# GENETICS AND TREATMENT OF DYSTONIA

Oksana Suchowersky, M.D., FRCPC, FCCMG
Professor of Medicine, Medical Genetics, and Psychiatry
Toupin Research Chair in Neurology

# DYSTONIA

Definition:

- abnormal sustained muscle contraction & postures
- may be associated with tremor and/or myoclonic movements
- may be alleviated by sensory tricks

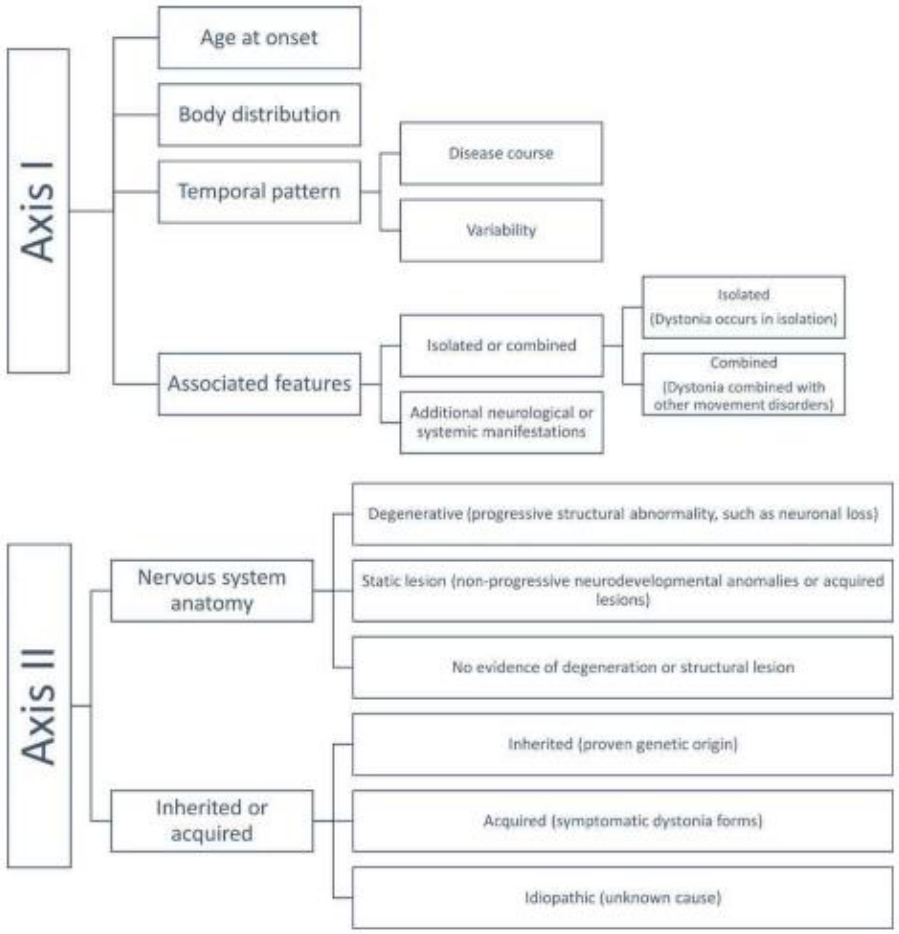
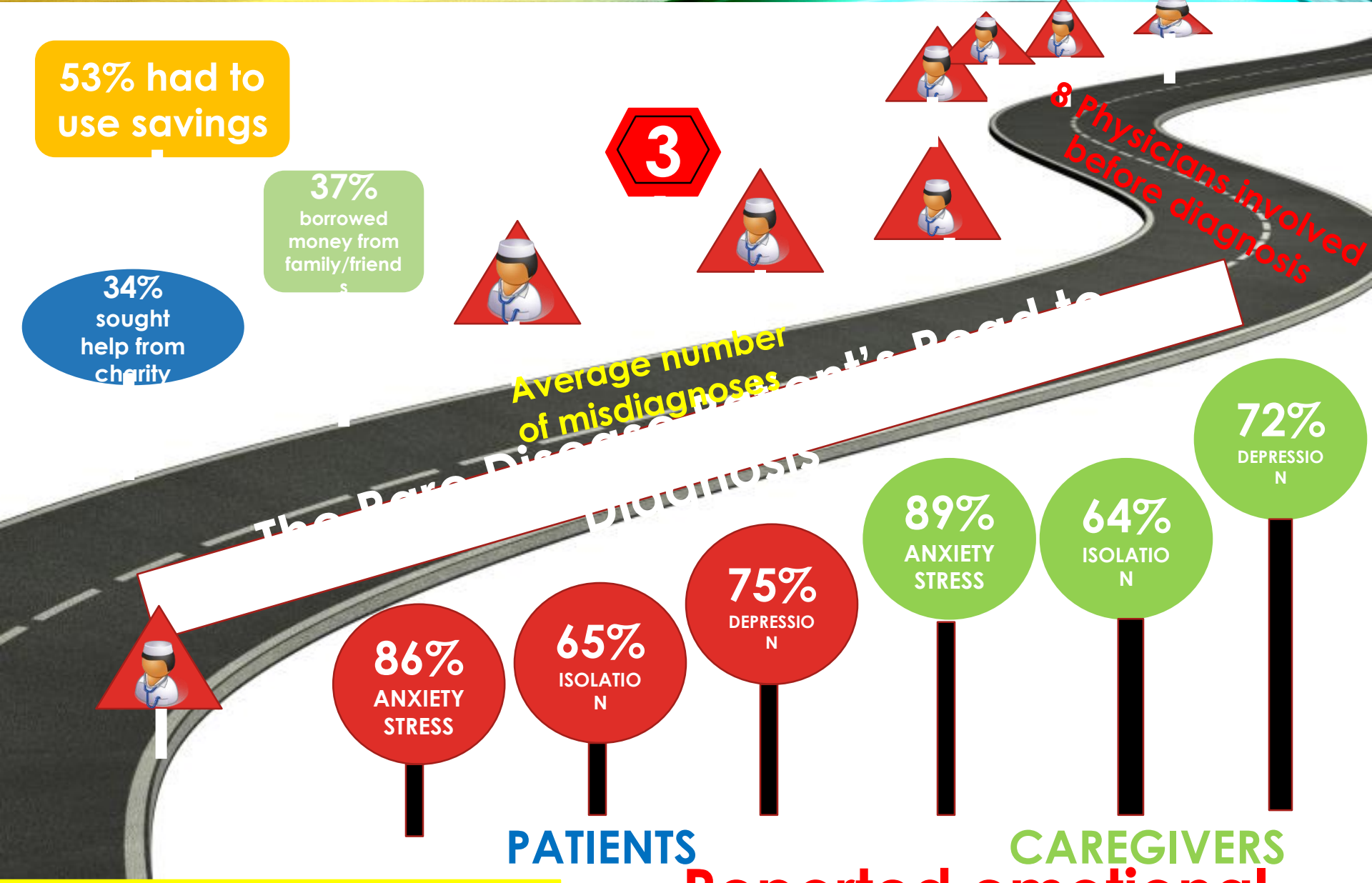



