Understanding Dystonia

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The Essentials

What, Why, How

What is **Dystonia**?

Dystonias are **movement disorders** often characterized by persistent (or intermittent) muscle contractions, often worsened by voluntary movements.

- ➔ Affect men, women, and children of all ages and background
- ➔ Can be associated with a wide variety of other neurological conditions

Several different forms:

- ➔ All forms share same repetitive, patterned, and often twisting involuntary muscle contractions
- ➔ Chronic but most do not have any effect on cognition or overall lifespan

Why **Dystonia** is relevant

- More than 200,000 people live with Dystonia
- Affects people of all ages
- Cause unknown; no known cure

Can affect every single individual

- Wildly unpredictable nature makes the disorder a detriment to the quality of life for afflicted individuals

Dystonia in Motion

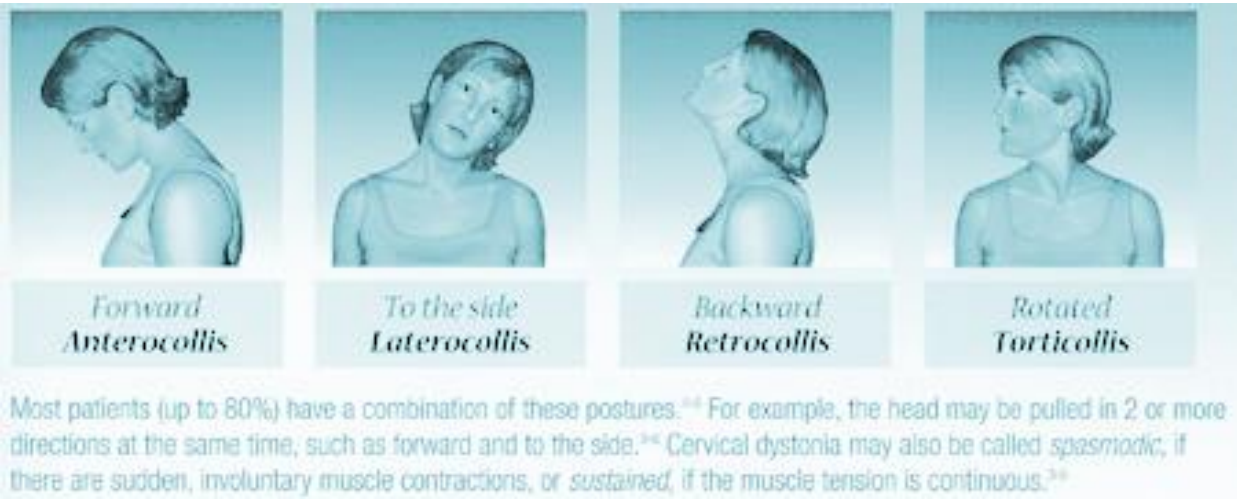
Types of **Dystonia** – What are they?

It depends on how you classify them.

- How many body parts are affected ?
  - Generalized - most or all of the body
  - Focal - one specific body part
  - Multifocal - two or more unrelated body parts
  - Segmental - two adjacent body parts
  - Hemidystonia - arm and leg on one, same side of the body
- What about different forms of focal dystonia?

Cervical Dystonia

- **Most common variant**
- Muscles in the neck pull to one side
- Can occur at any age
  - Most common in middle age
- 10% have spontaneous remission



Most patients (up to 80%) have a combination of these postures.[3,4] For example, the head may be pulled in 2 or more directions at the same time, such as forward and to the side.[3,4] Cervical dystonia may also be called *spasmodic*, if there are sudden, involuntary muscle contractions, or *sustained*, if the muscle tension is continuous.[3,4]

Blepharospasm

- Involuntary, forcible contraction of **muscles controlling eye blink**
- Increased or excessive blinking is early symptom
- May result in “functional blindness”
  - Eyes are stuck shut although eyeballs are healthy

Cranio-Facial Dystonia

- **Head, face, and neck**
  - Cranio-Facial Dystonia + Blepharospasm = Meige syndrome
  - Oromandibular Dystonia = jaw, lips, tongue
  - Spasmodic Dysphonia = larynx

Task-Specific Dystonia

- **Occur when undertaking a particular repetitive activity**
  - Writer's cramp
  - Typist's cramp
  - Pianist's cramp
  - Musician's Dystonia
    - Not only hands, but also mouth, lips, and voice

Breaking It Down

TL; DR: It’s more complicated than we know.

