UPDATE ON DYSTONIA: MIXED MOVEMENTS, NEW GENES

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DISCLOSURES

- I have no financial relationships with any for-profit corporations or entities
- I have received grant funding from non-profit entities to study pediatric dystonia


9yo boy with abnormal gait

HYPERKINETIC MOVEMENT DISORDERS

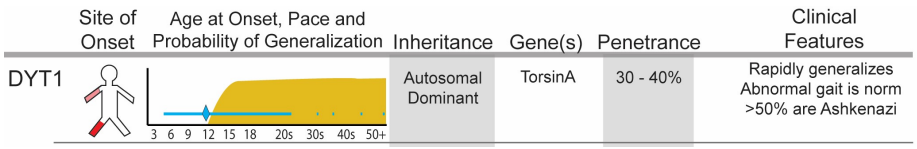
- Tics
- Chorea
- Tremor
- Myoclonus
- Dystonia

DYSTONIA

- Sustained muscle contraction, often leading to twisting movements or fixed postures. Often painful.
- Co-contraction of agonist-antagonist muscles; overflow to surrounding muscles not typically involved in that action.
- Predilection for over-learned actions – writing, typing, walking, speech, musical instruments
- Normal motor function in between triggering-tasks, normal in other body parts

3rd-most common movement disorder

Primary Dystonias



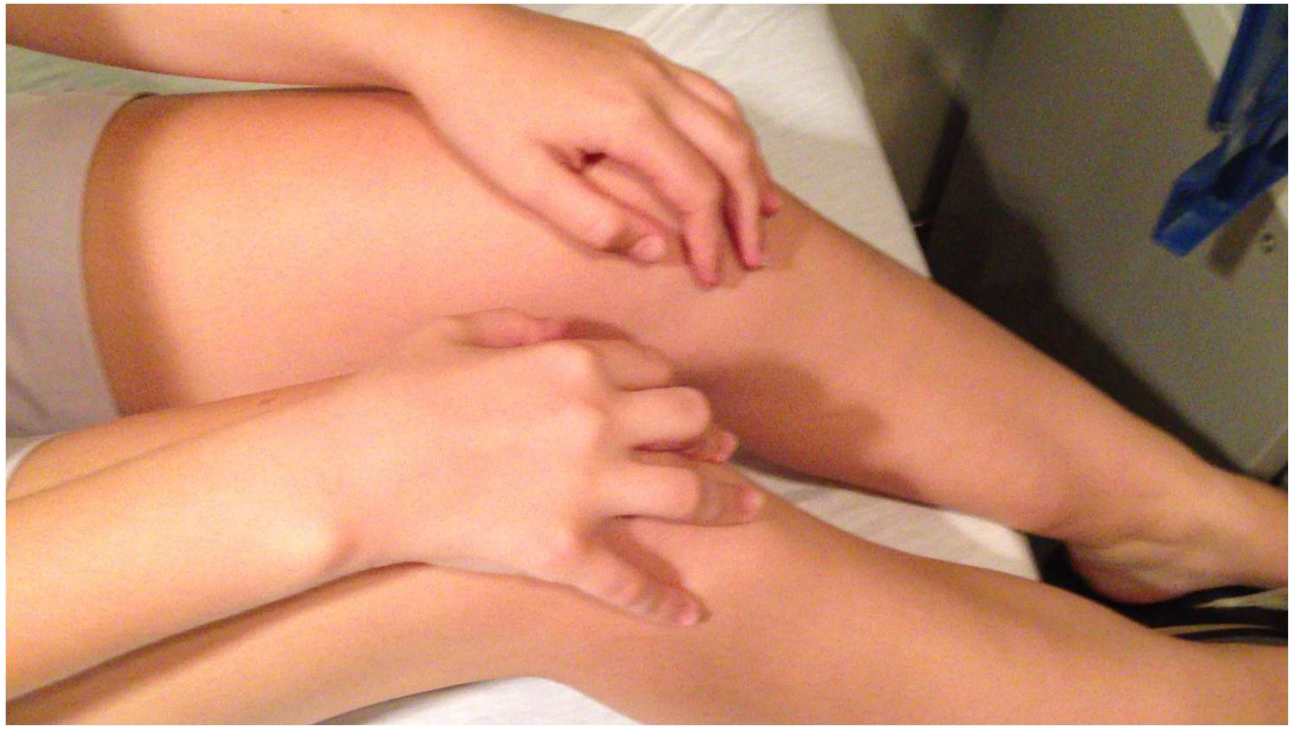
Inherited Dystonia
DYT-TOR1A

Match your patients:
- Site of Onset
- Age at Onset
- Rate of Progression
- Inheritance

