Combined & Complex Dystonias

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"Complex" Dystonia Is Not a Category in the New 2013 Consensus Classification

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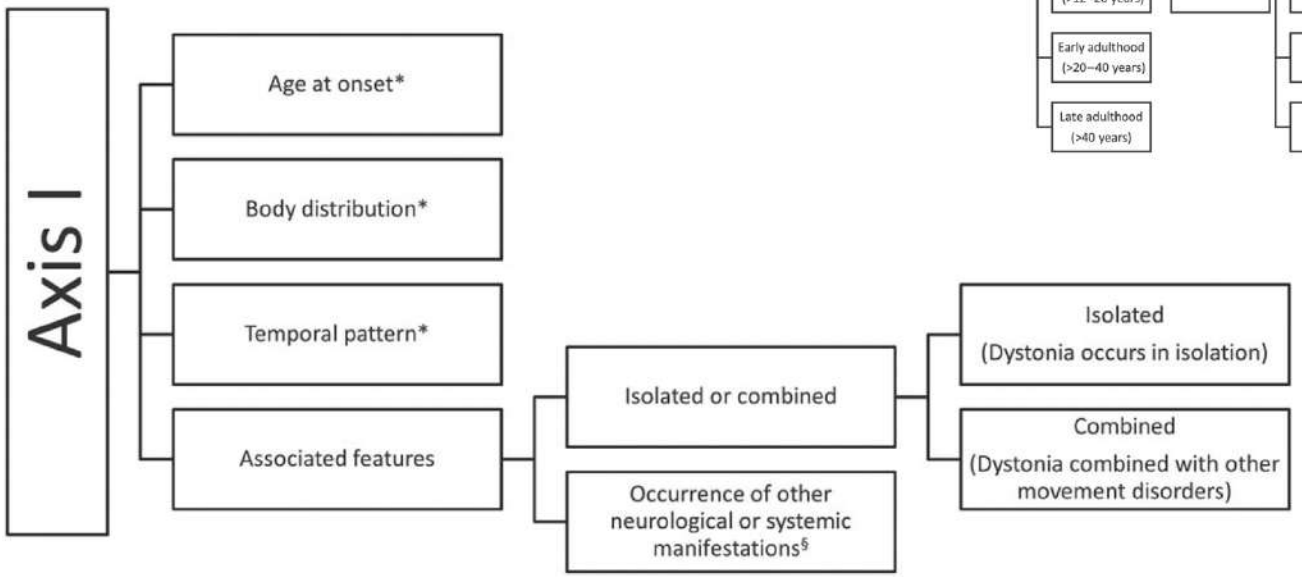
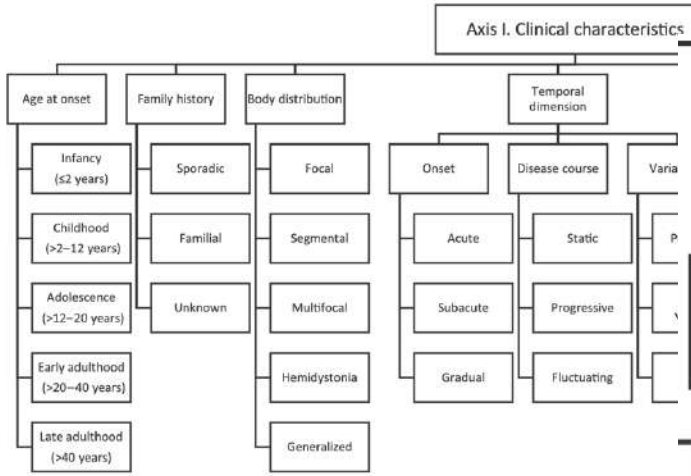
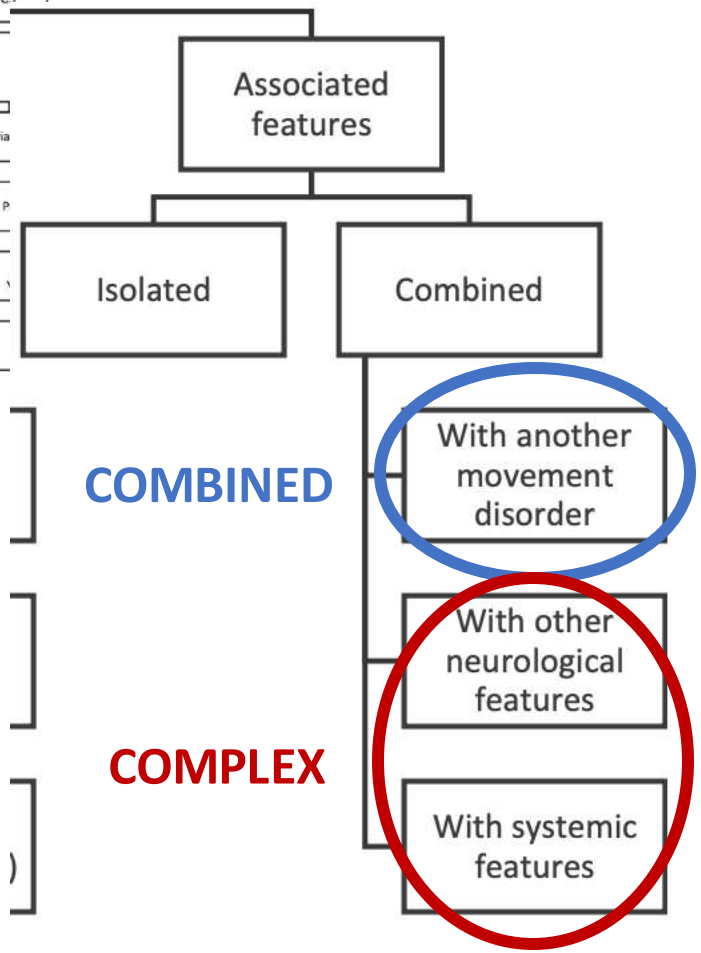


