Mount Sinai Beth Israel

Clinical spectrum of genetic pediatric movement disorders

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Objectives

- Review basic classification of pediatric hyperkinetic movement disorders.
- Describe the definition and phenomenology of dystonia, chorea and myoclonus.
- Become familiar with genetic pediatric movement disorders through video cases.

Disclosures

- I have no conflict of interest to disclose.
- I receive funding from the American Academy of Neurology Clinical Research Training Fellowship.

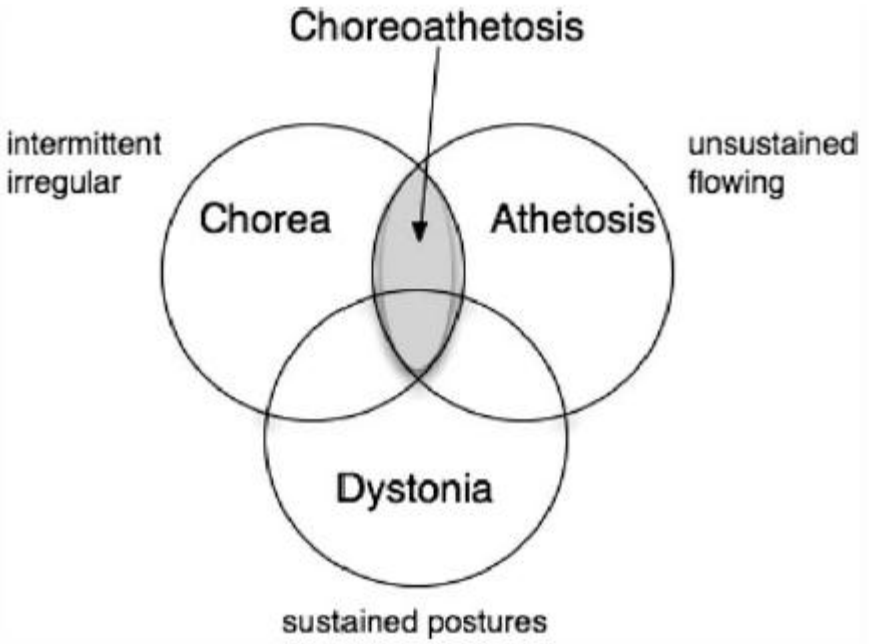
Hyperkinetic movement disorders

- Benign
- Acquired
- Genetic
  - Isolated
  - Neurometabolic/Complex

Kurian M Continuum 22 (4) 2016, Sanger TD et al, Movement Disorders, Vol. 25, No. 11, 2010

Hyperkinetic movement disorders

- Dystonia
- Chorea
- Athetosis
- Myoclonus
- Ballismus
- Tremor
- Tics
- Stereotypies



Kurian M Continuum 22 (4) 2016, Sanger TD et al, Movement Disorders, Vol. 25, No. 11, 2010

Dystonia

- Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned, twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Albanese A et al, Movement Disorders, Vol. 28, No. 7, 2013

Dystonia phenomenology

- Dystonic tremor
  - A spontaneous oscillatory, rhythmical, although often inconstant, patterned movement.
  - Null point when tremor is relieved by allowing the abnormal dystonic posture to fully develop.
- Overflow
  - unintentional muscle contraction of other regions which accompanies primary dystonic movement.
- Mirror dystonia
  - unilateral movement usually in the more severely affected side, when contralateral movements or actions are performed.
- Geste antagoniste (sensory trick)
  - Voluntary actions that specifically correct the abnormal posture or alleviate the dystonic movements.