And you will find a short list of genes to test

To read more about the primary dystonias: Waugh and Sharma, "Dystonia: From genotype to phenotype" *Neurology Clinics*, Nov 2013

DYSTONIA CAN BE FOCAL...



14yo with focal (on its way to being segmental) dystonia

BUT IN CHILDREN IS TYPICALLY GENERALIZED

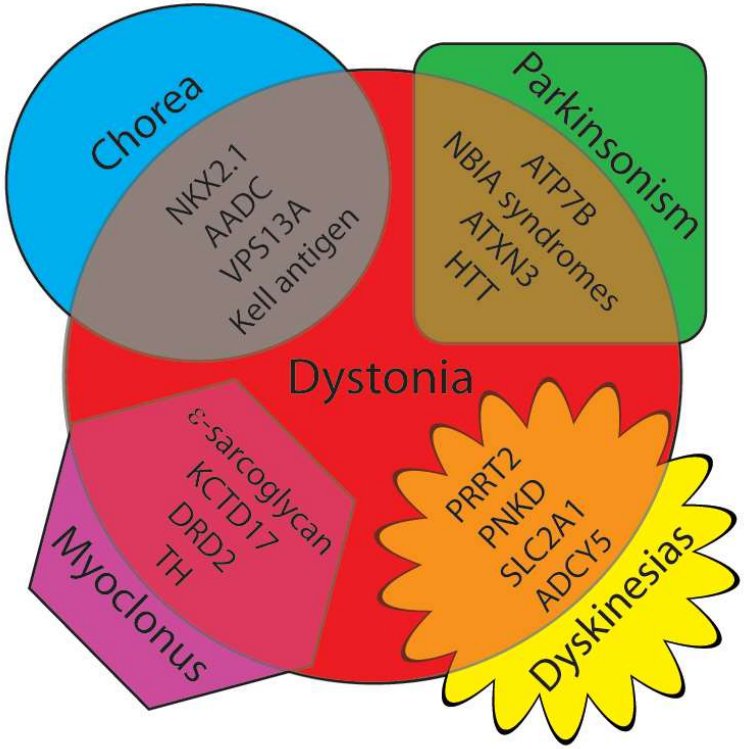
tonic storm
tures, severe
own,
yperthermia…

res barbiturate
pine coma to
status

ogenic Mutations in:
MJD (SCA3)
LRRK2

“Adult” Dystonias may Present in Childhood

INCREASING RECOGNITION OF MIXED MOVEMENT DISORDERS IN CHILDREN




A 6 YEAR OLD GIRL WITH
HYPERKINETIC MOVEMENTS

Diagnosis: ADYC5-related Dyskinesias
Leads to constitutively active adenylyl cyclase, dysregulated cAMP production

ADCY5 in mild cases presents with limited chorea.

Cases have been described with isolated dystonia, no chorea or dyskinesia, but these are uncommon.

Diagnosis: Benign Hereditary Chorea secondary to NKX2.1 mutation, leads to absence of inhibitory striatal interneurons

Dominantly inherited, fully penetrant.

