of diffuse hypomyelination on T_2-weighted images
GM2-gangliosidosis, AB variant	AR	*GM2A*	Indistinguishable from GM1-gangliosidosis
Leukodystrophies			

Table 4. continued from previous page.

Disorder	MOI	Gene(s)	Clues to the Diagnosis
Creatine deficiency syndromes		*GAMT*, *GATM*, *SLC6A8*	MR spectroscopy: no creatine peak
Pelizaeus-Merzbacher disease	XL	*PLP1*	Hypomyelination on MRI
Disorders of purine metabolism			
Lesch-Nyhan syndrome	XL	*HPRT1*	Self-mutilation; ↑ uric acid in plasma & urine
Mitochondrial disorders			
Leigh syndrome	AR, mt	Pathogenic variants in the mtDNA; nuclear genes [1]	Bilateral basal ganglia lesions on MRI; ↑ lactate levels on MR spectroscopy
Leber hereditary optic neuropathy	mt	Pathogenic variants in the mtDNA	Optic nerve changes on fundoscopy
MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes)	mt	Pathogenic variants in the mtDNA	Deep white matter changes & stroke-like lesions on MRI
MERRF (myoclonus epilepsy associated with ragged red fibers)	mt	Pathogenic variants in the mtDNA	Progressive myoclonus, epilepsy, & ataxia; muscle biopsy showing ragged red fibers; ↑ lactate in serum & CSF
POLG-related disorders	AR, AD	*POLG*	Progressive external ophthalmoplegia, ataxia
Deafness-dystonia-optic neuronopathy syndrome (Mohr-Tranebjaerg syndrome)	XL	*TIMM8A*	Dystonia (particularly oromandibular) & deafness
Other dystonia-deafness syndromes	AD	*SERAC1, SUCLA2*	Dystonia & deafness
	XL	*DDP*	Dystonia & deafness
Organic acidurias			
D-2-hydroxyglutaric aciduria	AR	*D2HGDH*	Newborn screening
Glutaric aciduria type 1	AR	*GCDH*	Newborn screening
Methylmalonic acidemia	AR	*MCEE*, *MMAA*, *MMAB*, *MMADHC, MMUT*	Newborn screening
Aminoacidurias			
Homocystinuria caused by cystathionine β-synthase deficiency	AR	*CBS*	Homocysteine levels ↑ in blood
Phenylketonuria	AR	*PAH*	Newborn screening
Hartnup disorder	AR	*SLC6A19*	Levels of neutral amino acids ↑ in urine
Disorders of biotin metabolism			
Biotinidase deficiency	AR	*BTD*	Newborn screening
Disorders of thiamine metabolism			
Biotin-thiamine-responsive basal ganglia disease	AR	*SLC19A3*	Recurrent subacute encephalopathy; symmetric & bilateral edematous lesions in caudate nucleus, putamen, & cortex on MRI
Disorders of galactose metabolism			
Classic galactosemia and clinical variant galactosemia	AR	*GALT*	Newborn screening

Table 4. continued from previous page.

Disorder	MOI	Gene(s)	Clues to the Diagnosis
Encephalopathy with uncertain pathogenesis			
Aicardi-Goutières syndrome	AD, AR	*ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *TREX1*	Early-onset encephalopathy; chilblain lesions
Disorders w/ataxia as a predominant feature, particularly AD SCA (e.g., SCA3) & AR early-onset ataxias (e.g., ataxia-telangiectasia)			

AD = autosomal dominant; AR = autosomal recessive; DWI = diffusion-weighted imaging; MOI = mode of inheritance; mt = mitochondrial; SCA = spinocerebellar ataxia; XL = X-linked

1. Genes associated with mitochondrial DNA-associated Leigh syndrome and NARP: *BCS1L, C20ORF7, C8ORF38, COX10, COX15, FOXRED1, MTFMT, NDUFA2, NDUFA9, NDUFA10, NDUFA12, NDUFAF2, NDUFAF6, NDUFS1, NDUFS3, NDUFS4, NDUFS7, NDUFS8, SDHA, SURF1*