Albanese A et al, Movement Disorders, Vol. 28, No. 7, 2013

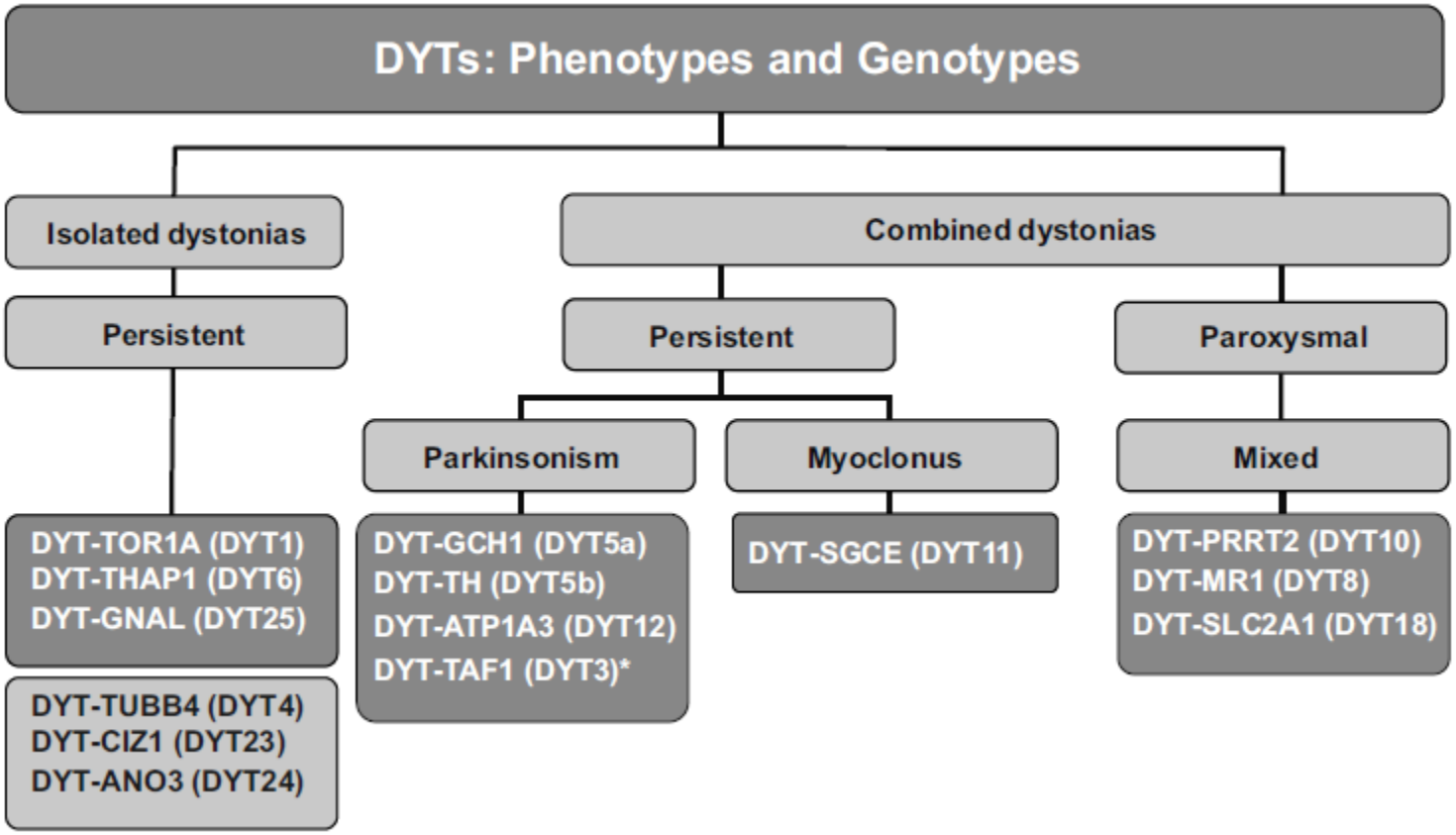
Dystonia classification

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

Albanese A et al, Mov Dis, Vol. 28, No. 7, 2013

Dystonia genes



C. Klein, Parkinsonism and Related Disorders (2014) S137–S142

Genetic dystonia in childhood

TABLE 7-2 DYT Classification of Primary Genetic Dystonia in Childhood

DYT Number	Paroxysmal/ Nonparoxysmal	Clinical Presentation	Pattern of Inheritance	Causative Gene
DYT1	Nonparoxysmal	Early-onset primary generalized idiopathic torsion dystonia	Autosomal dominant	*TOR1A*
DYT5a	Nonparoxysmal	Dopa-responsive dystonia	Autosomal dominant	*GCH1*
DYT5b	Nonparoxysmal	Tyrosine hydroxylase deficiency	Autosomal recessive	*TH*
DYT8	Paroxysmal	Paroxysmal nonkinesogenic dyskinesia	Autosomal dominant	*MR1*
DYT10	Paroxysmal	Paroxysmal kinesogenic dyskinesia	Autosomal dominant	*PRRT2*
DYT11	Nonparoxysmal	Myoclonus dystonia	Autosomal dominant	*SGCE*
DYT12	Nonparoxysmal	Rapid-onset dystonia-parkinsonism	Autosomal dominant	*ATP1A3*
DYT18	Paroxysmal	Paroxysmal exercise-induced dyskinesia	Autosomal dominant	*SLC2A1*
DYT23	Nonparoxysmal	Myoclonus dystonia	Autosomal dominant	*CACNA1B*
DYT26	Nonparoxysmal	Myoclonus dystonia	Autosomal dominant	*KCTD17*

Kurian M Continuum 22 (4) 2016

Video cases

DYT1-TOR1A

- Oppenheim's dystonia
- Most common form of genetic dystonia
  - 90% of generalized dystonia in Ashkenazi Jewish (AJ) population
  - 40-60% of generalized dystonia in non AJ population
- Childhood onset (~ age 13), range 1-28 y.
- Almost always (95%) starts in a limb
- 2/3 will progress to generalized or multifocal dystonia
- 20% remain focal dystonia
- Increased rate of recurrent major depression
- Good response to THP and sustained benefit from bilateral GPi DBS

Ozelius L and Lubarr N, GeneReviews, Nov 2016

DYT1-TOR1A

- Majority of cases are caused by a 3-base pair deletion (GAG) in exon 5 of *TOR1A.*
- *DYT1* is inherited in an autosomal dominant fashion.
- However, there is reduced penetrance of 30%.
- *TOR1A* encodes a nuclear envelope heat shock protein in the AAA+ ATPase family (torsinA).

- THAP1 (*DYT6*) binds to the *TOR1A* promoter and decreases its expression.

Ozelius L and Lubarr N, GeneReviews, Nov 2016; Kaiser FJ et al, Ann Neurol 2010

Video case

DYT6-THAP1

- Age of onset ~16.1 – 24 y. (5-38 y.)
- 50% present as cranial or cervical dystonia
- Prominent laryngeal involvement
- Frequent progression to involve multiple body regions
- Autosomal dominant inheritance with 60% penetrance
- Two homozygous families have been described
- Founder effect in the Amish-Mennonites
- > 50 mutations described across populations
- Explains 1-2% of all idiopathic dystonia cases

Fuch T et al, Nat Gen, 2009; Lohmann K et al, Eur J of Hum Gen 2012; Xiromerisiou G et al Mov Dis, 2012