Definition and Classification of Dystonia

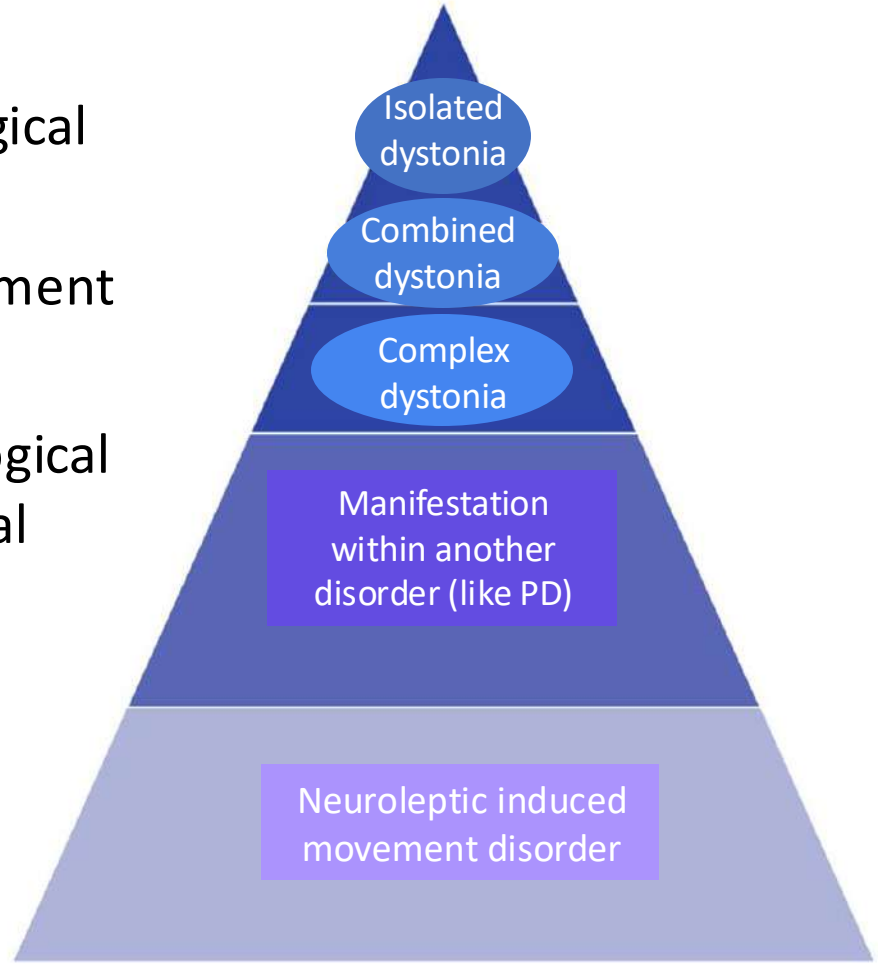
Alberto Albanese, MD,[1,2*] Kailash P. Bhatia, MD, DM, FRCP,[3] Victor S.C. Fung, PhD, FRACP,[4] Mark Hallett, MD,[5] Joseph Jankovic, MD,[6] Christine Klein, MD,[7] Joachim K. Krauss, MD,[8] Anthony E. Lang, MD, FRCPC,[9,10] Jonathan W. Mink, MD, PhD,[11] Sanjay Pandey, DM,[12] Jan K. Teller, MA, PhD,[13] Marina A.J. Tijssen, MD,[14,15] Marie Vidailhet, MD,[16,17,18] and H.A. Jinnah, MD, PhD[19,20]