Neurodegenerative diseases

- Huntington disease. The cardinal movement disorder in Huntington disease is chorea, at least in adults. However, about 10% of individuals with Huntington disease have childhood onset (referred to as Westphal variant), which typically manifests as (1) focal or segmental dystonia (rather than chorea) that gradually becomes generalized and (2) parkinsonism [Bruyn & Went 1986]. Craniocervical dystonia including risus sardonicus is common and is often accompanied by speech and swallowing problems. Childhood-onset Huntington disease is more common when the pathogenic variant is paternally inherited. It is accompanied by a larger number of CAG repeats [Went et al 1984].
- Chorea-acanthocytosis is characterized by severe orolingual dystonia leading to chewing problems and sometimes mutilation of the lips, tongue, or cheeks (so called "eating dystonia") [Schneider et al 2007]. Other characteristic movement abnormalities include generalized chorea, motor and vocal tics, intermittent head drop, and sometimes parkinsonism.
- McLeod neuroacanthocytosis syndrome is defined as absent expression of the Kx erythrocyte antigen and weakened expression of Kell blood group antigens causing red blood cell acanthocytosis and compensated hemolysis. It is a multisystem disorder manifesting with sensorimotor axonopathy, muscle weakness, neuropsychiatric and cognitive disturbances, and movement disorders, particularly generalized chorea and orolingual dystonia.
- Rett syndrome. Asymmetric crural or generalized dystonia is common in Rett syndrome [Temudo et al 2008]. It occurs almost exclusively in girls because it is embryonic lethal in males. Following a near-normal early development affected girls develop autism, dementia, epilepsy, spastic paraparesis or tetraparesis, and characteristic stereotypies (hand clapping, knitting movements, or body rocking). After an initial rapid progression, symptoms usually stabilize, so that these individuals often survive into adulthood.

Disorders leading to brain calcification

- Primary familial brain calcification can present with dystonia in addition to cognitive and psychiatric symptoms. Vascular and brain parenchymal calcification, consisting primarily of calcium phosphate, is found in the basal ganglia and other brain areas including the cerebellum, thalamus, and brain stem.

Disorders of heavy metal metabolism

- Wilson disease, a disorder of copper metabolism, typically includes craniocervical dystonia that can be severe, early speech and swallowing problems, and other bulbar signs.
- Hypermanganesemia with dystonia, polycythemia, and cirrhosis resembles Wilson disease but is caused by disturbances of manganese metabolism. It is characterized by early-onset generalized dystonia and

adult-onset parkinsonism. Serum manganese levels are elevated and brain MRI examination shows hyperintensities in the basal ganglia as well as in the subthalamic and dentate nuclei typical for hypermanganesemia.

Neurodegeneration with brain iron accumulation (NBIA) is a group of disorders characterized by progressive iron storage in the brain and abnormal iron accumulation in the basal ganglia, which is evident as hypointense lesions predominantly (but not exclusively) in the globus pallidus and substantia nigra pars reticulata on T_2-weighted images. On T_1-weighted images, these regions are isointense. See NBIA Overview.