Video cases

Dopa responsive dystonia *GTPCH1*

- Clinical presentation
  - Mean age of onset 5-8.5 y. (0-54)
  - Male: Female 1 : 2.5-4
  - Limb onset dystonia leg>> arm, equinovarus posturing
  - Brisk DTRs and ankle clonus
  - Diurnal fluctuation
  - Improvement on low dose L-dopa
  - Mild Parkinsonism in particular in adult onset
- Non motor symptoms
  - Depression, anxiety, OCD possibly due to low 5-HT levels
  - Excessive sleepiness, nightmares
  - Normal to borderline intellectual functioning

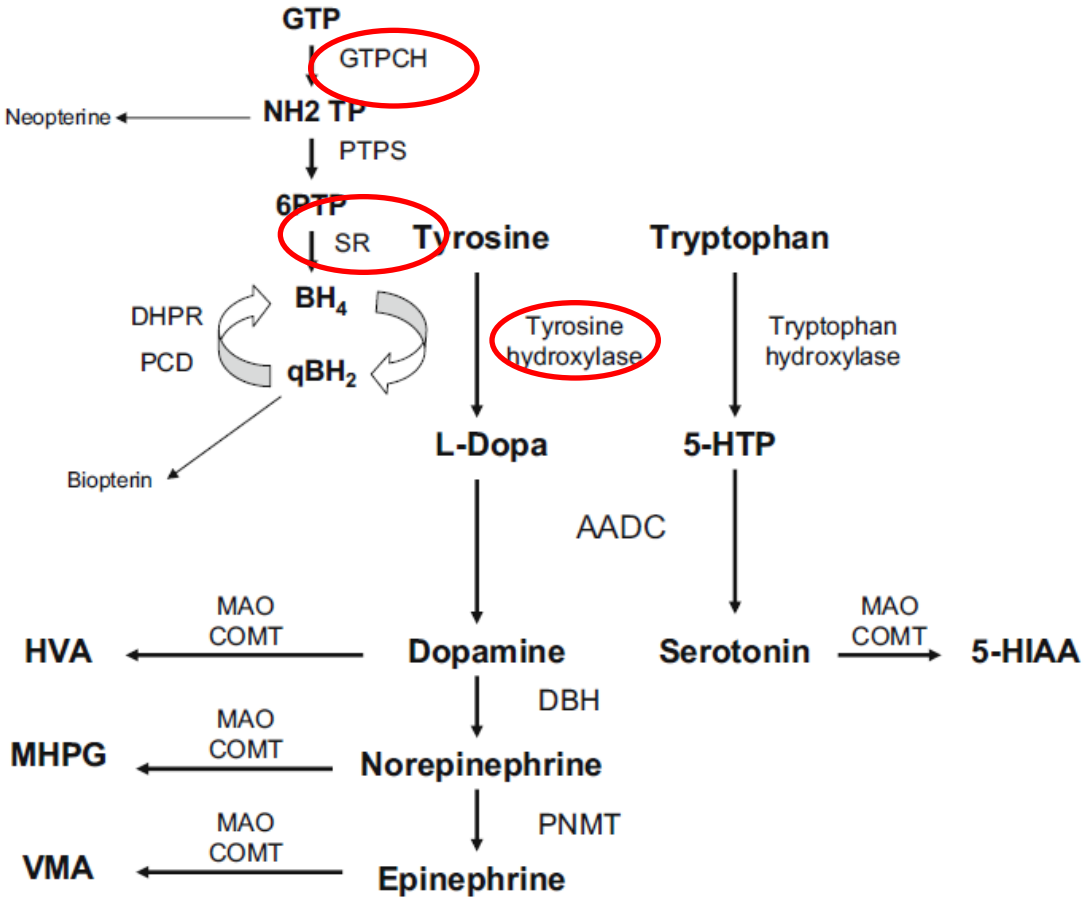
C.Marecos J Inherit Metab Dis. 2014 Jul;37(4):619-26, S.Wijemanne J. Nat. Rev. Neurol. 11, 414–424 (2015)

DYT5-GTPCH1

- Treatable form of genetic dystonia
- AD form
  - Most common DRD
  - Prevalence 0.5 to 1 per million
  - Penetrance 38% vs 87% ; Male: Female 1 : 2.5-4
  - > 100 mutations in gene including large indels of chr. 14q22.1–14q22.2
- AR form
  - More severe phenotype with spasticity and oculogyric crisis
  - Neonatal hyperphenylalaninemia
  - Possibly requires higher doses of L-dopa

C.Marecos J Inherit Metab Dis. 2014 Jul;37(4):619-26, S.Wijemanne J. Nat. Rev. Neurol. 11, 414–424 (2015)

The dopamine pathway



R. Pons, J Inherit Metab Dis (2009) 32:321–332

Treatment and diagnosis *GTPCH1*

- L-dopa trial
  - < 6 yo: 1-10 mg/kg/day
  - > 6 yo: 50 mg TID x 1 week and slowly increase to 200 mg TID
  - Response should be evaluated after 1 month
  - Typical patients have good response with 50–200 mg levodopa daily
  - Dyskinesias /fluctuations infrequent in *GTPCH1*
  - Safe during pregnancy I Trender-Gerhard, J Neurol Neurosurg Psychiatry 2009
- Lumbar puncture and/or genetic testing

HA Jinnah, Neurol Clin 33 (2015) 77–100, S.Wijemanne J. Nat. Rev. Neurol. 11, 414–424 (2015)