2025 Mov Disord

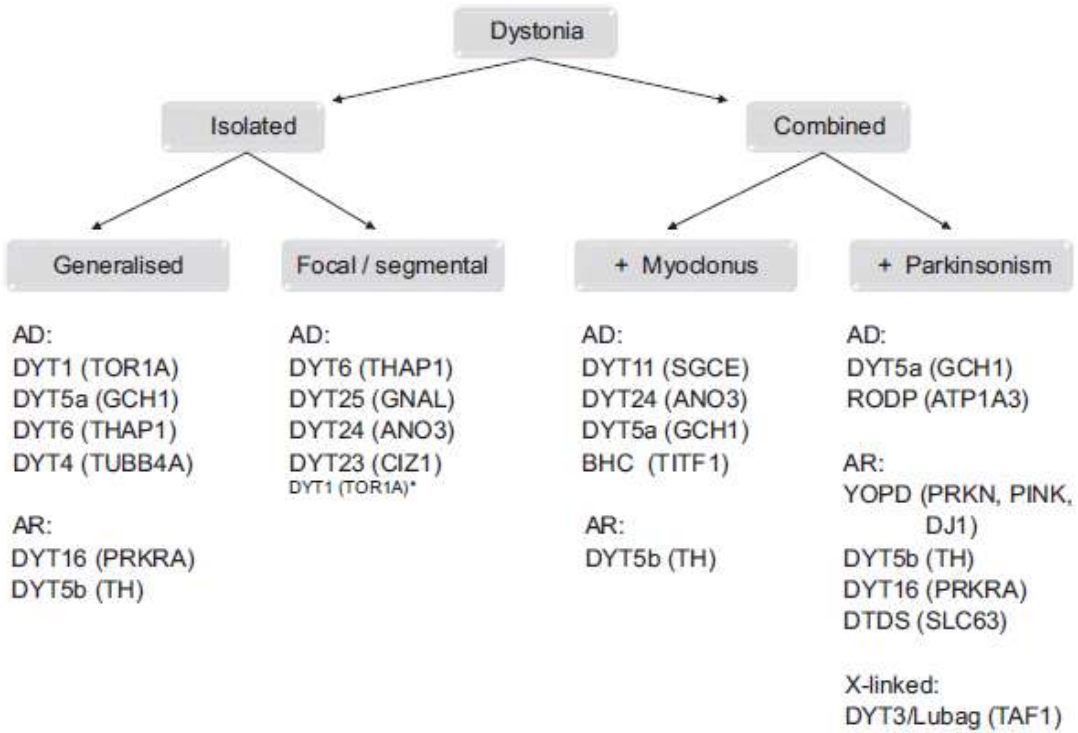




- **Isolated dystonia** if there is no other motor or neurological features, other than tremor
- **Combined dystonia** if it is accompanied by other movement disorders, such as *parkinsonism and myoclonus*
- **Complex dystonia** if it is accompanied by other neurological features like corticospinal signs, epilepsy, developmental delay, or by systemic features like liver disease, kidney disease