Recognize the possibility for concurrent lung and/or thyroid disease in patient or family. 25-40% have all three manifestations: brain-lung-thyroid syndrome

KMT2B - DYT28

- KMT2B - lysine-specific histone methyltransferase 2B
- Early-onset, complex dystonia with frequent cognitive impact
- Focal motor onset (usually leg) with progression in caudocranial pattern
- Prominent oromandibular, laryngeal and cervical involvement
- Communication difficulties: common, 2°/2 dysarthria, low speech volume

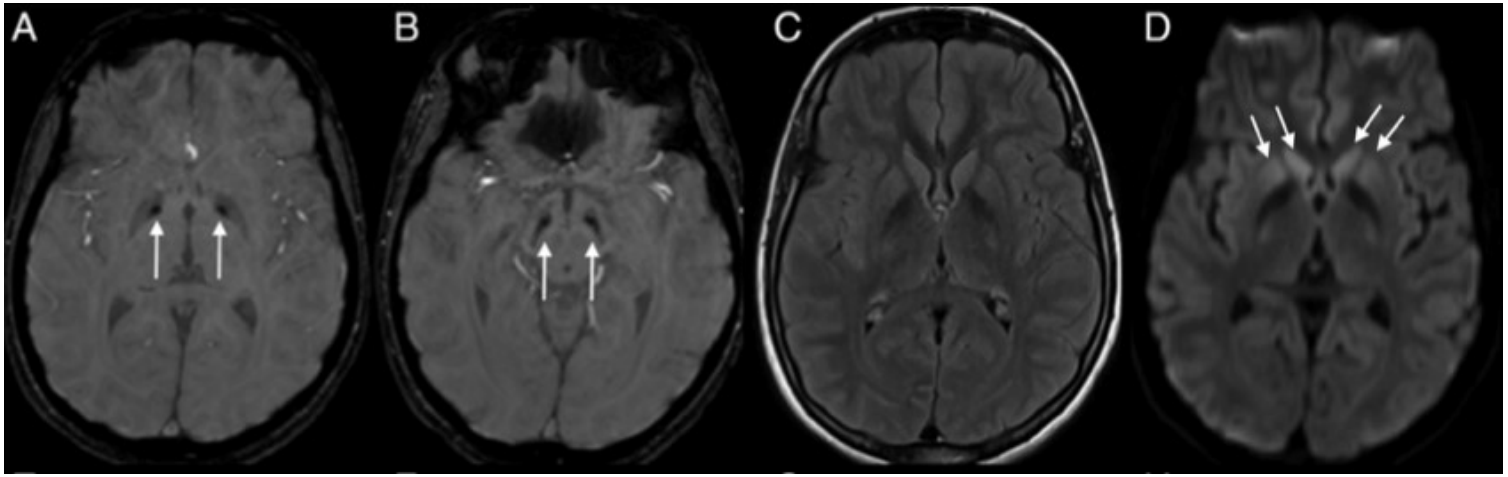
KMT2B - DYT28

- Largest case-series to date, 52 new patients, 81 patients from prior reports. Accepted in *Brain*
- Chr deletions, protein truncating variants had earlier onset, higher burden of systemic disease than those with missense variants.
- 94.7% were *de novo* mutations
- Unexpected recognition that KMT2B can present solely with developmental delay / intellectual disability, without dystonia
- Significant improvement with DBS – except for laryngeal dystonia

IDIOPATHIC TRUNCAL DYSTONIA

- 15yo girl from a Persian Gulf-area state, born to consanguineous parents, had normal intellectual and motor development until 12y
- Dystonia generalized over 2 years, leading to wheelchair dependence and the inability to sit without support
- Baseline Burke-Fahn-Marsden motor score was 86.5/120; disability score was 27/30.
- She developed bradykinesia, freezing of gait. Cognition unchanged.
- Medical treatment was ineffective, leading us to pursue DBS.

WHAT DOES THIS MRI SUGGEST?