Video cases

DYT12-ATP1A3

- *ATP1A3* encodes the Na+/K+ ATPase alpha 3 subunit
- Mutations in *ATP1A3* cause a spectrum of disorders
  - rapid onset dystonia parkinsonism (RDP)
  - alternating hemiplegia of childhood (AHC)
  - cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome
  - epileptic encephalopathy
  - relapsing encephalopathy with cerebellar ataxia
  - rapid adult onset ataxia
  - CAPOS with hemiplegic migraine

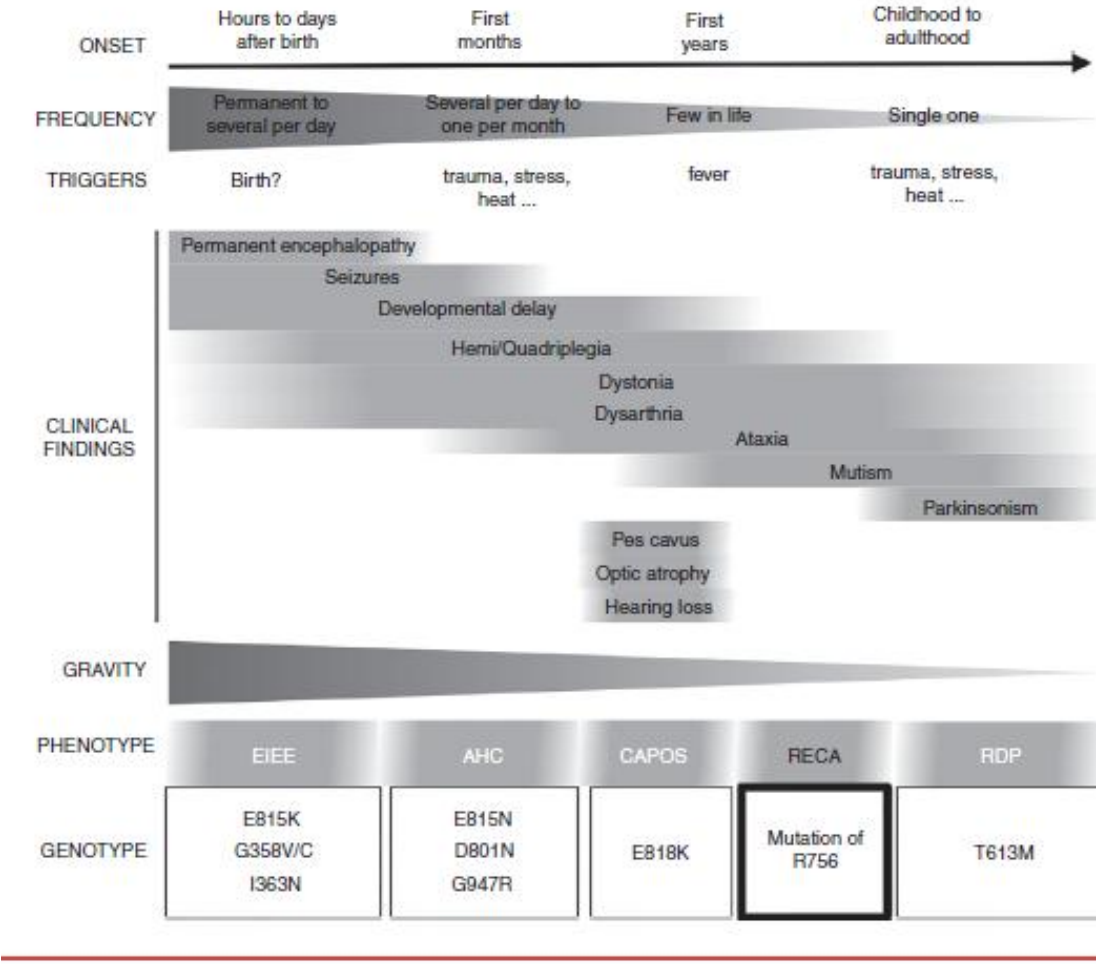
Heinzen EL et al, Lancet Neurol 2014; Demos MK, et al. Orphanet J Rare Dis. 2014

RPD

- Rapid-onset dystonia parkinsonism
- Sudden onset of dystonic posturing, postural instability and/or bradykinesia over hours to days
- Onset can be triggered by exercise, ETOH, trauma, infection, stress
- Rostro-caudal progression with marked cranial involvement
- Associated with psychiatric disease
- Autosomal dominant transmission