Grütz&Klein, 2021



Balint&Bhatia, 2015

Monogenic forms of dystonia

Isolated dystonia

- DYT-ANO3
- DYT-EIF2AK2
- DYT-GNAL
- DYT-HPCA
- DYT-KMT2B
- DYT-PRKRA
- DYT-THAP1
- DYT-TOR1A
- DYT-VPS16
- DYT-AOPEP

Combined dystonia

- DYT-COX20
- DYT-DNAJC12
- DYT-SLC39A14
- DYT/PARK-ATP1A3
- DYT/PARK-GCH1
- DYT/PARK-TAF1
- DYT/PARK-TH
- DYT/CHOR-GNAO1
- MYC/DYT-KCTD17
- MYC/DYT-SGCE

Complex dystonia

- DYT-ACTB
- DYT-ATP7B
- DYT-BCAP31
- DYT-DCAF17-(NBIA)
- DYT-DDC
- DYT-FITM2
- DYT-IRF2BPL
- DYT-MECR
- DYT-mt-ND6
- DYT-OPA1
- DYT-PANK2-(NBIA)
- DYT-SERAC1
- DYT-SLC19A3
- DYT-SUCLA2
- DYT-TIMM8A
- DYT-TUBB4A
- DYT-VAC14
- DYT/CHOR-ACAT1
- DYT/CHOR-ADAR1
- DYT/CHOR-FOXG1
- DYT/CHOR-GCDH
- DYT/CHOR-HPRT
- DYT/CHOR-MUT
- DYT/CHOR-PCCA/PCCB
- DYT/PARK-CP-(NBIA)
- DYT/PARK-GLB1
- DYT/PARK-PLA2G6-(NBIA)
- DYT/PARK-PTS
- DYT/PARK-QDPR
- DYT/PARK-SLC6A3
- DYT/PARK-SLC30A10
- DYT/PARK-SPR
- ATX/DYT-SQSTM1

Disorders that usually present with other phenotypes but can have predominant dystonia

