근긴장이상

안 태 범
경희대학교 의과대학 신경과학교실

Dystonia

Tae-Beom Ahn
Department of Neurology, Kyung Hee University

Definition

- Movement disorder
- Sustained or intermittent contraction of muscles
- Abnormal, often repetitive, movements, postures, or both
- Patterned, twisting, and may be tremulous
- Often initiated or worsened by voluntary action
- Associated with overflow muscle activation

Epidemiology

- Prevalence
- Rochester, Minnesota; 3.4/10000 (generalized dystonia), 30/100000(focal dystonia)
- Ashkenazi Jew; 1/6000 ~ 1/2000
- Focal dystonia; 6 – 14/100000 (Japan) vs 11- 14/100000 (Western Europe)

Etiologies

- Idiopathic
- Hereditary; primary, neurodegenerative
- Acquired diseases; vascular, infectious, hypoxic, trauma, metabolic, drug, automimmune, etc

Pathology

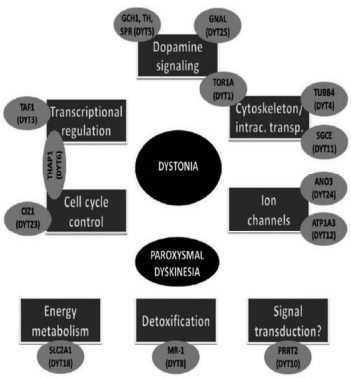
- No distinct pathology; primary dystonia, dopa-responsive dystonia, tardive dystonia
- Neurodegenerative lesions; neurodegeneration with brain iron accumulation (NBIA)
- Structural lesions; stroke, tumor

Genetics

- Autosomal dominant
- Autosomal recessive; DYT5b(TH gene), DYT16(PRKRA gene), dopamine transporter deficiency syndrome (SLC63 gene), Young-onset parkinsonism (PARKIN, DJ1 & PINK1 genes)
- X-linked; DYT3 (Lubag's, TAF1 gene)

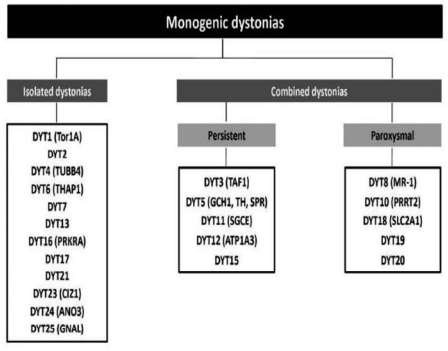
Mono-genetic dystonia

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[d]	2q	Paroxysmal nonkinesigenic dyskinesia 2 (PKND2)	ADom	Unknown	Unconfirmed (clinical overlap with PNKD1; locus very close to *DYT8*)
DYT21[e]	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



Isolated vs combined dystonia

Isolated dystonia				
DYT1 (TOR1A)	AD	Childhood	Generalized; rarely focal	Starting in legs and spreading; sparing of larynx and neck; can be jerky
DYT4 (TUBB4A)	AD	Adolescence – early adulthood	Focal, segmental, generalized	Rare cause of isolated dystonia, prominent laryngeal ('whispering dysphonia') and oromandibular involvement; TUBB4A mutations present more often as the complex H-ABC spectrum
DYT6 (THAP1)	AD	Adolescence – early adulthood	Generalized > segmental	Prominent laryngeal involvement; rostrocaudal gradient
DYT23 (CIZ1)	AD	Adolescence – adulthood	Focal	(tremulous) cervical dystonia; rare/awaiting confirmation
DYT24 (ANO3)	AD	Childhood – adulthood	Focal, segmental	Tremulous cervical dystonia; cranial, laryngeal, UL involvement; can present with isolated arm tremor or as a myoclonus-dystonia
DYT25 (GNAL)	AD	Childhood – adulthood	Focal, segmental, rarely generalized	Cervical dystonia; head or tremor; laryngeal dystonia; generalization in 10%; hyposmia in some cases
Combined dystonia				
With myoclonus				
DYT11 (SGCE)	AD	Childhood – adolescence	Focal, segmental, generalized	Neck and arm dystonia with shock-like, lightening jerks; usually no leg involvement; alcohol responsiveness; psychiatric comorbidity
DYT5a (GCH1)	AD	Childhood	Generalized	Diurnal variation and dopa responsiveness; parkinsonism/myoclonus possible
DYT5b (TH)	AR	Infancy – childhood		
Benign hereditary chorea (ITITF1)	AD	Infancy	Generalized	Onset with chorea which can be replaced by a myoclonus-dystonia phenotype during the disease course; associated thyroid and respiratory disorders
Myoclonus-dystonia (CACNA1B)	AD	Childhood – adulthood	Focal, segmental, generalized	Resembles partly DYT11; distinctive action myoclonus of legs
With parkinsonism				
DYT3 (TAF1)	X-linked	Adulthood	Focal, segmental, multifocal, generalized	Filipino males from Panay; marked oromandibular involvement with dysphagia possible
DYT16 (PRKRA)	AR	Childhood – adolescence	Generalized	Onset in LL or UL; marked laryngeal or oromandibular involvement; striking retrocollis or opisthotonus possible; can also present with parkinsonism
RODP (ATP1A3)	AD	Childhood – adulthood	Focal, segmental, generalized	Abrupt onset after triggers; rostrocaudal gradient with prominent bulbar involvement; no response to levodopa
DTDS (SLC63)	AR	Childhood – adulthood	Focal, segmental, generalized	Poor response to levodopa
Young onset Parkinson's disease (PARKIN; PINK1; DJ-1)	AR	Childhood – adulthood	Limb dystonia	Dystonia may be the presenting symptom before parkinsonism becomes evident