Heinzen EL et al, Lancet Neurol 2014; Demos MK, et al. Orphanet J Rare Dis. 2014

Genotype-phenotype correlation



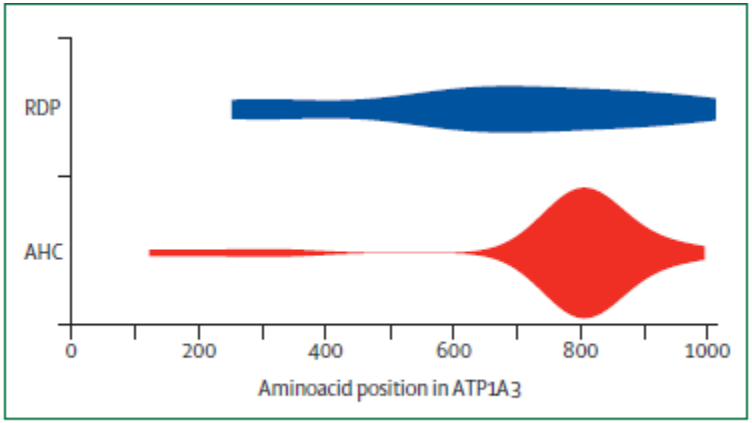


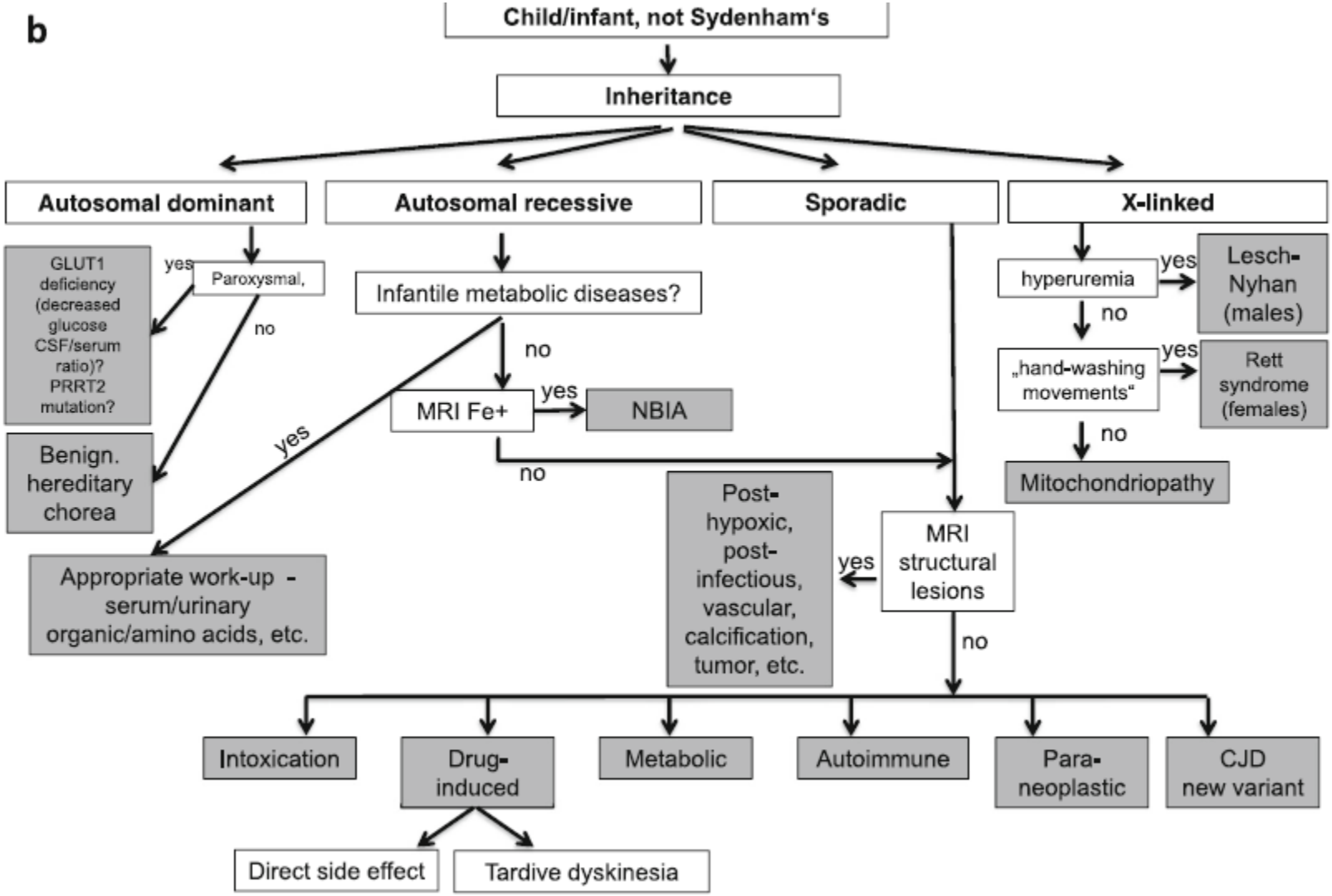
Figure 3: **Density plot showing the distribution of AHC and RDP mutations in *ATP1A3***

Heinzen EL 2014, Dard R et al Dev Med & Child Neur 2015

Chorea

- Chorea refers to brief involuntary movements of limbs, trunk, neck, or face that rapidly travel from region to region in an irregular, flowing, nonstereotyped pattern.