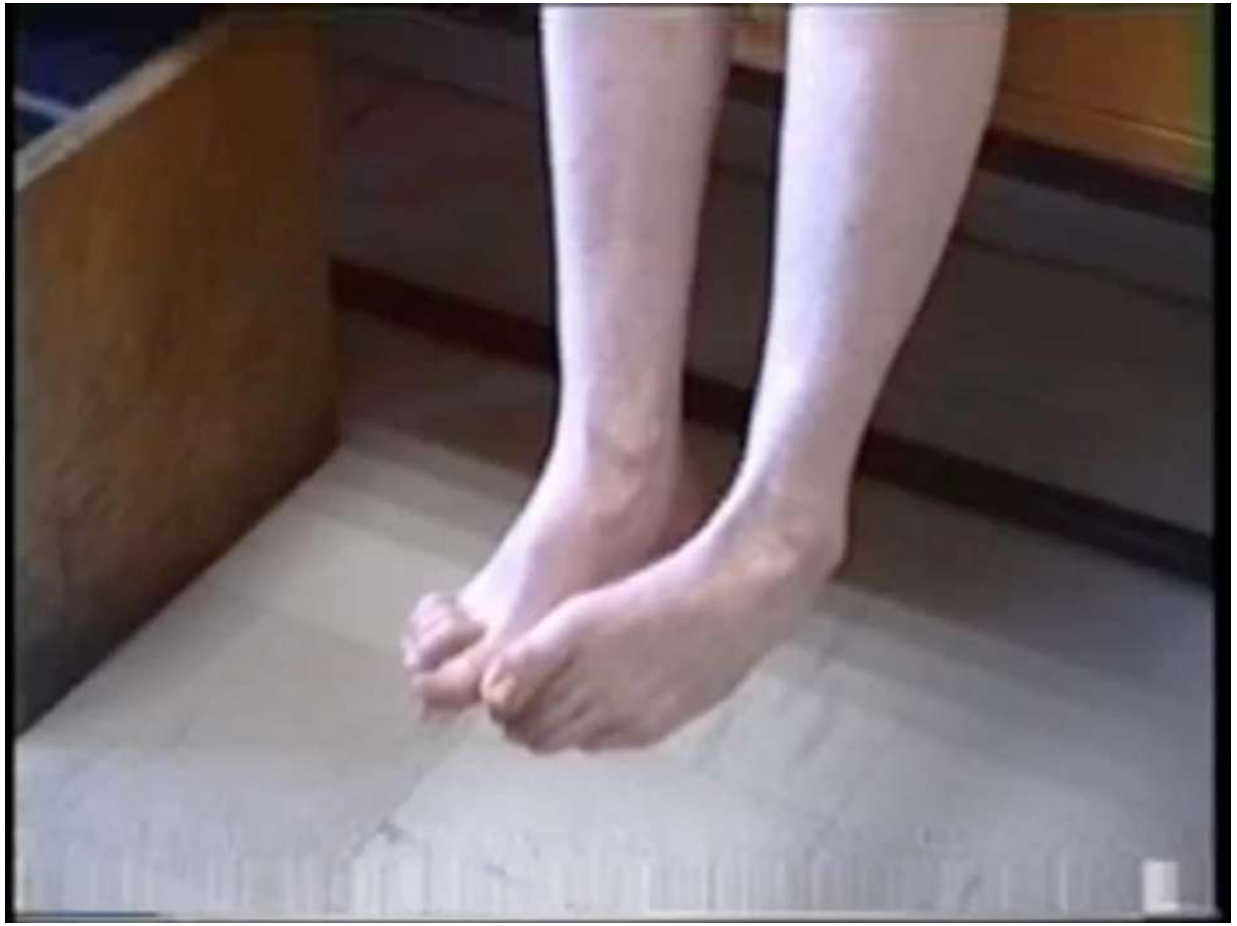
- ATX-ATXN3
- HSP-C19orf12-(NBIA)
- HSP/ATX-FA2H-(NBIA)
- HSP/ATX-KIF1C
- CHOR-FTL-(NBIA)
- PARK-DNAJC6
- PARK-WDR45-(NBIA)