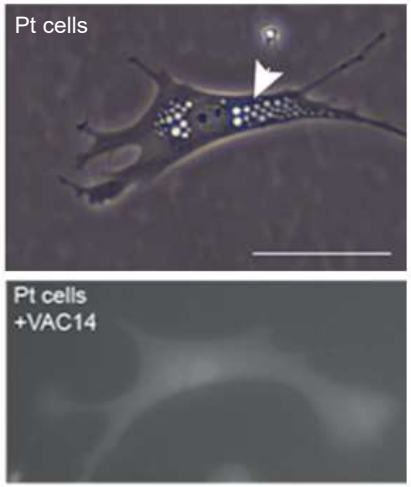


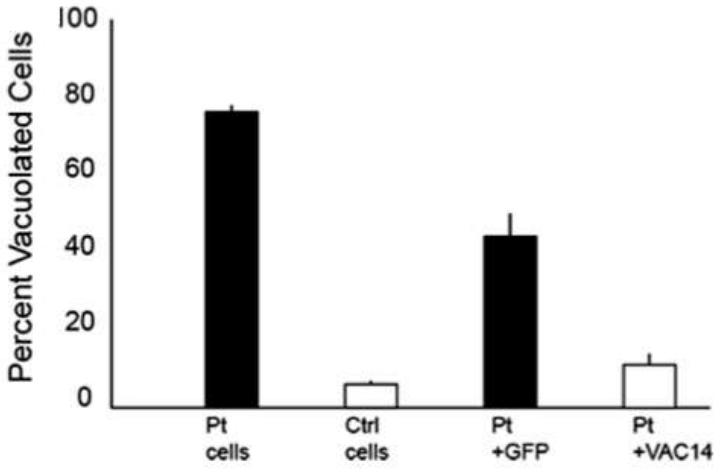
SWI SWI FLAIR DTI - Trace

- Neurodegeneration with Brain Iron Accumulation (NBIA) panel: Normal
- Microarray demonstrated extensive loss of heterozygosity (LOH, >3%). Review of all genes in LOH regions included VAC14

VAC14-RELATED DYSTONIA-PARKINSONISM

- Homozygous VAC14 missense VUS (p.Lys651Glu).
  Variant had not been described previously in gnomAD, 1000 Genomes
- In-silico modeling: 1 predicted pathogenic, 2 predicted benign