Motor phenomenology

Dystonia & voluntary action

- Voluntary movement; purposeful, anticipated, goal-directed movement produced by will
- Dystonia is typically influenced by voluntary movement or voluntarily maintained posture
- Action dystonia → resting dystonia
- Fixed dystonia
- Advanced stage
- Secondary causes
- Consider psychogenicity

Motor phenomenology

Dystonic tremor

- Spontaneous, oscillatory, rhythmical, often inconstant, patterned movement
- Tremor appears in the same muscles with dystonia

* Tremor associated with dystonia

- Exacerbation by an attempt to maintain primary posture
- Sometimes difficult to distinguish from essential tremor

Motor phenomenology

Null point

- Dystonia minimized at certain posture
- Dystonic tremor can occur when a patient tries to correct the abnormal postures → when the patient stops resisting the dytonic pulling, the tremor ceases

Motor phenomenology

Overflow

- Unintentional muscle contraction accompanying dystonia
- Anatomically distinct from primary dystonic movement
- Commonly occurs at the peak of dystonia

Motor phenomenology

Mirror dystonia

- Unilateral posture or movement the same or similar to dystonia
- Elicited by contralateral movements
- Usually in the more severely affected side

Motor phenomenology

Alleviating maneuver (sensory tricks or gestes antagonistes)

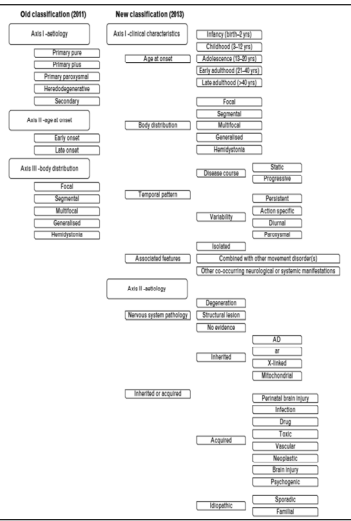
- Voluntary actions
- Correct abnormal posture or alleviate dystonic movements
- Usually simple movements ("gestes") such as mild touch
- Not forceful opposition to abnormal muscle contractions of dystonia

TABLE 3. Proposed classification of dystonia

Axis I. Clinical characteristics
- 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

Axis II. Etiology
- 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

Old vs *New* classification of dystonia



Axis I. Clinical characteristics

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)

Table 12.5 Three ways to classify torsion dystonia

1. By age at onset

A. Early-onset: ≤26 years

B. Late-onset: >26 years

(Fahn, Jankovic, Hallet, 2011)

Axis I. Clinical characteristics

Body distribution

- **Focal:** Only one body region such as blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia, writer's cramp
- **Segmental**: Two or more contiguous body regions such as cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bi-brachial dystonia
- **Multifocal**: Two noncontiguous or more (contiguous or not) body regions
- **Generalized:** The *trunk* & at least 2 other sites, with or without *leg* involvement
- **Hemidystonia**: Multiple regions in unilateral body

Axis I. Clinical characteristics

Temporal pattern

- **Persistent**: approximately the same extent throughout the day
- **Action-specific:** only during a particular activity or task
- **Diurnal fluctuations:** fluctuating during the day, w/ recognizable circadian variations in occurrence, severity & phenomenology
- **Paroxysmal**: Sudden self-limited episodes of dystonia usually induced by a trigger w/ return to preexisting neurological state

Axis I. Clinical characteristics

Associated features

- **Isolated dystonia:** the only motor feature (except tremor)

- Not related to etiology

- **Combined dystonia**: combined with other movement disorders (such as myoclonus, parkinsonism, etc.)