- Mitochondrial membrane protein-associated neurodegeneration is characterized by dystonia that frequently involves limbs and occasionally becomes generalized [Hogarth et al 2013]. Associated features are parkinsonism with varying combinations of bradykinesia, rigidity, tremor and postural instability, cognitive decline progressing to dementia, prominent neuropsychiatric abnormalities, and motor neuronopathy. Brain MRI shows a distinctive pattern of brain iron accumulation with T_2-weighted/gradient echo hypointensities in the substantia nigra and globus pallidus, often with unique T_2-weighted hyperintense streaking between the hypointense internal and external globus pallidus.
- Fatty acid hydroxylase-associated neurodegeneration presents in childhood with spastic tetraparesis, ataxia, and often generalized dystonia, followed by episodic neurologic decline. Brain MRI typically demonstrates T_2-weighted hypointensity in the globus pallidus, confluent T_2-weighted white matter hyperintensities, and profound pontocerebellar atrophy [Kruer et al 2010].
- Neuroferritinopathy typically presents with progressive adult-onset chorea or dystonia and subtle cognitive deficits. The movement disorder involves additional limbs within five to ten years and becomes more generalized within 20 years. When present, asymmetry remains throughout the course of the disease. The majority of affected individuals develop a characteristic orofacial action-specific dystonia induced by speech leading to dysarthria and dysphonia. Frontalis overactivity, orolingual dyskinesia, and dysphagia are also common. Brain MRI often shows cystic lesions in the basal ganglia and bilateral pallidal necrosis, in addition to iron accumulation in the caudate, globus pallidus, putamen, substantia nigra, and red nuclei.
- Pantothenate kinase associated neurodegeneration (PKAN) accounts for approximately 50% of NBIA. In classic PKAN, onset is early, usually before age six years and progression is rapid. Affected children often present with dystonic gait, dysarthria, and limb rigidity. Corticospinal tract involvement causes spasticity. A central region of hyperintensity in the globus pallidus with surrounding hypointensity on T_2-weighted images ("eye-of-the-tiger sign") is pathognomonic for PKAN and is highly correlated with the presence of biallelic *PANK2* pathogenic variants.
- *PLA2G6*-associated neurodegeneration (PLAN) comprises a continuum of three phenotypes with overlapping clinical and radiologic features: classic infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (atypical NAD), and *PLA2G6*-related dystonia-parkinsonism. Progressive dystonia associated with dysarthria and behavioral abnormalities including hyperactivity and impulsivity is common in NAD (onset age ~4 years), but not in INAD. *PLA2G6*-related dystonia-parkinsonism is characterized by juvenile parkinsonism associated with pyramidal signs, dementia, psychiatric features, and cerebral and cerebellar atrophy without brain iron accumulation on MRI [Paisan-Ruiz et al 2009, Hayflick et al 2013].
- Beta-propeller protein-associated neurodegeneration is characterized by developmental delay with further regression in early adulthood and by progressive dystonia, parkinsonism, and dementia. Seizures, spasticity, and disordered sleep are also common. Although the parkinsonism is L-dopa responsive, nearly all affected individuals have early motor fluctuations and develop disabling dyskinesia. Brain MRI shows iron deposition in the substantia nigra and globus pallidus, with a characteristic "halo" of T_1-weighted hyperintense signal in the substantia nigra [Hayflick et al 2013].

Lipid storage disorders

- Niemann-Pick type C, juvenile variant, is a sphingomyelin storage disease with onset in preschool or early school years, characterized by splenomegaly, behavioral abnormalities, ataxia, and supranuclear gaze palsy. Progressive generalized dystonia typically involving the orofacial muscles is also common.

Mitochondrial disorders

- Leigh syndrome, a progressive neurodegenerative disorder, is characterized by developmental regression and signs of brain stem dysfunction including respiratory abnormalities and nystagmus. Other common manifestations include optic atrophy, ophthalmoparesis, failure to thrive, hypotonia, weakness, spasticity, ataxia, seizures, bulbar problems, and dystonia. The characteristic neuropathologic features are symmetric necrotic lesions in the basal ganglia, cerebellum, thalamus, brain stem, and optic nerves [Lera et al 1994].
- Leber hereditary optic neuropathy typically presents in young adults as painless subacute bilateral visual failure. Dystonia can be part of the clinical presentation [Wang et al 2009].
- Deafness-dystonia-optic neuronopathy syndrome (Mohr-Tranebjaerg syndrome) is characterized by profound sensorineural hearing loss in early childhood that precedes the onset of dystonia which ranges from the first to the sixth decades (peaking in the second and third decades). Dystonia tends to be focal, segmental, or multifocal in distribution at onset, with a predilection for the upper body, variably involving the head, neck, and upper limbs [Ha et al 2012]. In most affected males dystonia generalizes regardless of the onset age.

Organic acidurias

- Glutaric aciduria type 1 (OMIM 231670) caused by glutaryl-CoA-dehydrogenase deficiency is associated with gliosis and neuronal loss in the basal ganglia resulting in dystonia [Harting et al 2009]. The classic clinical scenario is acute encephalopathy triggered by infection or immunization with rapid onset of chorea and hypotonia, followed in months and years by the gradual development of severe generalized dystonia. Dystonia at rest with action-induced exacerbation, which profoundly interferes with any voluntary movement, is often incapacitating. Dysarthria and dysphagia are also common, whereas cognitive functions can be preserved. Early diagnosis and special diet can prevent encephalopathic crises and thus improve the prognosis considerably.