What causes **Dystonia**?

We don’t know.

But **maybe** it has something to do with abnormality or damage to basal ganglia, etc. in controlling movement.

- ➔ Neurotransmitter problem?
- ➔ Problems with brain’s generation of movement commands?

The kicker? **We often can’t see it with MRI.**

Not that we are aware, anyway.

What can we say about its origin?

- **Idiopathic dystonia**
  - No clear cause
  - Vast majority of cases
- **Genetic**
  - Some dominant inheritance
  - Can vary in severity and presentation
  - One mutated gene is sufficient to cause symptoms
- **Acquired dystonia**
  - CNS/PNS damage; Trauma or Stroke
  - Possible consequence of medication
  - Birth injury (i.e. hypoxia or hemorrhage)
  - Infection
  - Toxins
  - Often plateaus; does not spread

Table 1 2013 classification of dystonia[1]

Axis I: clinical characteristics	Axis II: etiology
Age at onset	**Neuropathology**
Infancy (0–2 years)	Degenerative
Childhood (3–12 years)	Structural lesion
Adolescence (13–20 years)	No degeneration/structural lesion
Early adulthood (21–40 years)	**Etiology**
Late adulthood (>40 years)	Inheritance pattern
Body distribution	Autosomal dominant
Focal	Autosomal recessive
Segmental	X-linked recessive
Multifocal	Mitochondrial
Generalized	Acquired cause
Hemidystonia	Perinatal brain injury
Temporal pattern	Infection
Disease course	Drug
Static	Toxic
Progressive	Vascular
Variability	Neoplastic
Persistent	Brain injury
Action-specific	Psychogenic
Diurnal	Idiopathic
Paroxysmal	Sporadic
Associated features	Familial
Isolated	
Combined	
Co-occurring manifestations	

Genetic Predisposition

DYT1 mutation

- Dominant inheritance
- Begins in childhood
- Affects limbs and then progresses to cause significant disability
- Some carriers may not develop symptoms of dystonia

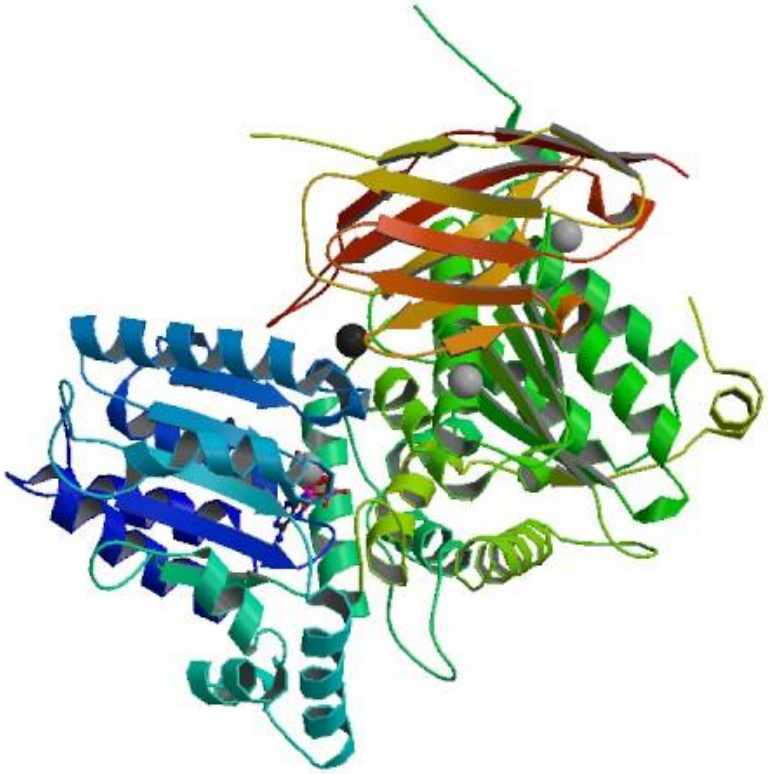
Recent diagnoses

- DYT6 mutation
  - Multiple forms present
- DYT3 mutation
  - Parkinsonism
- DYT11 mutation
  - Myoclonus - brief muscle contractions
- DYT12
  - Rapid onset, parkinsonism