**Figure 1** Hierarchical organization of Axis I (clinical characteristics) and Axis II (etiology) of the dystonia classification.

Albanese A, Di Giovanni M, Lalli S; Eur J Neurol 2018 Jul, 13762




# 7+YEARS TO DIAGNOSIS

## Reported emotional impact

# DYSTONIA - CLASSIFICATION

**Primary Dystonia**

sporadic

inherited

- DYT1

**Dystonia – plus syndrome**

PD, PSP, MSA, CBGD

inherited

- dopa-responsive dystonia (DYT 5)
- dystonia – myoclonus (DYT 11)
- Huntington's disease
- Wilson's disease
- Fahr's disease

**Secondary Dystonia**

mitochondrial disorders

ceroid lipofuscinosis

hexosaminidase A & B

hypoparathyroidism

neurotoxic

- carbon monoxide, manganese

head injury

infectious

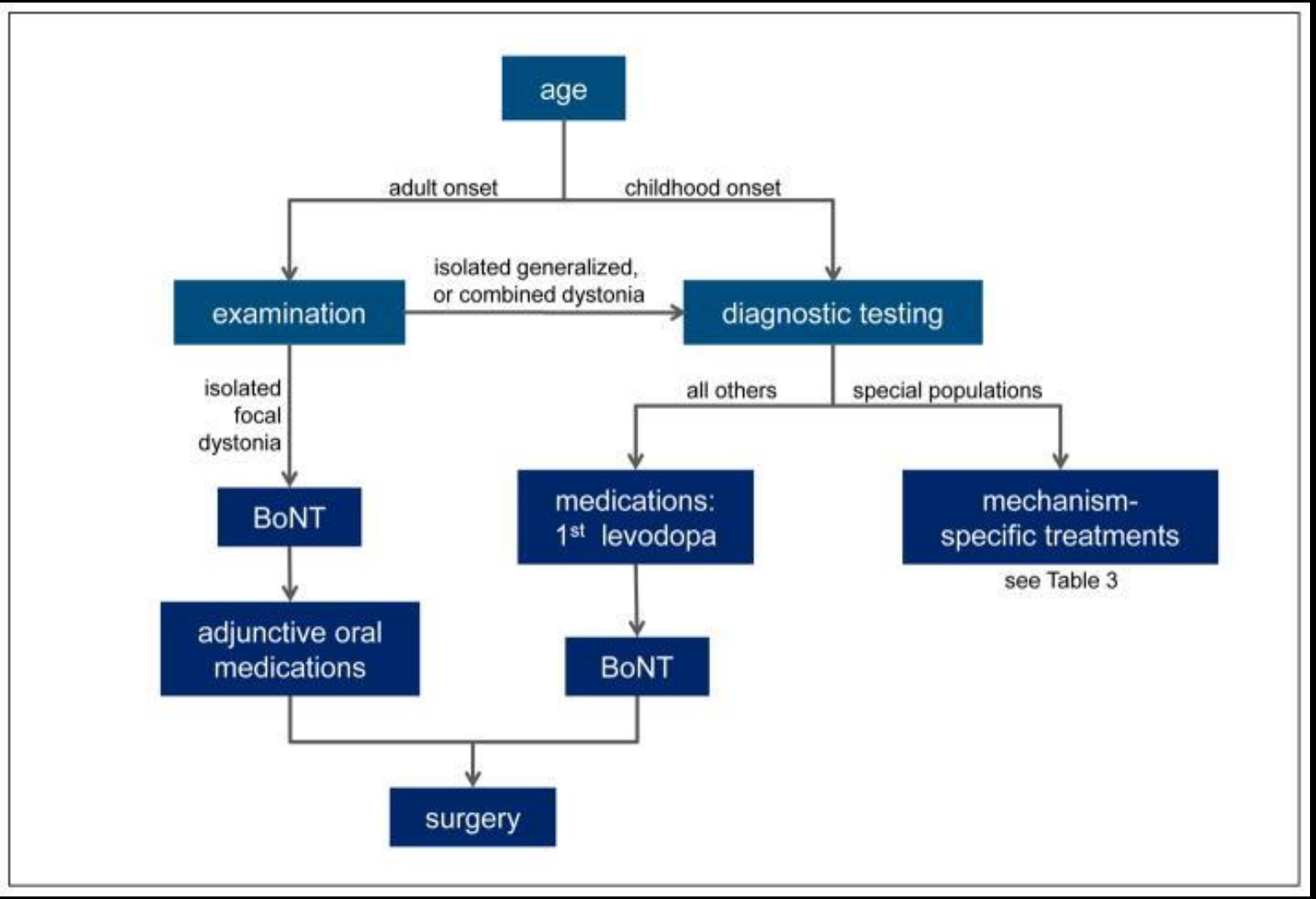
post infectious

paraneoplastic

drug induced

structural

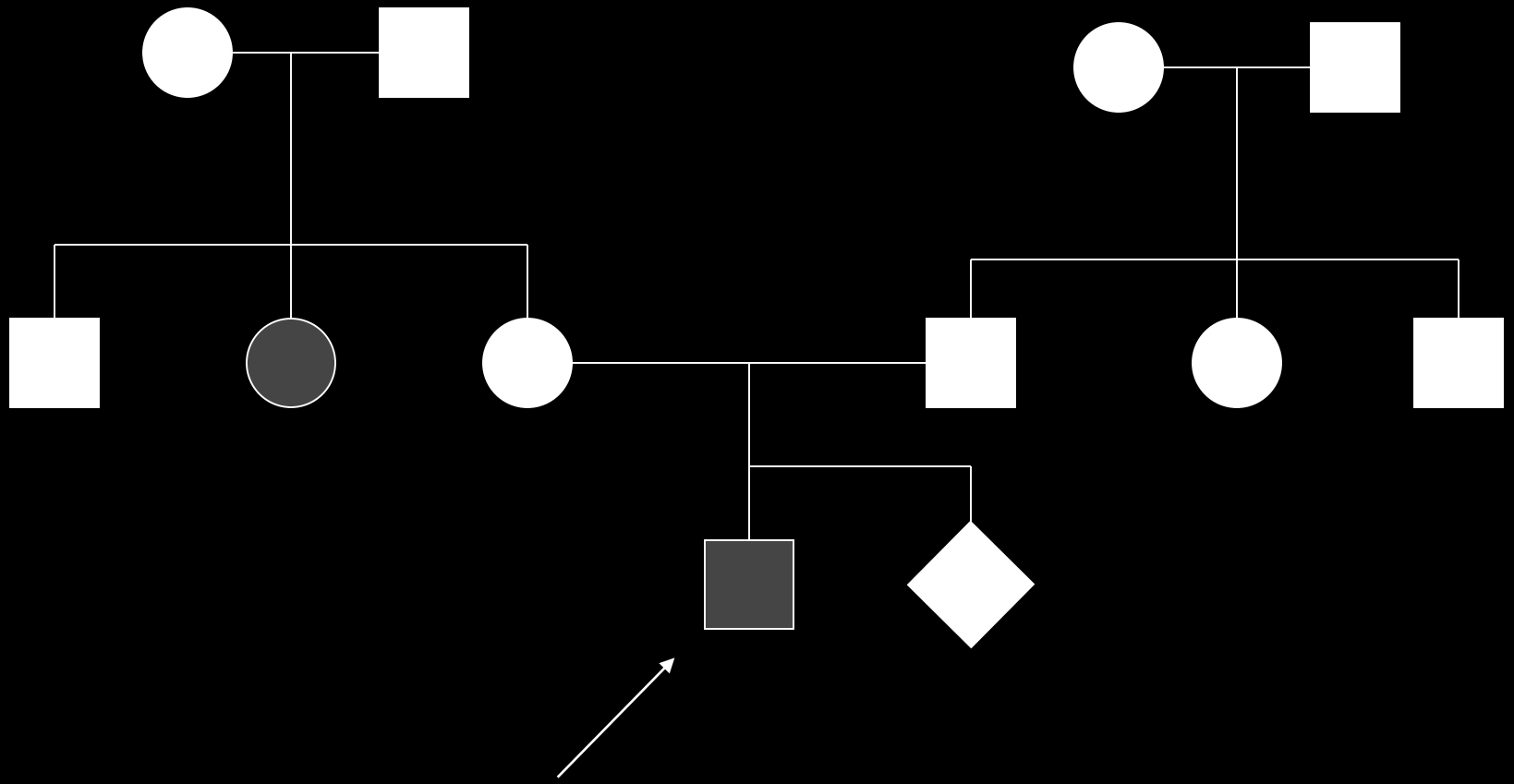
# METHODICAL STRATEGY FOR DIAGNOSIS OF DYSTONIA




Diagnosis and Treatment of Dystonia, Jinnah H. A. Neurol Clin. 2015 Feb; 33(1): 77-100