Disorders of thiamine metabolism

- Biotin-thiamine-responsive basal ganglia disease typically presents in childhood with subacute episodes of encephalopathy triggered by febrile illness and characterized by confusion, dysarthria, dysphagia, and external ophthalmoplegia. The disease is progressive and leads to persistent severe dystonia, quadriparesis, or coma and death if untreated. Symptoms resolve within a few days following administration of high doses of biotin and thiamine. The precise mechanism by which biotin and thiamine improve symptoms is unclear. Brain MRI typically shows symmetric and bilateral lesions in the caudate nucleus and putamen, infra- and supratentorial brain cortex, and brain stem [Tabarki et al 2013].

Other Genetic Causes of Complex Dystonia

Of note, both autosomal dominant spinocerebellar ataxias (SCAs) and autosomal recessive ataxias can be associated with dystonia (see Hereditary Ataxia). The most common of the autosomal dominant SCAs (i.e., SCA1, SCA2, SCA3, and SCA6) together account for more than half of all affected families. Signs of cerebellar dysfunction are often accompanied by other clinical features [Schmitz-Hübsch et al 2008]. Dystonia is sometimes present and can be the most prominent sign.

Dystonia is also part of the clinical presentation in some autosomal recessive ataxias including Friedreich ataxia, ataxia with vitamin E deficiency, ataxia-telangiectasia (A-T), and ataxia with oculomotor apraxia type 1 (AOA1) and type 2 (AOA2). Dystonia in these disorders typically involves the craniocervical region and the arms [Fogel

& Perlman 2007]. In A-T, AOA1, and AOA2 difficulty with head-eye coordination related to saccadic failure is common.

Non-Genetic Causes of Dystonia

Table 5. Non-Genetic Causes of Dystonia

Cause	Etiology	Examples
Acquired brain lesions	Hypoxic insults	Cerebral palsy Bronchopulmonary dysplasia
	Infections	Creutzfeldt-Jakob disease Mycoplasma pneumonia Japanese B encephalitis Tuberculosis
	Parainfectious disorders	Reye syndrome Subacute sclerosing panencephalitis
	Autoimmune disorders	Multiple sclerosis Antiphospholipid-antibody syndrome
	Metabolic disorders	Kernicterus Hypoparathyroidism Central pontine myelinolysis
	Vascular insults	Stroke Arteriovenous malformation
	Traumatic brain injury	
	Space-occupying lesions	
	Intoxications	Carbon monoxide Manganese
Drug-induced dystonia	Neuroleptics	
	Anticonvulsants	
Psychogenic dystonia		

Complex dystonias caused by brain lesions. Typically, acquired brain lesions that cause dystonia affect the ipsilateral putamen, thalamus, and/or globus pallidus, resulting in contralateral hemidystonia [Marsden et al 1985, Münchau et al 2000] (i.e., as a rule hemidystonia results from circumscribed contralateral brain lesions). For unknown reasons dystonia resulting from such brain lesions develops months after the initial insult. Aberrant reorganization has been postulated but remains unproven. Also, although the distribution of weakness and sensory symptoms can usually be predicted on the basis of lesion location, the development of dystonia after basal ganglia lesions are identified is not predictable as most individuals with such lesions do not develop dystonia.

The most common and clinically relevant cause of dystonia due to (gross or subtle) brain lesions is cerebral palsy (CP). Dystonia (along with chorea) is the presenting and prevailing finding in persons with dyskinetic CP, but can also be observed in other forms of CP (e.g., spastic hemiparesis, spastic paraparesis, or spastic tetraparesis) [Johnston 2004]. In children with dyskinetic CP, generalized dystonia often evolves between ages two and six years; however, onset of dystonia can be delayed for several years [Saint Hilaire et al 1991]. Involvement of oromandibular, lingual, and pharyngeal muscles is common, leading to characteristic risus sardonicus, speech problems, and dysphagia. In addition, limb and axial dystonia can be common. Physical disability can be very severe; cognitive ability is often not impaired.