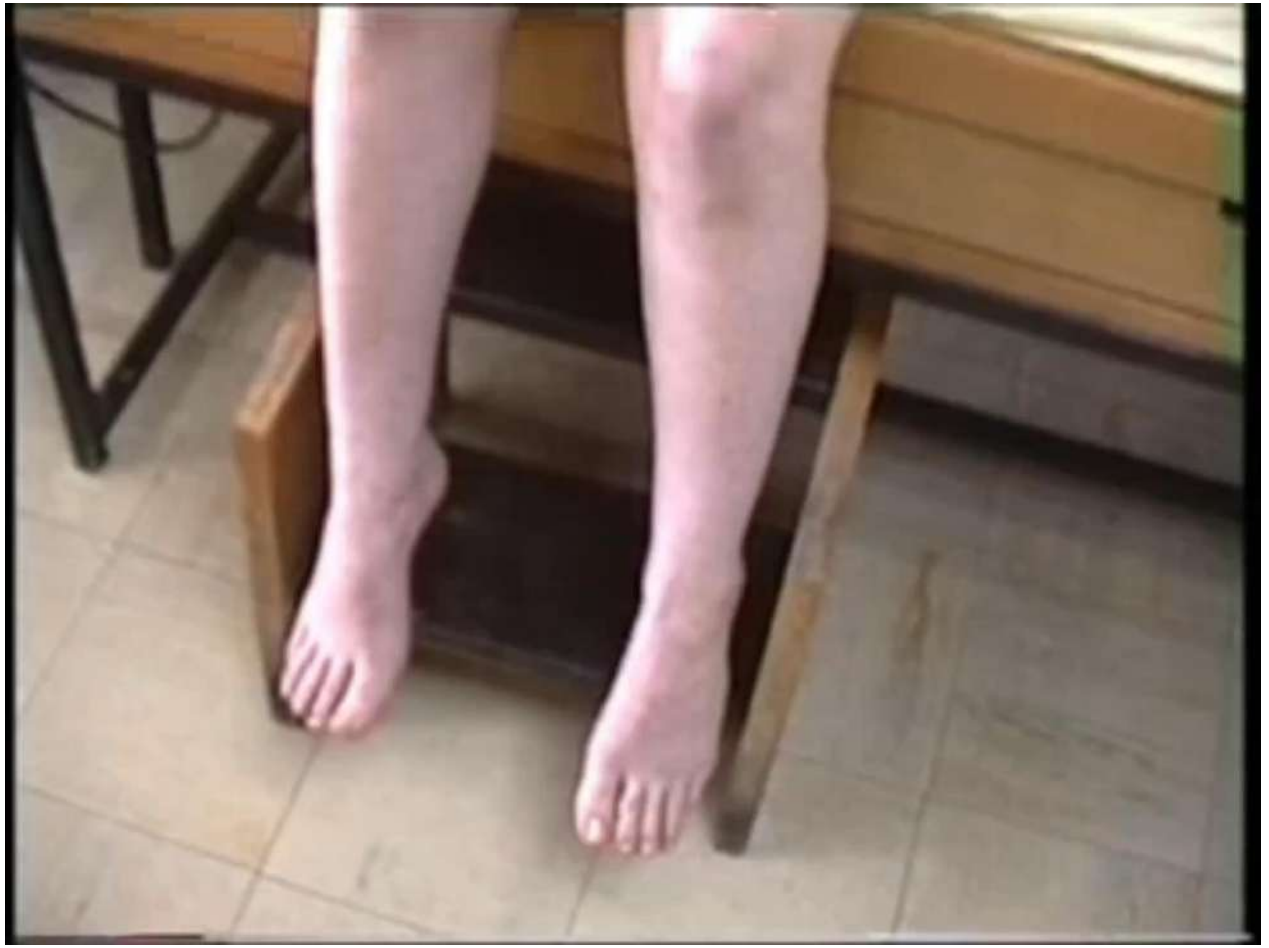
List of genes causing neurodevelopmental delay and dystonia

(Conditions where less prominent dystonia can be encountered in the setting of predominant developmental disorders or epileptic encephalopathy)