- Not necessarily predominant movement disorder

- **Occurrence of Other Neurological or Systemic Manifestations**

Syndrome recognition

Early-Onset Generalized Isolated Dystonia

- Beginning in childhood often progresses to generalized involvement, sometimes quite rapidly
- Familial or sporadic
- Genetically defined or without known cause

- DYT1 (TorsinA); AD w 30% penetrance
- DYT6 (THAP1); AD 60% penetrance

Syndrome recognition

Focal or Segmental Isolated Dystonia with Onset in Adulthood

- **Cervical dystonia**: cervical muscles involvement resulting in abnormal head, neck, & shoulder positions
- **Blepharospasm**: orbicularis oculi, procerus, corrugator muscles, insidious onset, with eye irritation or dryness followed by excessive blinking, especially in bright light
- **Oromandibular dystonia**: affecting the jaw muscles w prominent jaw opening or closing, often additional involvement of the tongue, facial, pharyngeal muscles
- **Laryngeal dystonia** ("spasmodic dysphonia"): a task-specific form, affecting voice by causing either adduction or abduction of the muscles responsible for phonation

Syndrome recognition

Dystonia-Parkinsonism

- Hereditary form
- Combine dystonia & parkinsonian features, sometimes w pyramidal tract involvement or other neurological deficits
- Non-motor features, including cognitive decline
- Dopa-responsive dystonia (DRD), Wilson's disease, Parkin, PINK1, DJ-1, X-linked dystonia-parkinsonism/Lubag (DYT3), rapid-onset dystonia-parkinsonism (DYT12), neurodegeneration with brain iron accumulation (NBIA; PANK2, PLA2G6, neuroferritinopathy, etc)

Syndrome recognition

Myoclonus Dystonia

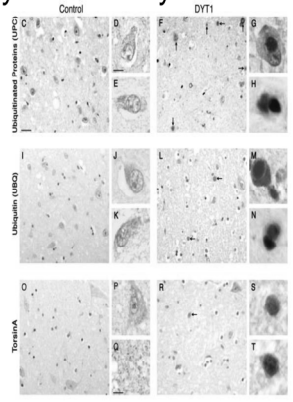
- Rapid jerky movements may occur in dystonia patients
- In a limb, be mistaken for distinct myoclonic jerks
- Myoclonus dystonia (DYT11); a variable combination of dystonia and myoclonus

Axis II. Etiology

Nervous system pathology

- Degeneration (progressive structural abnormality, such as neuronal loss)
- Static lesions (non-progressive neurodevelopmental anomalies or acquired lesions)
- No evidence of degeneration or structural lesion

Pathology of DYT1 dystonia



Axis II. Etiology

Inherited

- Autosomal dominant: DYT1, DYT5, DYT6, DYT11, rapid-onset dystonia-parkinsonism (DYT12), neuroferritinopathy (NBIA3), dentatorubral-pallidoluysian atrophy, Huntington disease
- Autosomal recessive: Wilson disease, PKAN (NBIA1), PLAN (NBIA2), Parkin (PARK2), other metabolic disorders
- X-linked recessive: Lubag (DYT3), Lesch-Nyhan syndrome, Mohr-Tranebjaerg syndrome
- Mitochondrial: Leigh syndrome, Leber optic atrophy and dystonia

Axis II. Etiology

Acquired

- Perinatal brain injury: dystonic cerebral palsy, delayed-onset dystonia;
- Infection: viral encephalitis, encephalitis lethargica, subacute sclerosing panencephalitis, HIV, tuberculosis, syphilis, etc
- Drug: levodopa & dopamine agonists, neuroleptics, anticonvulsants, calcium channel blockers
- Toxic: manganese, cobalt, carbon disulfide, cyanide, methanol, disulfiram, 3-nitropropionic acid
- Vascular: ischemia, hemorrhage, AVM, aneurysm
- Neoplastic: brain tumor, paraneoplastic encephalitis
- Brain injury: head trauma, brain surgery, electrical injury
- Psychogenic (functional)

Axis II. Etiology

Idiopathic

- Sporadic
- Familial

DYT system

- Human Genome Organization Gene Nomenclature Committee
- 'Historical' listing
- Erroneous statistical aw linked genetic markers
- Implying 'dystonic' disorders
- 'Complete' list of inherited disorders

DYT, gone astray?