Drug-induced dystonia can occur in adults and children. The two main forms are acute dystonic reactions and tardive dystonia.

- **Acute dystonic reactions** result within hours or days of taking a dopamine-blocking medication (mostly neuroleptics). They usually manifest as oromandibular or cervical dystonia and subside when the causative medication is discontinued.
- **Tardive dystonia** results from use of all classes of neuroleptics and usually can manifest at any time (ranging from several days to many years after beginning use of the medication) [Kiriakakis et al 1998]. At its onset, tardive dystonia is usually focal but often progresses over months or years. The craniocervical region is typically involved.

  The manifestations of tardive dystonia are often indistinguishable from those of primary focal dystonia; however, retrocollis and axial involvement are characteristic. Like DYT1 dystonia, the site of onset tends to ascend from the lower limbs cranially as the mean age of onset increases [Kiriakakis et al 1998]. Other abnormal movements can include orofaciolingual dyskinesias, abnormal breathing rhythm due to involvement of the diaphragm, and truncal hypokinesia. Tardive dystonia tends to persist and is difficult to treat. Chances of remission are greater in persons who have taken neuroleptics for shorter periods or in whom neuroleptics are discontinued.

Psychogenic dystonia. Diagnostic criteria for psychogenic dystonia have been proposed [Williams et al 1995]. "Clinically definite" psychogenic dystonia is diagnosed in individuals: (1) in whom persistent symptoms are relieved by psychotherapy, suggestion, or placebo; or (2) who fail to manifest dystonia when they feel that they are not being observed. Other criteria for "clinically definite" psychogenic dystonia, such as "dystonia is incongruent with classic dystonia, or inconsistencies are noted in the examination," are more equivocal.

Positive signs of psychogenic dystonia include: sudden onset and remissions (e.g., following a psychological or physical trauma); a history of somatization; co-contraction of agonists and antagonists without abnormal postures; distractibility; suggestibility; fluctuating severity within short periods; discrepancies between objective signs and disability; and psychopathologic abnormalities. None of these signs, however, is diagnostic.

In individuals with a confirmed diagnosis of psychogenic dystonia, psychotherapy should be undertaken promptly since early initiation of treatment is associated with a better prognosis.

Criteria mentioned above and knowledge about the natural history of psychogenic dystonia are predominantly based on studies in adults; however, reports in children with psychogenic movement disorders including dystonia suggest that similar "rules" also apply to children [Schwingenschuh et al 2008].

Evaluation Strategy

Once the diagnosis of dystonia has been established in an individual, the following approach can be used to determine the specific cause of dystonia to aid in discussions of prognosis and genetic counseling. Establishing the specific cause of dystonia for a given individual usually involves a medical history, physical examination, neurologic examination, and neuroimaging, as well as detailed family history and use of molecular genetic testing. It is especially important to look for treatable causes of dystonia such as dopa-responsive dystonia (DYT-GCH1, DYT-TH, and DYT-SPR), Wilson disease, and other rare metabolic disorders and toxic or drug-related associations.

History

Prenatal and birth history should be documented, particularly any history of birth asphyxia or drug history, and especially the use of antidopaminergic agents or L-dopa.

Clinical Findings

Important features are age of onset, site of onset, presence or absence of other neurologic abnormalities, and presence of non-neurologic abnormalities (e.g., developmental delay, dysmorphic features). Presence or absence of associated findings may help distinguish among isolated dystonia, combined dystonia, and complex dystonia.

Delineation of the dystonia phenotype and the clinical course, the first step when evaluating persons with dystonia, can be diagnostic. For example,

- Sudden onset of dystonia over a range of ages is compatible with rapid-onset dystonia-parkinsonism (DYT-ATP1A3) (formerly DYT12).
- Many dystonias can be triggered or exacerbated by nonspecific factors, such as stress, fatigue, action, or certain postures.
- A "therapeutic" response to alcohol is characteristic of myoclonus-dystonia (DYT-SGCE), and improvement with L-dopa supports a diagnosis of dopa-responsive dystonia (DYT-GCH1, DYT-TH, and DYT-SPR).

Family History

A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records including the results of molecular genetic testing, neuroimaging studies, and the results of autopsy examinations.