Genetic Dystonia: DYT1 Mutation

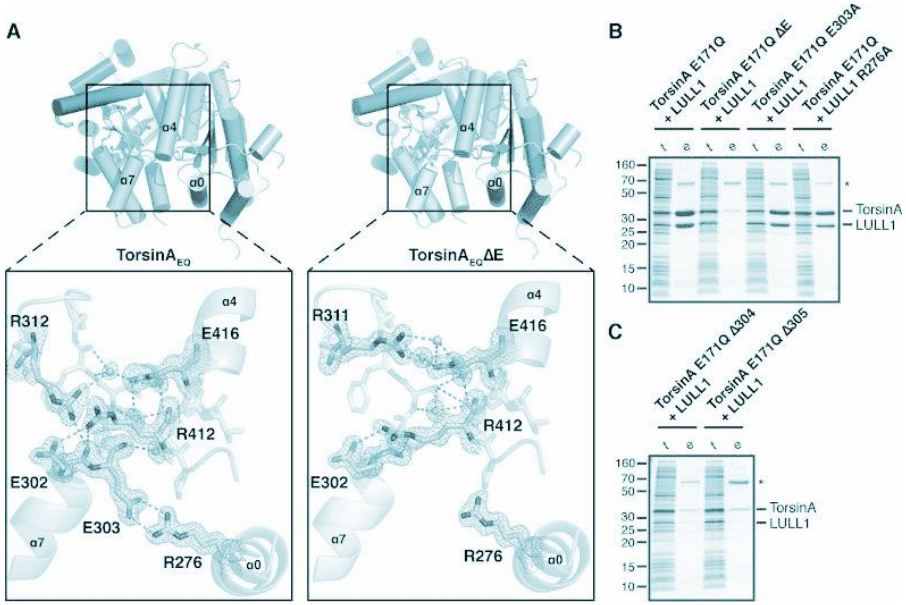
DYT1 Mutation

- TOR1A
  - 3 base GAG (E) deletion on Exon 5
- 30-40% penetrance
- Dominant inheritance
- Early onset generalized dystonia in lower distal extremities
- Progressively worsens in severity and affected areas



TorsinA-LULL1 complex

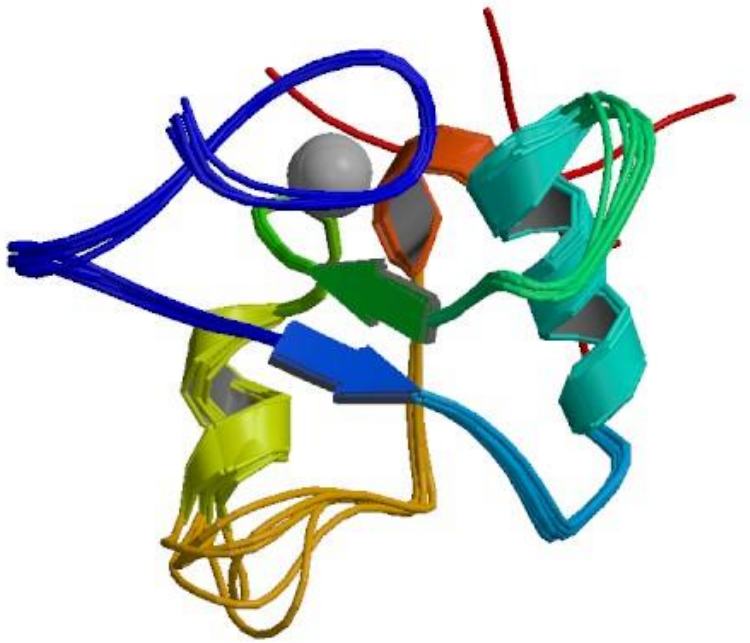
GYT1 Mutation lowers TorsinA binding afinnity for LULL1