- *ARX*
- *CTNNB1*
- *GNB1*
- *SUCLG1*
- *VPS41*
- *YY1*

Yarahmadi et al., 2025



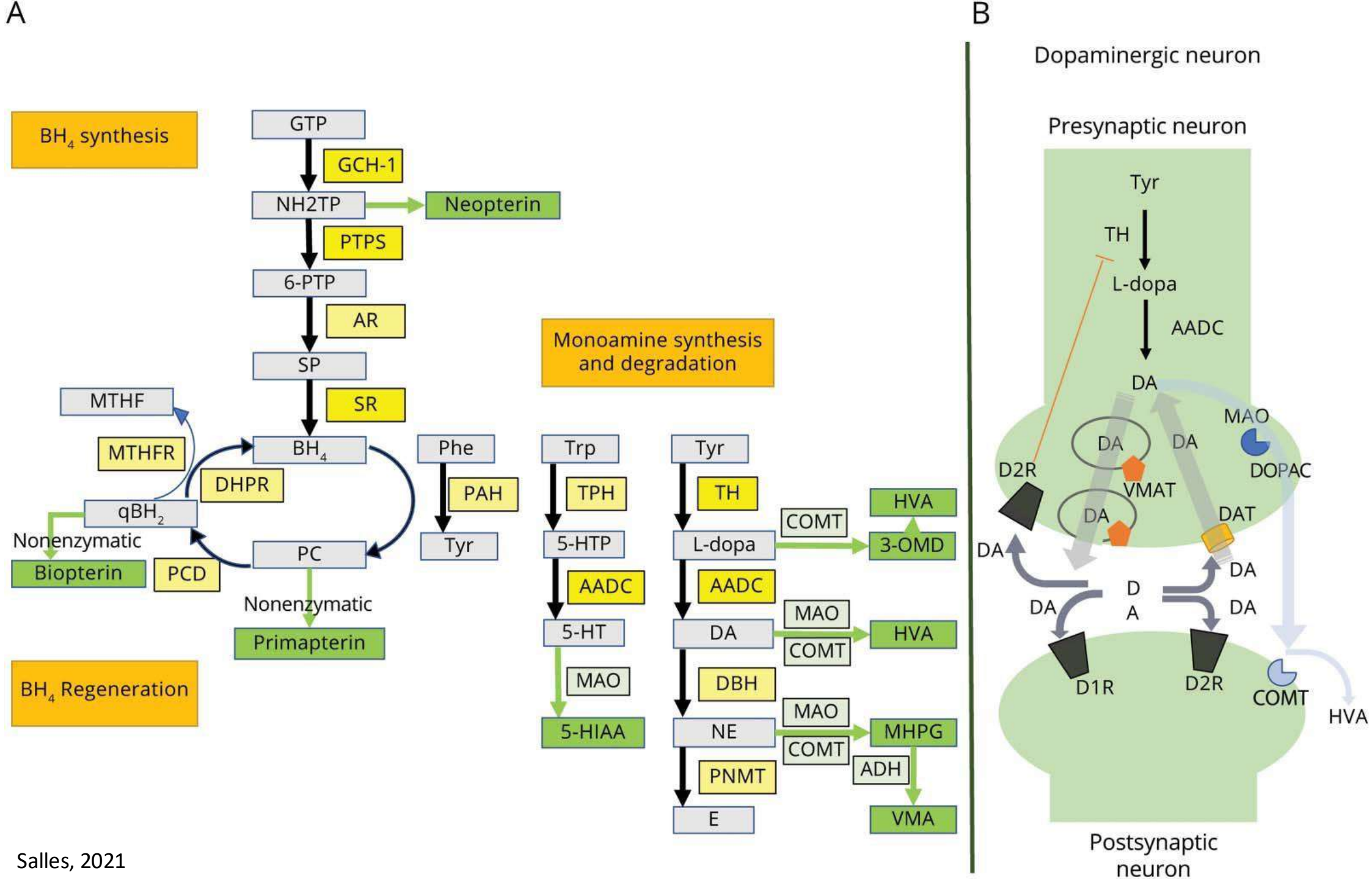


Under treatment

Dystonias combined with parkinsonism

Gene (previous DYT symbol)	Inheritance	Age at onset	Body region involved at onset	Distribution	Body parts involved	Additional features
GCH1(DYT5a)	AD (rarely AR)	Btw. 1—6. decade	Lower ext	Often generalized	Lower ext, body, upper ext	• Diurnal fluctuations • Parkinsonism • Spasticity
TH(DYT5b)	AR	<1 year	Lower ext	Often generalized	Lower ext, body, upper ext, orofacial region	• Parkinsonism • Ptosis • Occulogyric crises • Growth retardation • Encephalopthy • Myoclonus
SPR	AR	<1 year	Lower ext	Often generalized	Lower ext, body, upper ext, orofacial region	• Parkinsonism • Axial hypotonia • Growth retardation • Occulogyric crises • Muscle weakness • Cognitive dysfunction

Balint et al., 2018


A
BH4 synthesis
GTP
GCH-1
NH2TP
Neopterin
PTPS
6-PTP
AR
SP
SR
MTHF
MTHFR
BH4
DHPR
qBH2
Nonenzymatic
Biopterin
PCD
PC
Nonenzymatic
Primapterin
Phe
PAH
Tyr
BH4 Regeneration
Monoamine synthesis and degradation
Trp
TPH
5-HTP
AADC
5-HT
MAO
5-HIAA
Tyr
TH
L-dopa
AADC
DA
DBH
NE
PNMT
E
COMT
HVA
3-OMD
MAO
COMT
HVA
MAO
COMT
ADH
MHPG
VMA
B
Dopaminergic neuron
Presynaptic neuron
Tyr
TH
L-dopa
AADC
DA
MAO
DA
DA
D2R
DOPAC
VMAT
DA
DAT
DA
DA
DA
DA
D1R
D2R
COMT
HVA
Postsynaptic neuron