Testing

Non-DNA-based clinical tests for the following are available (also see Table 4):

- Dopa-responsive dystonia (DYT-GCH1, DYT-TH, and DYT-SPR). Trial of L-dopa, abnormal phenylalanine loading test, measurement of the concentration of total biopterin (BP) (most of which exists as BH4) and neopterin (NP) (the by-product of the GTPCH1 reaction) in CSF is useful for the diagnosis of GTPCH1-deficient DRD. In GTPCH1-deficient dopa-responsive dystonia, the concentrations of BP and NP in CSF are low, whereas in TH-deficient dopa-responsive dystonia, the concentrations of both BP and NP in CSF are normal.
- Primary familial brain calcification (bilateral striatopallidodentate calcinosis). Brain calcification is best detected using CT scanning [Manyam et al 1992].
- Neurodegeneration with brain iron accumulation. Iron deposition is detected on brain MRI.
- Chorea-acanthocytosis. Peripheral blood films show acanthocytosis; serum creatine kinase concentration may be elevated.
- McLeod neuroacanthocytosis syndrome. Expression of Kell antigens is weak.
- Diagnostic workup in persons with dystonia and cerebellar signs – even when cerebellar signs are subtle – should include testing for spinocerebellar ataxia if family history suggests autosomal dominant inheritance.

Molecular Genetic Testing

Molecular genetic testing approaches can include a **multigene panel**, **comprehensive genomic sequencing**, and **single-gene testing**.

Option 1

A multigene panel focused on dystonia that includes the gene(s) of interest. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change

over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing (when clinically available) includes exome sequencing and genome sequencing. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Option 3

Single-gene testing. In contrast to genomic testing, single-gene testing relies on the clinician developing a hypothesis about which specific gene to test based on the individual's clinical findings, ethnicity, and/or the order in which pathogenic variants in a given gene most commonly occur.

- In individuals of Ashkenaki Jewish ancestry, targeted testing for the specific *TOR1A* pathogenic variant, a three-base pair deletion (NM_000113.2:c.907_909delGAG) in the coding region can be considered first.
- In individuals without clinical findings or ethnic background to suggest a specific gene, single-gene testing is rarely useful and typically NOT recommended given the genetic heterogeneity of dystonia; a multigene panel or comprehensive genomic testing are generally used in lieu of single-gene testing.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Genetic counseling. While hereditary, isolated, and combined dystonias are usually inherited in an autosomal dominant manner, complex dystonias are often inherited in an autosomal recessive or mitochondrial manner. In general, X-linked forms are rare but should be considered. Genetic counseling and risk assessment depend on determination of the specific cause of an inherited dystonia in an individual.

Importantly, most dominant forms of dystonia are characterized by reduced penetrance, which can be lower than 50%. For two hereditary dystonias, mechanisms affecting penetrance have been identified:

- DYT-SGCE only manifests when *SGCE* pathogenic variants are paternally inherited due to maternal imprinting of this gene [Müller et al 2002].
- Penetrance of the GAG deletion in *TOR1A*, is reduced from about 35% to 3% in individuals who also have a heterozygous NM_000113.2:646G>C (p.Asp216His) variant in *TOR1A* on the other allele [Risch et al 2007].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Individuals with an autosomal dominant dystonia inherit the pathogenic variant from one parent or have the disorder as the result of a *de novo* pathogenic variant.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant may include molecular genetic testing or clinical evaluation if molecular genetic testing is not available.
- The family history may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate molecular genetic testing and/or clinical evaluation have been performed.
- Note: Due to reduced penetrance, there may be asymptomatic family members or several generations of individuals with the pathogenic variant who remain symptom free.

Sibs of a proband

- The risk to sibs depends on the genetic status of the proband's parents: if one of the proband's parents has a pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Because many of the inherited dystonias demonstrate incomplete penetrance, not all individuals who inherit the pathogenic variant will develop dystonia.

Offspring of a proband

- Each child of an individual with autosomal dominant dystonia has a 50% chance of inheriting the pathogenic variant.
- Because many of the inherited dystonias demonstrate incomplete penetrance, not all individuals who inherit the pathogenic variant will develop dystonia.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the dystonia-related pathogenic variant, his or her family members may be at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one dystonia-related pathogenic variant).
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes are asymptomatic.