- TorsinA protein expressed in substantia nigra
- Chaperone
- ATPase activity with LULL1 and LAPP1
- GYT1 Glu deletion reduces binding with LULL1 protein

Genetic Dystonia: Other Examples

- **GYT6: THAP1 mutation**
  - Mutations reduce stability and gene regulation ability
  - Penetrance varies with variant
- **DYT3: Reduced TAF1 expression**
  - Transcription initiation factor



THAP1 Zinc Finger Domain

Dystonia Cause Takeaways

- **Vast Majority of cases are idiopathic**
  - Less than 1% have genetic link
- Rarer Familial forms with a genetic cause
- Affected genes are involved in a large variety of biological activities
- Mutations have a large variance in penetrance

“There are no medications to prevent dystonia or slow its progression.”

Fixing It

Stop the abnormal movements at one or multiple levels of the nervous system.

Medication

- **Anticholinergic agents**
  - Trihexyphenidyl, benztropine
  - Block acetylcholine
- **GABAergic agents**
  - Regulate neurotransmitter GABA
  - Benzodiazepines
    - Diazepam, lorazepam, clonazepam, baclofen
- **Dopaminergic agents**
  - Act on the dopamine system
  - Tetrabenazine
    - Can cause weight gain and involuntary, repetitive muscle movements
  - Levodopa can manage Dopa-Responsive Dystonia

Medication (cont'd)

- **Botulinum Toxin**
  - Prevents muscle spasms in muscle when injected directly
  - Often used in combination with other forms of treatment, including physical therapy

Drugs: Mechanisms of Action

- **Anticholinergic agents - trihexyphenidyl**
  - M1 muscarinic acetylcholine receptor agonist
  - Partial block to cholinergic activity in CNS - initially indicated for Parkinson's
- **GABAergic agents - diazepam**
  - Binds to benzodiazepine receptors, mediating muscle relaxation and anticonvulsion, coupled (supposedly) to GABAa receptors
  - Enhances effects of GABA via increased binding affinity
  - GABA opens Cl- channel, resulting in "over-hyperpolarization"

Drugs: Mechanism of Action, Cont. (via DrugBank)

- **Dopaminergic agents - tetrabenazine**
  - Reversible vesicular monoamine transporter type 2 **inhibitor**
  - Acts within basal ganglia and promotes depletion of serotonin, norepinephrine, and dopamine; decreases uptake
  - **Keep in mind:** dopamine is required for fine motor movement
- **Levodopa - Dopa-Responsive Dystonia**
  - Supplementation of dopamine through administration of precursor levodopa, compensating for low dopamine levels by exogenous introduction of dopamine to the brain

Drugs: Mechanism of Action, Cont. (via DrugBank)

- **Serotype A Mechanism of Action**
  - Cleaves SNAP-25 at carboxyl terminus
  - Blocks acetylcholine from vesicle fusion
  - Acetylcholine inhibition restored after SNARE protein complex turnover