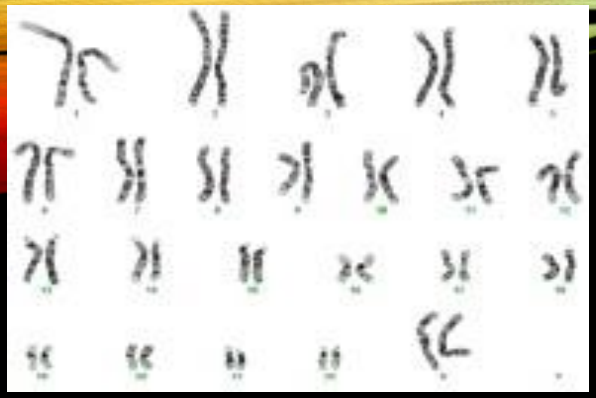
# GENETIC TESTING

# FAMILY HISTORY



# BUT THE FAMILY HISTORY WAS "NEGATIVE"

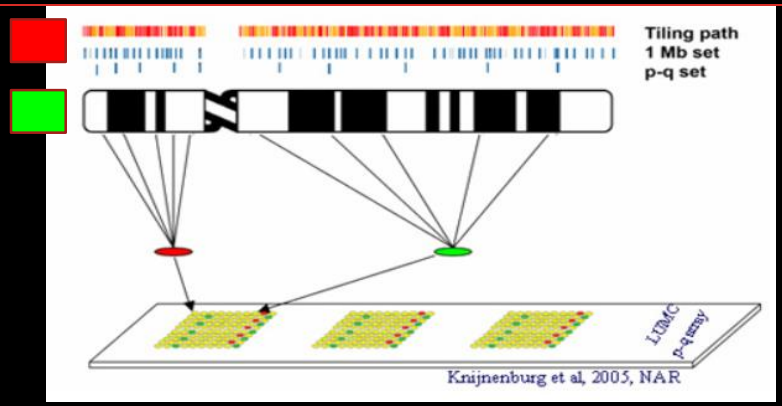
- 'Real life' reasons:
  - early unrelated deaths
  - diagnoses not shared with rest of family
  - family history not known!
  - wrong diagnosis or phenocopies
  - non-paternity
  - adoption



KARYOTYPE

=

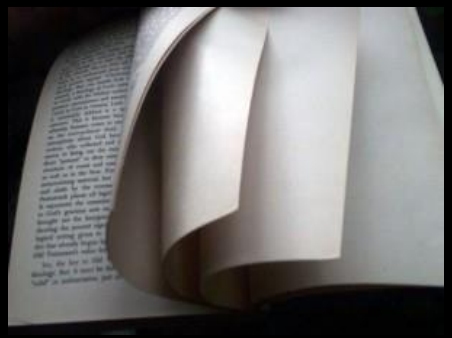
5-10 Mb




COMPARATIVE GENOMIC HYBRIDIZATION

=

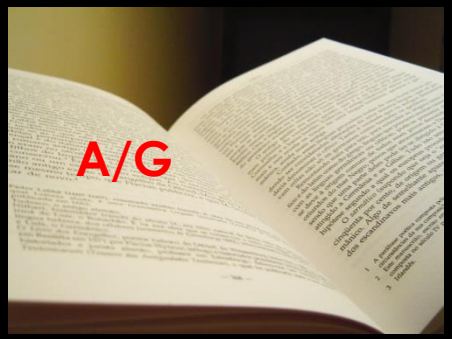
140 kb



SEQUENCING

=

1bp



# Next Generation Sequencing (N

ARGETED
ANELS (group of genes)
WES: Whole EXOME sequencing (protein coding

on-TARGETED
GS: WHOLE GENOME SEQUENCING

# GENETICS OF IDIOPATHIC DYSTONIA

- 20% have family history
- autosomal recessive
  - both copies of gene abnormal
- autosomal dominant
  - one copy abnormal
- X-linked
  - boys affected