- Erroneous designation
- DYT14 family → DYT5
- DYT9 & DYT18 → the same

- Dystonia, not always major feature
- Myoclonus; Myoclonus dystonia (DYT11)
- Parkinsonism; Lubag(DYT3), RODP(DYT12)

- Dystonic disorders w/o DYT loci
- Wilson disease, Lesch-Nyhan, glutaric aciduria, deafness-dystonia syndrome

New classification; Summary 1

- Differentiation btw clinical features & etiologies, a new step
- Abandon traditional terms such as "primary" "secondary" "dystonia plus"
- Age stratification instead of cutoff age (26 yo)
- "Generalized"; *trunk* involvement required
- Paroxysmal form as a major subtype

New classification; Summary 2

- Unresolved issues
- Differentiation from *pseudodystonia*
- *Psychogenic* dystonia included as a form of acquired dystonia
- Subtle *neuropathologic* change, criteria?
- DYT system untouched

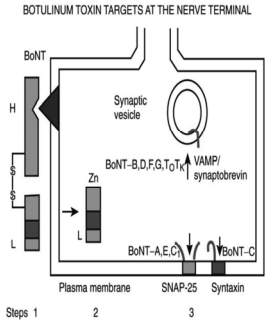
Acquired vs Pseudodystonia

Axis II. Etiology	Dystonic (tonic) tics
Nervous system pathology	Head tilt (vestibulopathy, trochlear nerve palsy)
Evidence of degeneration	Bent spine, camptocormia, scoliosis
Evidence of structural (often static) lesions	Atlanto axial and shoulder subluxation
No evidence of degeneration or structural lesion	Arnold-Chiari malformation
Inherited or acquired	Soft tissue neck mass
Inherited	Congenital muscular torticollis
• Autosomal dominant	Congenital Klippel-Feil syndrome
• Autosomal recessive	Satoyoshi syndrome
• X-linked recessive	Dupuytren's contractures
• Mitochondrial	Trigger digits
Acquired	Neuromuscular causes (Isaacs syndrome, etc.)
• Perinatal brain injury	Spasms (hypocalcemia, hypomagnesemia, alkalosis)
• Infection	Orthopedic and rheumatological causes
• Drug	Sandifer syndrome
• Toxic	Deafferentiation (pseudoathetosis)
• Vascular	
• Neoplastic	
• Brain injury	
• Psychogenic	
Idiopathic	
• Sporadic	
• Familial	

Medical treatment

- Levodopa
- Anticholinergics
- Baclofen: oral, intrathecal
- Tetrabenazine
- Anticonvulsants (carbamazepine, pregabalin, levetiracetam)
- Muscle relaxants:
- Benzodiazepines (clonazepam, lorazepam, diazepam, alprazolam)
- Other relaxants (tizanidine, cyclobenzaprine, metaxalone, carisoprodol, methocarbamol, orphenadrine)
- Sodium oxybate (salt of gamma-hydroxybutyrate)
- Clozapine
- Botulinum toxin

Botulinum toxin



Medical use

Focal dystonia
Blepharospasm
Lid apraxia
Oromandibular-facial-lingual dystonia
Cervical dystonia (torticollis)
Laryngeal dystonia (spasmodic dysphonia)
Task-specific dystonia (occupational cramps)
Other focal dystonias (idiopathic, secondary)
Other involuntary movements
Voice, head, and limb tremor
Palatal myoclonus
Hemifacial spasm tics

Inappropriate contractions
Strabismus
Nystagmus
Myokymia
Bruxism
Stuttering
Painful rigidity
Muscle contraction headaches
Lumbosacral strain and back spasms
Radiculopathy with secondary muscle spasm
Spasticity
Spastic bladder
Achalasia (esophageal, pelvirectal)
Other spasmic disorders
Other potential applications
Protective ptosis
Cosmetic (wrinkles, facial asymmetry)
Debarking dogs
Other