Hermann A &. Walker RH, Curr Neurol Neurosci Rep (2015) 15



Hermann A &. Walker RH, Curr Neurol Neurosci Rep (2015) 15

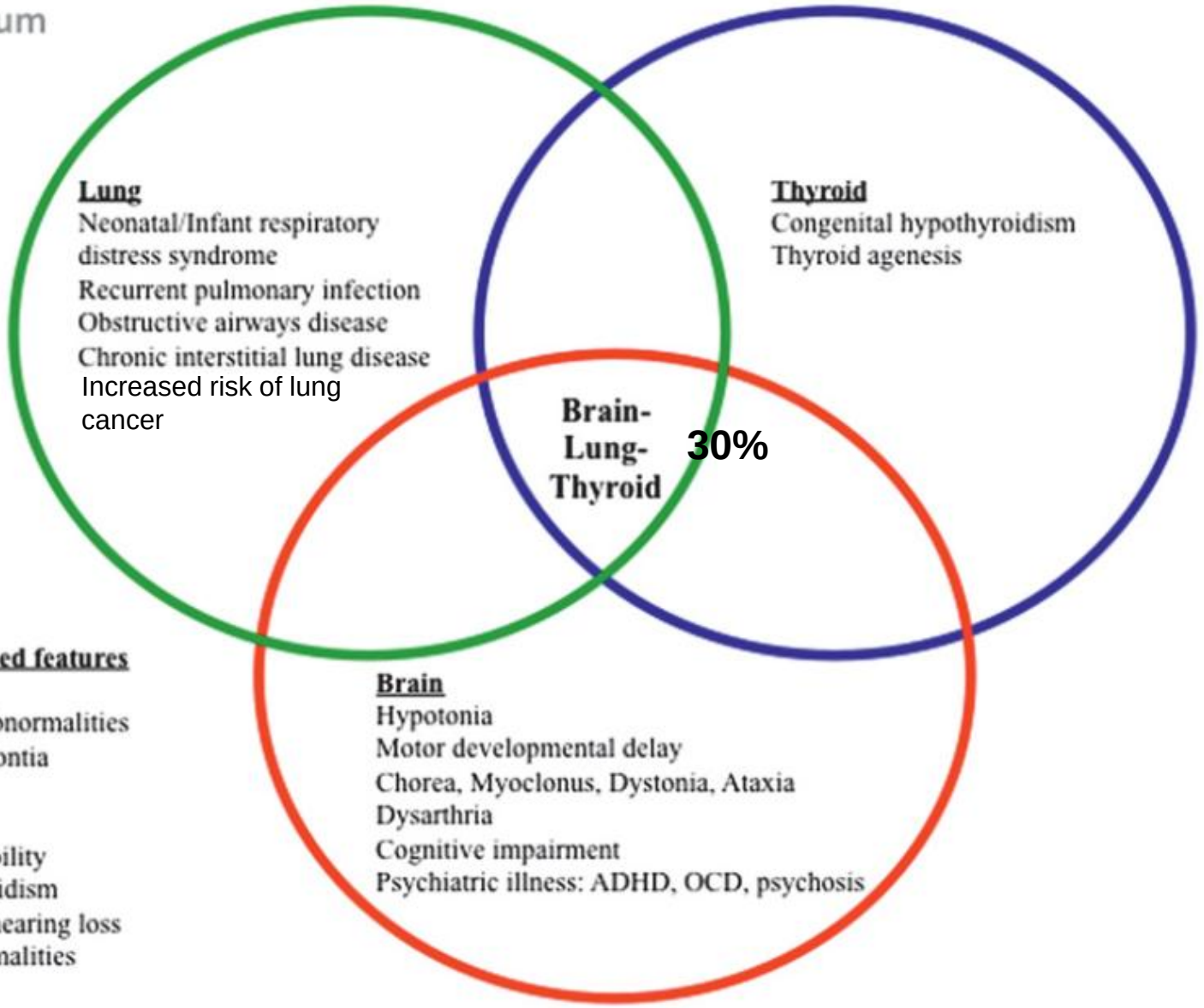
Video cases

Benign Hereditary Chorea

- Autosomal dominant disorder or sporadic mutation
- The most common cause is *TITF1/TTF1/NKX2.1* gene mutations or large chr. 14q13.3 deletions
- Neurological presentation
  - Onset 2.5- 3 y.
  - Motor delay and hypotonia followed by hyperkinetic movements; chorea, dystonia, myoclonus, ataxia
  - Non progressive
  - MRI brain may show anatomical variants

Gilbert DL, 2009, DeVries BBA, 2000, Kleiner-Fisman G, 2007, Peall KJ et al 2015

Clinical Spectrum of Benign Hereditary Chorea



Other associated features

Malignancy
Urinary tract abnormalities
Hypo-/Oligo-dontia
Short stature
Webbed neck
Joint hypermobility
Hypoparathyroidism
Sensorineural hearing loss
Skeletal abnormalities

Peall KJ et al 2015

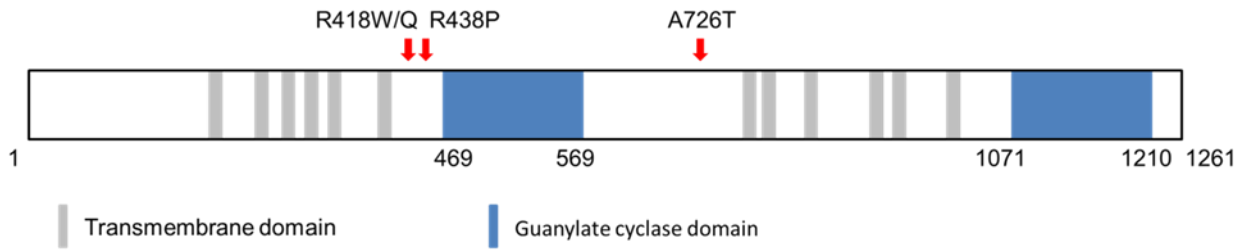
When to suspect *TITF1*

- Childhood onset of hypotonia in association with a hyperkinetic movement disorder plus
  1. Hypothyrodism, neonatal respiratory distress or recurrent respiratory infections (B-T-L triad)
  2. Isolated non-progressive chorea with onset < 5 yo
  3. Childhood onset non-progressive ataxia
  4. Dominant family history of thyroid disease, chorea, ataxia, motor delay, ADHD or psychosis
  5. Mild dysmorphic features: short stature, oligodontia, hypospadias, bulbous nose, CHD
  6. MRI findings of cystic pituitary gland, empty sella, agenesis of corpus callosum

Meijer IA et al, CNS Ohio 2014

ADCY5

- Mutations in *ADCY5* are the second cause of “Benign Hereditary Chorea”.
- *ADCY5* encodes an adenylyl cyclase, which is mainly expressed in the striatum.
- Autosomal dominant inheritance or de novo mutations.
- Over 8 mutations and 27 cases reported.