# NOW

- over 200 genes associated with dystonia

- in most - environmental factors in genetically predisposed person

**Table 1** Isolated and combined forms of dystonia with an established genetic cause

| Acronym | Phenotype | Mutational spectrum | Protein function |
|---|---|---|---|
| Isolated dystonia | | | |
| DYT-TOR1A | Early-onset generalized dystonia (also known as Oppenheim dystonia or DYT1 dystonia) | In most cases, the same mutation (c.904_906delGAG; p.302delGlu) | ATPases associated with a variety of cellular activities, considered to function as a molecular chaperon |
| DYT-THAP1 | Adolescent-onset dystonia with mixed phenotype (or DYT6 dystonia) | About 100 different mutations | Transcription factor |
| DYT-GNAL | Adult-onset segmental dystonia | About 30 different mutations | Involved in signal transduction |
| DYT-ANO3 | Late-onset craniocervical dystonia | Many different mutations, pathogenicity often not clear (no segregation) | Calcium-activated chloride channels |
| Combined dystonia | | | |
| DYT-GCH1 | Dopa-responsive dystonia (also known as Segawa syndrome or DYT5 dystonia) | More than 100 different mutations | Rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin |
| DYT-ATP1A3 | Rapid-onset dystonia-parkinsonism (or DYT12 dystonia) | About 20 different mutations | Catalytic subunit of an ionic pump |
| DYT-PRKRA | Dystonia-parkinsonism (DYT16) | One confirmed mutation (c.665C > T, p.Pro222Leu) | Protein kinase with function in stress response |
| DYT-SGCE | Myoclonus dystonia (DYT11) | About 80 different mutations | Probably transmembrane protein; function largely unknown |

Lohmann K, Klein C. Curr Neurol Neurosci Rep (2017) 17:26

# TREATMENT

# TREATABLE DYSTONIAS

| Disorder | Typical age at onset | Typical characteristics of dystonia | Other typical clinical features | Treatment |
|---|---|---|---|---|
| **Ataxia with vitamin E deficiency** | childhood to early adulthood | rare patients present with dystonia instead of ataxia | ataxia, neuropathy | vitamin E supplementation |
| **Autoimmune movement disorders** | any age | focal or generalized dystonia | systemic signs of autoimmune disease | treat autoimmune process |
| **Cerebral creatine deficiency type 3** | infancy | generalized dystonia | developmental delay, myopathy | creatine |
| **Dystonia with brain manganese accumulation** | childhood | progressive generalized dystonia | Parkinsonism, liver disease, polycythemia | chelation therapy |
| **Methylmalonic aciduria** | childhood | static generalized dystonia following encephalopathic crisis | developmental delay, encephalopathic crisis, renal insufficiency, pancytopenia | avoid or treat aggressively any intercurrent illness, protein restriction |
| **Niemann Pick type C** | early childhood to early adulthood | progressive generalized dystonia | dementia, ataxia, spasticity, seizures, supranuclear gaze palsy | miglustat |
| **Rapid onset dystonia-Parkinsonism** | early childhood to late adulthood | bulbar or generalized dystonia following encephalopathic crisis | psychomotor disability | avoid or treat aggressively any intercurrent illness, protein restriction |

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# MEDICAL TREATMENT OF PRIMARY DYSTONIA

- levodopa
- dopamine agonists
- tetrabenazine
- neuroleptics
  - atypical
  - typical