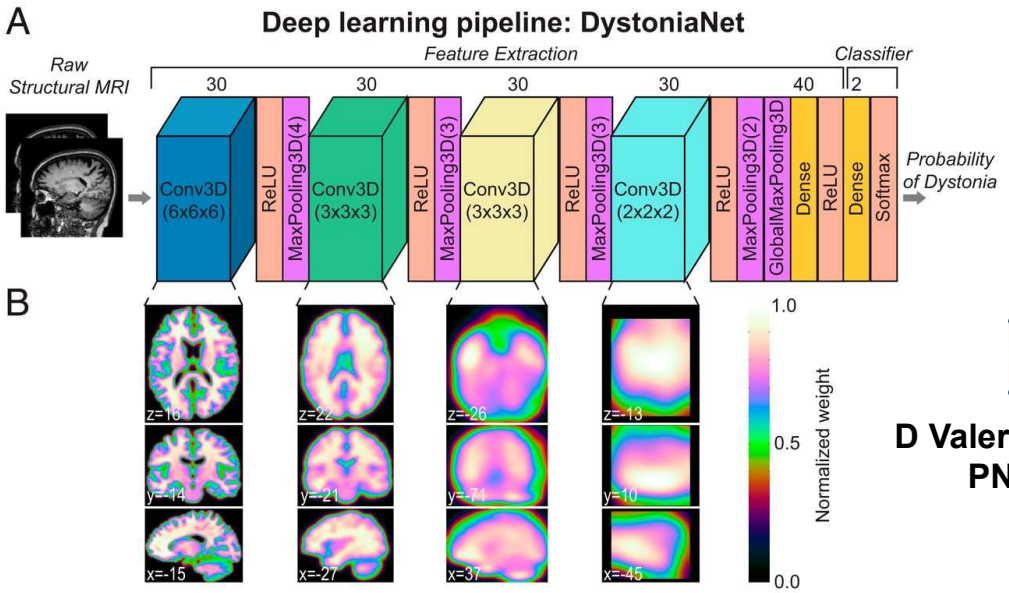




de Gusmao, 2019, Mov Dis Clin Prac

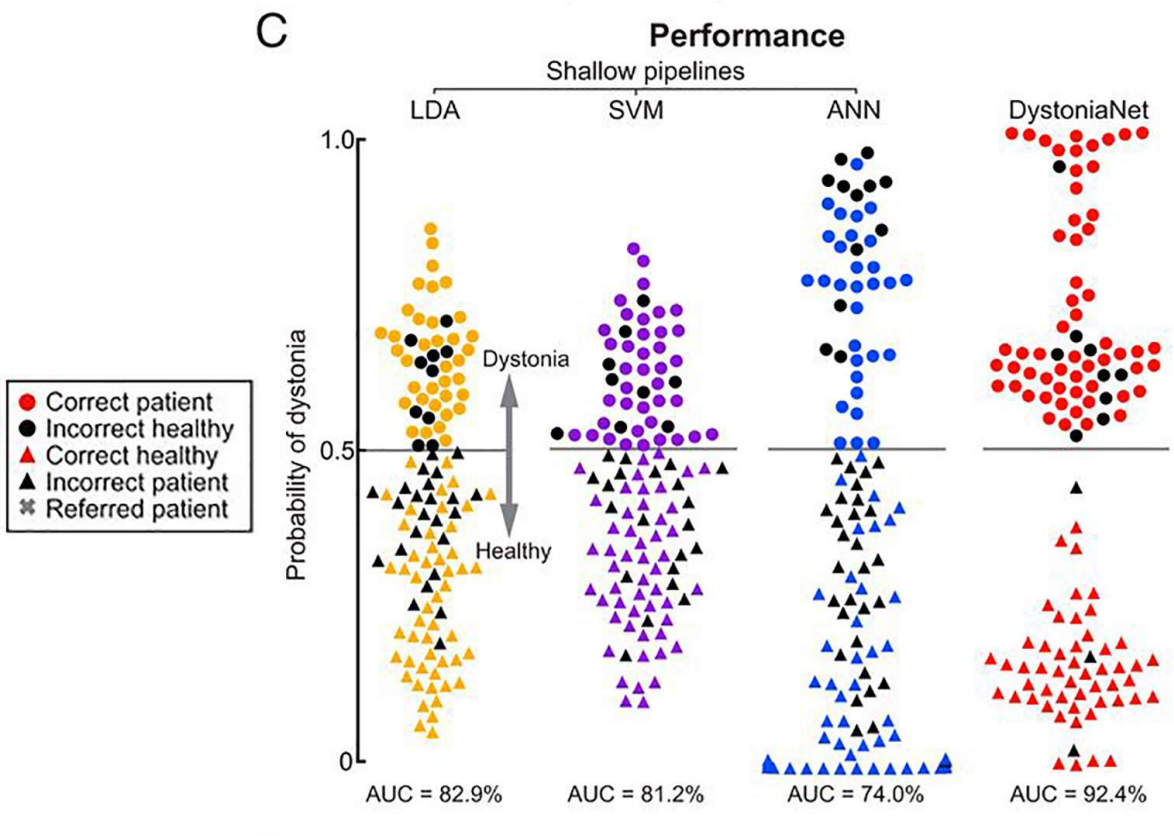
CAN A MACHINE DIAGNOSE DYSTONIA?

- Movement Disorders Neurologists are rare, and unevenly distributed
- Mean delay in diagnosis of Cervical Dystonia? 5-7 years in US, Canada
  - Bertram and Williams, J Clin Neurosci, 2016
  - Jog et al., Can J Neurol Sci, 2011
- Neuroimaging has failed to reliably Identify structural abnormalities
  - Voxel based morphometry
  - Region-of-Interest functional or structural connectivity
  - PET/SPECT-derived network analyses
- Even promising Neuroimaging-based methods cannot be applied to single patients, and do not generalize from one form of dystonia to others



PNAS

D Valeriani, and K Simonyan
PNAS Oct. 20, 2020



From Figure 4, Valeriani and Simonyan, PNAS Oct. 20, 2020

WHEN ASSESSING DYSTONIA:

- Q1: Primary or Secondary?
  - Big implications for prognosis, treatment choice
- Q2: Focal or generalized?
  - Focal dystonias can be treated with focal treatments (Botox injections)
  - Below the age of 27, most dystonias go on to generalize – be aggressive in your treatment, as things are likely to get worse.
- Q3: Is this (1) dystonia in isolation? (2) a compound movement disorder? or (3) is dystonia one symptom in a larger encephalopathic process?
- Q4: Will this patient benefit from Deep Brain Stimulation (DBS)?

THANK YOU

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