Chang FCF et al, Movement Disorders 2016, Mencacci N et al, Neurology 2015

Clinical features

- Onset ~ 0-2 y.
- Motor and speech delay, axial hypotonia
- Mixed hyperkinetic movement disorder with characteristic facial chorea-myoclonus
- Pyramidal signs
- Impaired vertical gaze
- Normal or decreased cognition
- Paroxysmal worsening, triggered by stress
- Characteristic hypotonic facial and wide-based, staggering gait with adducted knees
- Phenotype is not benign; CP mimicker

Meijer IA et al, J Child Neur 2016

Clinical features

Clinical Features	No. of Cases (Where Reported)	% (n = 20)	% (Where Reported)	Our Series
Presentation				
Birth to 6 months	4/19	20	21	3/7
7 months to 2 years	7/19	35	37	3/7
>2 years	8/19	40	42	1/7
Syndrome				
CWEDD	5/20	25	25	5/7
MD	1/20	5	5	1/7
IOIC	1/20	5	5	1/7
COPCD	2/20	10	10	0/7
FDFM	6/20	30	30	0/7
EOADCD	2/20	10	10	0/7
BHC	3/20	15	15	0/7
Gene mutation				
c.1252C>T	10/20	50	50	5/7
c.1252C>G	1/20	5	5	1/7
c.1253G>A	1/20	5	5	1/7
c.2176G>A	6/20	30	30	0/7
c.2088+1G>A	2/20	10	10	0/7
Phenomenology				
Chorea	18/19	90	95	6/7
Facial dyskinesia	11/20	55	55	5/7
Axial hypotonia	8/16	40	50	6/7
Dystonia	14/17	70	82	6/7
Myoclonus	3/11	15	27	2/7
Spasticity	6/20	30	30	3/7
Intellectual disability	2/20	10	10	2/7
upward gaze palsy	7/13	35	54	4/7
Motor regression	6/20	30	30	2/7
Epilepsy	1/19	5	5	0/7

Clinical Features	No. of Cases (Where Reported)	% (n = 20)	% (Where Reported)	Our Series
Duration of episodic exacerbation				
Minutes to hours	8/10	40	80	6/7
Hours to days	1/10	5	10	0/7
Constant	1/10	5	10	1/7
Exacerbating factors				
Action	8/16	40	50	6/7
Stress	10/16	50	63	4/7
Awakening	3/16	15	19	0/7
Drowsiness	7/16	35	44	6/7
Improvement with				
Clonazepam	4/15	20	27	4/7
Clobazem	2/15	10	13	2/7
Carbamazepine	1/15	5	7	1/7
Propranolol	1/15	5	7	NT
Acetazolamide	2/15	10	13	NT
Trihexyphenidyl	3/15	15	20	0/7
Tetrabenazine	2/15	10	13	NT
Caffeine	1/15	5	7	1/7
Action	1/15	5	7	0/7

Chang FCF et al, Movement Disorders 2016
Mencacci N et al, Neurology 2015

DBS therapy in *ADCY5*

Mutation	c.2080_2088del, p.K694_M696	c.1252C>T (p.R418W)	c.1252C>T (p.R418W)
Gender	Male	Female	Female
Ethnic background	Caucasian/Puerto Rican	Caucasian	Caucasian
Initial symptom	Continuous generalized choreoathetosis	Sleep myoclonus	Episodic choreiform movements with dystonic posturing
Age of onset	5 months	12 months	13 months
Age at exam or report	3 years	8 years	32 years
Development	Significantly delayed: cannot sit or roll over, significant head lag 5 months after DBS: began making midline movements and purposeful vocalization	Sat: 18 months Walked: 3 years Delayed speech	Sat: 18 months Walked with assistance: 2.5 years Delayed speech
Cognitive function	Significantly delayed	Normal	Low average
Other features	Diffuse hypotonia	Hypotonia, myoclonus	Hypotonia
Initial movements	Continuous hyperkinetic movements (choreoathetosis, ballism)	Myoclonus followed by hyperkinetic movements (dystonia and choreoathetosis)	Choreoathetosis episodic with dystonic posturing
DBS target	Bilateral GPi	Bilateral GPi	Bilateral GPi
Pre-DBS severity scale (patients 2-3: BFM)	Not applicable	BFM 45 BFM Disability 3	BFM 75.5 BFM Disability 25
Post-DBS severity scale (patients 2-3: BFM)	Not available	BFM 38 (6 months postoperative) BFM Disability 3 (6 months postoperative)	BFM 38 BFM Disability 24 (3 years postoperative)
Duration post-DBS	10 months	8 months	3 years
Post-DBS	Mild improvements in choreoathetosis, sleep, and mild gains in developmental milestones Improvement in prior failure to thrive	Mild improvements in myoclonus, dystonia, clarity of speech and ambulation	Episodic choreoathetoid and dystonic movements improved; can use a communication board more effectively, and steer electric wheelchair with joystick

- Our patient had significant clinical improvement of dystonia, speech, sialorrhea and gait which translated into improved BFM motor and disability scores at one year and 3 years post op.
- Positive responses to stimulation up to 3 years, however long-term efficacy not yet demonstrated

Dy ME et al, J Child Neurol. 2016, Meijer et al, J Child Neurol 2016

Myoclonus

- Myoclonus is characterized by a sudden, jerky, shock-like movement.
- Positive myoclonus is generated by contraction of muscles due to excitatory inputs.
- Negative myoclonus is defined as the sudden loss of muscle tone (e.g., asterixis).