Offspring of a proband. All offspring are obligate heterozygotes (carriers) for a pathogenic variant in a dystonia-related gene.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a dystonia-related pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the dystonia-related pathogenic variants in the family.

Mitochondrial Inheritance – Risk to Family Members

Parents of a proband

- **Single mtDNA deletions**
  - Mitochondrial DNA (mtDNA) deletions generally occur *de novo* and thus affect only one family member.
  - When single mtDNA deletions are transmitted, inheritance is from the mother.
  - The predisposition to form multiple mtDNA deletions can be inherited as an autosomal dominant or an autosomal recessive trait.
- **Mitochondrial DNA single-nucleotide variants and duplications**
  - Mitochondrial DNA single-nucleotide variants and duplications may be transmitted through the maternal line.
  - The father of a proband is not at risk of having the mtDNA pathogenic variant.
  - The mother of a proband (usually) has the mtDNA pathogenic variant and may or may not have symptoms.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the mother: if the mother has the mtDNA pathogenic variant, all sibs are at risk of inheriting it.
- When a proband has a single mtDNA deletion, the current best estimate of the recurrence risk to sibs is 1/24 [Chinnery et al 2004].

Offspring of a proband

- Offspring of males with a mtDNA pathogenic variant will not inherit the variant.
- All offspring of females with a mtDNA pathogenic variant are at risk of inheriting the pathogenic variant.
- A female harboring a heteroplasmic mtDNA single-nucleotide variant may transmit a variable amount of mutated mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same nuclear family [Poulton & Turnbull 2000].

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if she has a mtDNA pathogenic variant, her sibs and mother are also at risk.

X-Linked Inheritance

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the dystonia-related pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the dystonia-related pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.

- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier.

Sibs of a male proband. The risk to sibs depends on the genetic status of the proband's mother:

- If the mother of the proband has the dystonia-related pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant will be heterozygotes (carriers) and will not typically be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the dystonia-related pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a proband. Affected males will transmit the pathogenic variant to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending on their gender, may be at risk of being carriers or of being affected.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant and the aunts' offspring, depending on their gender, may be at risk of being heterozygotes (carriers) for the pathogenic variant or of being affected.

Heterozygote (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the dystonia-related pathogenic variant has been identified in the proband.

Related Genetic Counseling Issues

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Mutation of nuclear DNA. Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for dystonia are possible.

Mutation of mitochondrial DNA (mtDNA). Prenatal molecular genetic testing and interpretation for mtDNA disorders is difficult because of mtDNA heteroplasmy. The percentage level of mutated mtDNA in a chorionic villus sampling (CVS) biopsy may not reflect the percentage level of mutated mtDNA in other fetal tissues, and the percentage level may change during development and throughout life [Hellebrekers et al 2012].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Dystonia Coalition**

The Dystonia Coalition is a collaboration of medical researchers and patient advocacy groups that is working to advance the pace of clinical and translational research in the dystonias to find better treatments.

www.rarediseasesnetwork.org/cms/dystonia

- **Dystonia Europe**
  Square de Meeus 37
  4th Floor
  Brussels Hoofdstedelijk Gewest 1000
  Belgium
  Phone: 46 739 98 49 61
  Email: sec@dystonia-europe.org
  www.dystonia-europe.org
- **Dystonia Medical Research Foundation**
  One East Wacker Drive
  Suite 1730
  Chicago IL 60601-1905
  Phone: 800-377-3978 (toll-free); 312-755-0198
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  www.dystonia-foundation.org
- **Dystonia Society**
  89 Albert Embankment
  3rd Floor
  London SE1 7TP
  United Kingdom
  Phone: 0845 458 6211; 0845 458 6322 (Helpline)
  Fax: 0845 458 6311
  Email: support@dystonia.org.uk
  www.dystonia.org.uk
- **Medline Plus**
  Dystonia
- **German Dystonia Registry**
  Germany
  www.dystract.cio-marburg.de
- **Global Dystonia Registry**
  www.globaldystoniaregistry.org

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