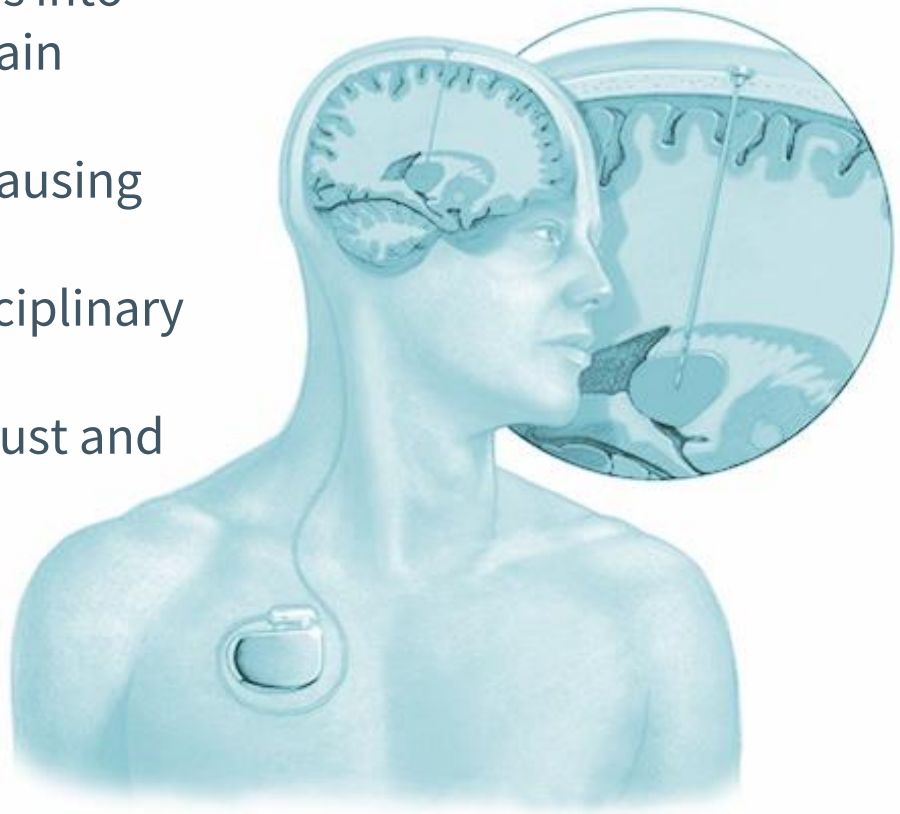
Disease: Proposed Mechanisms of Action (via NCBI)

- Evidence implicating the **basal ganglia** in dystonia is largely attributed to old studies prior to the 2000s that used CT or MRI imaging
  - However, studies have been continued in recent years with PET studies of regional metabolic activity
- Lesions in the **cerebellum** or its pathways through the brainstem have also been indicated in some forms of dystonia
  - In some cases, removal of the posterior fossa lesions causes preeminent cervical dystonia to remit
- There have also been studies linking limb dystonias with focal lesions of the **thalamus**

- Inconsistencies are linked to different types of dystonia

Surgery

- **Deep Brain Stimulation**
  - Implantation of electrodes into movement-controlling brain regions
  - Blocks electrical signals causing symptoms
  - Conducted by an interdisciplinary team of physicians
  - Intensive follow-up to adjust and optimize DBS settings



DBS in Everyday Life

Surgery and Physical Therapy

- **Thalamotomy** - intentional damage to small regions of the thalamus
- **Pallidotomy** (globus pallidus)

- Anterior Cervical **Rhizotomy** - Severance of nerves deep in the neck near the spinal cord
- Selective Peripheral **Denervation** - Removal of nerves at muscle

Treatment for **Musician's Dystonia**

Clinical Trials

Dysport versus Botox:

- Patients were given either Dysport® (abobotulinumtoxinA) or Botox® (onabotulinumtoxinA)
- Measured TSUI (impairment scale) of cervical dystonia patients at baseline and after 4 weeks of treatment of drugs
- Reported lower TSUI measurements on Botox

	Dysport® (abobotulinumtoxinA)	Botox® (onabotulinumtoxinA)
Participants Analyzed [Units: Participants]	**94**	**94**
Reduction of Total Tsui Score at 4 Weeks From Baseline [Units: Units on a scale] Mean (Standard Deviation)	**-3.98 (3.89)**	**-4.77 (4.10)**

*"Incobotulinum Toxin A (Xeomin®) As A Treatment For Focal Task-Specific **Dystonia** Of The Musician's Hand"*

- ➔ **Frown Line Treatment**
- ➔ Botulinum toxin (BoNT) prevents muscle contraction by blocking ACh release
- ➔ EMG or Ultrasound used to locate individual muscle(s) affected in focal dystonia
- ➔ More accurately relax overactive muscles

Dystonia: Main Takeaways

- ➔ Dystonia is a group of disorders that affects more than 200,000 people
- ➔ Only symptoms treated
- ➔ Many different causes/explanations
  - ◆ None are fully understood
    - Genetic
      - Low penetrance
      - Low correlation
    - Anatomical
      - Multiple brain regions
      - Suggest motor system disorder
  - ◆ Comorbid with other neurological diseases

End

References

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