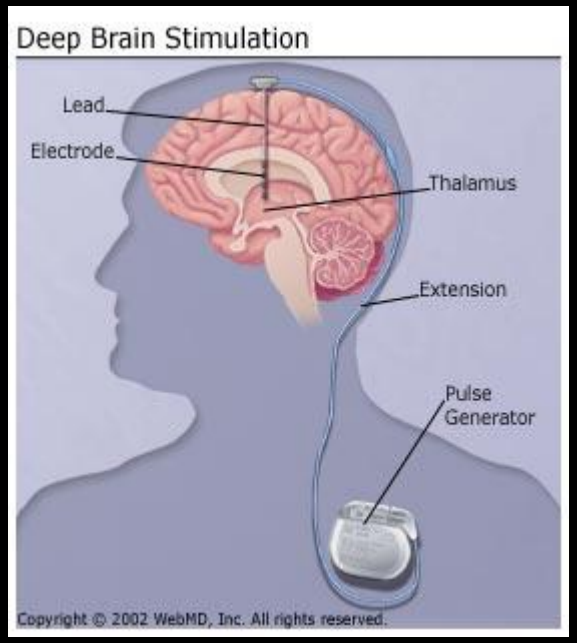
# MEDICAL TREATMENT OF PRIMARY DYSTONIA

- muscle relaxants
  - Baclofen, clonazepam
- anti-epileptics
- others
  - cannabinoids

# GENERALIZED DYSTONIA

- levodopa trial
- Marsden Cocktail (high dose anticholinergics, neuroleptic, tetrabenazine)
- botulinum toxin injections supplemental

# DEEP BRAIN STIMULATION OF GPI




Demonstrated long term benefit

Primary generalized dystonia

Secondary dystonias

# FOCAL DYSTONIAS

- adult onset, non-progressive
- types:
  - blepharospasm
  - cervical
  - oromandibular
  - occupational

# BOTULINUM TOXINS

- onabotulinum toxin  type A
- abobotulinum toxin type A
- incobotulinum toxin type A
- rimabotulinum toxin type B




# ONABOTULINUM TOXIN A TREATMENT

| Disorder | Dose range (U) | Mean dose (U) |
|---|---|---|
| Cervical dystonia | 70 – 400 | 222 |
| Hemifacial spasm | 12.5 – 70 | 29.4 |
| Blepharospasm | 25 – 100 | 51.5 |
| Focal / segmental | 30 – 300 | |
| Writer's cramp | 30 – 200 | 77.4 |
| Meige's syndrome | 70 – 200 | 110 |
| Lower extremity | 175 – 300 | 253 |
| Jaw opening | 200 | 200 |
| Jaw closing | 200 | 200 |

Hsiung et al. Movement Disord.2002: 17:1288

# LONG TERM BENEFITS

| Disorder | No. of patients with sustained benefits observed at 2 yr (%) | No. of patients with sustained benefits observed at 5 yr (%) |
|---|---|---|
| Cervical dystonia | 72/106 (68) | 39/62 (63) |
| Hemifacial spasm | 67/70 (96) | 35/40 (88) |
| Blepharospasm | 33/36 (92) | 18/20 (90) |
| Focal / segmental | | |
| Writer's cramp | 8/14 (57) | 5/9 (56) |
| Meige's syndrome | 4/5 (80) | 2/3 (67) |
| Lower extremity | 2/2 (100) | 2/2 (100) |
| Jaw opening | 0/1 (0) | |
| Jaw closing | 1/1 (100) | 1/1 (100) |
| Total | 187/235 (80) | 102/135 (76) |

Hsuing et al. Movement Disord. 2002: 17;1288-93

# NOVEL THERAPIES

- acetyl hexapeptide 8
- amlodipine
- subdermal delivery of toxin
- liquid abobotulinum A
- TMS

# CONCLUSIONS

- Generalized dystonia
  - levodopa trial
  - DBS surgery

- Secondary dystonias
  - combination therapy
  - surgery less effective

# CONCLUSIONS

- Focal dystonia
  - botulinum toxin is safe and effective with long term use
  - dose parameters and time between injections need to be respected
  - in short term studies, there are no significant differences in efficacy or side effect profile among different types of botulinum A (Botox, Xeomin, Dysport) and B (Myobloc)

# THANK YOU