Chang V et al, Curr Treat Options Neurol 2008; Levy A , Curr Treat Options Neurol 2016

Table 1. Classification of myoclonus

Etiology	**Phenomenology**
Physiologic	Distribution
Hypnic jerks	Focal
Hiccups	Segmental
Anxiety-induced	Multifocal
Exercise-induced	Generalized
Essential	Stimulus
Sporadic	Spontaneous
Hereditary	Action
Epileptic	Reflex (stimulus-induced)
Childhood epilepsies	Timing
Progressive myoclonic epilepsies	Rhythmic
Symptomatic	Irregular
Metabolic (hepatic, renal, electrolyte disturbances)	Periodic
Toxicities	**Pathophysiology**
Storage diseases	Cortical
Trauma (posthypoxic)	Focal
Neoplastic/paraneoplastic (opsoclonus-myoclonus)	Multifocal
Infections	Generalized
Dementia (Creutzfeldt-Jakob)	Subcortical
Other neurodegenerative	Thalamic
Atypical parkinsonism	Brainstem
Other basal ganglia degeneration	Reticular
Spinocerebellar degeneration	Hyperexplexia (startle)
	Palatal
	Spinal
	Segmental
	Propriospinal
	Peripheral

Chang V et al, Curr Treat Options Neurol 2008; Levy A , Curr Treat Options Neurol 2016

Video case

Myoclonus Dystonia

- Median age of onset 5-8 y (1.5-18 y)
- Usually presents as truncal and upper limb myoclonus with cervical dystonia and/or writer's cramp
- In early childhood can present with upper body myoclonus and dystonia OR lower limb dystonia with later onset myoclonus
- Ataxia
- Psychiatric symptoms
  - OCD, anxiety-related disorders, and alcohol dependence (Peall KJ et al, Ann Clin Transl Neurol. 2015)

Peall, K.J., Kurian, M.A., Wardle, M. et al. J Neurol 261: 2296, 2014;
Sheridan MB et al, Clin Genet 2013: 84: 368–372

DYT11-SGCE

- *SGCE* mutations explain 50% of individuals with definite M-D
- Single gene mutation vs contiguous gene syndrome
- Autosomal dominant inheritance with variable penetrance
- Penetrance is nearly complete when transmitted by the father because *SGCE* is maternally imprinted and preferentially expressed from the paternal allele

Roze E et al, Movement Disorders, Vol. 30, No. 6, 2015;
Sheridan MB et al, Clin Genet 2013: 84: 368–372

SGCE plus syndromes

A

Table 4 Clinical characteristics of cases with contiguous gene deletions involving *SGCE*

Cases	Deletion size (Mb)	Genes involved	Clinical characteristics
This study			
Case 1	2.3	*PPP1R9A, PEG10, SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L*	Short stature, language delay
Case 2	2.3	*PPP1R9A, PEG10, SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L*	Short stature
Case 3	2	*PEG10, SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6*	Intrauterine growth retardation, microcephaly short stature, joint laxity
Case 4	1.9	*SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6*	Microcephaly, short stature, cognitive impairment
Case 5	0.7	*PEG10, SGCE, CASD1, COL1A2*	Short stature, psychosis
DeBerardinis et al.			
Case 1	9–16.5	*SGCE* (and contiguous genes, not further defined)	Intrauterine growth retardation, microcephaly short stature, dysmorphic facies, language delay
Asmus et al.			
Case 1	1.63	*PEG10, SGCE, COL1A2*	Short stature, joint laxity, dental caries,
Case 2	4.99	*PEG10, SGCE, COL1A2, PEX1, KRIT1*	joint laxity, blue sclerae, cerebral cavernous malformations
Case 3	8.78	*PEG10, SGCE, COL1A2, PEX1, KRIT1, DLX5*	Dysmorphic facies, dental caries, cognitive impairment, split-hand split-foot syndrome
Saugier-Veber et al.			
Case 1	1.88	*SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6*	Intrauterine growth retardation, microcephaly, short stature, joint laxity, cognitive impairment
Dale et al.			
Case 1	0.17	*SGCE, CASD1*	Language delay, cognitive impairment
Case 2	0.17	*SGCE, CASD1*	Nil
Case 3	0.17	*SGCE, CASD1*	Psychosis

B Silver Russell syndrome 2e to maternal uniparental disomy

Peall KJ et al, J Neurol (2014) 261:2296–2304; Sheridan MB et al, Clin Genet 2013: 84: 368–372

Myoclonus Dystonia

- Treatment
  - Clonazepam
  - Zonisamide Hainque E Neurology. 2016 May 3;86(18):1729-35
  - Bilateral GPi DBS therapy

- New myoclonus dystonia genes:
  - KCTD17 Mencacci NE et al, AJHG 96, 938–947, June 4, 2015
    - More severe dystonia phenotype
  - CACNA1B Groen JL et al Human Molecular Genetics, 2015, Vol. 24, No. 4

Roze E et al, Movement Disorders, Vol. 30, No. 6, 2015,
Sheridan MB et al, Clin Genet 2013: 84: 368–372

Conclusion

- This presentation highlights the clinical and genetic complexity of hyperkinetic pediatric movement disorders.
- Genetic diagnosis is important for family counseling and therapeutic considerations.
- Utility of whole exome sequencing in sporadic cases with a complex neurological phenotype in particular in the field of movement disorders.

Questions?

Thank you!

- Dr. T. Pearson (Washington U.) and Dr. N. Lubarr (HackensackUMC)
- Dr. S. Bressman, Dr. Saunders-Pullman and colleagues (Mount Sinai Beth Israel)
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- American Academy of Neurology Clinical Research Training Fellowship