Salles, 2021

DYT/PARK-GCH1 (AD) (Segawa disease)

The **most common** inherited dystonia in children

- Age at onset: 9-11
- 2.5-4 x more common in female

0.5 cases per million
5%–10% of primary dystonias in childhood and adolescence

- AD, penetrance is higher in women (87%) compared with men (35%)
- Average delay to diagnosis: 9.1---15.2

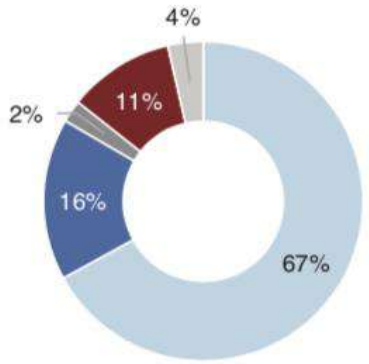
250 pathologic variants in GTP cyclohydrolase 1 (14q 22.1–22.2)

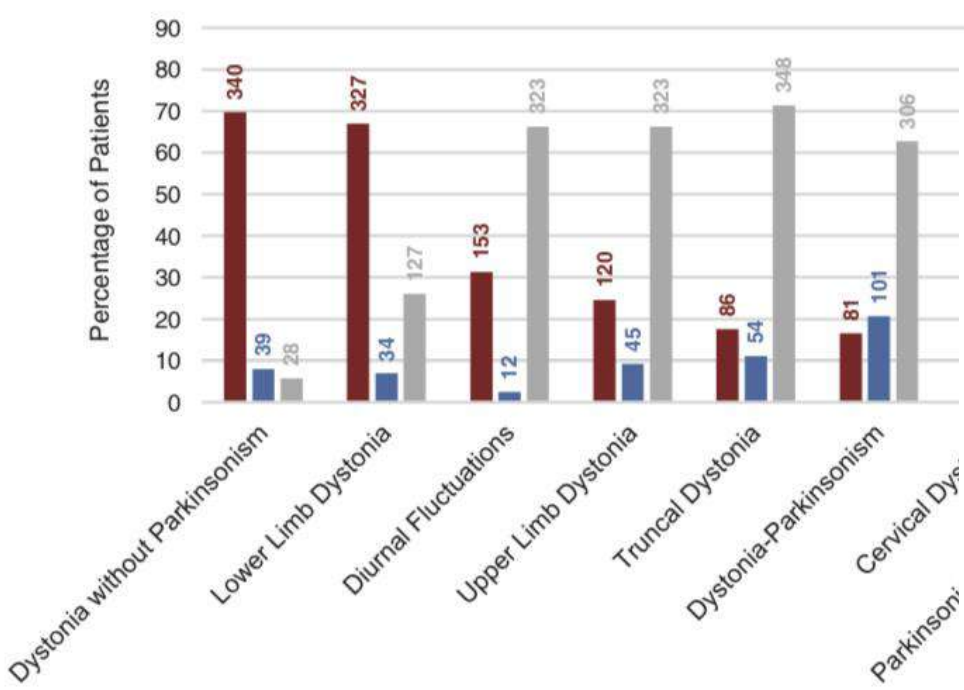
- Dystonia starts from lower limbs (esp. in early onset cases) and gait is disturbed
- Mild parkinsonism, brisk tendon reflexes
- *Diurnal fluctuations in motor symptoms (sleep benefit)* ***80-94%***
- Dramatic and sustained response to low-dose L-DOPA treatment (70-100%)
- Mostly misdiagnosed as cerebral palsy
- Mood disorders, generalized anxiety, agoraphobia, and obsessive-compulsive disorder (serotonin ptw dysfxn)

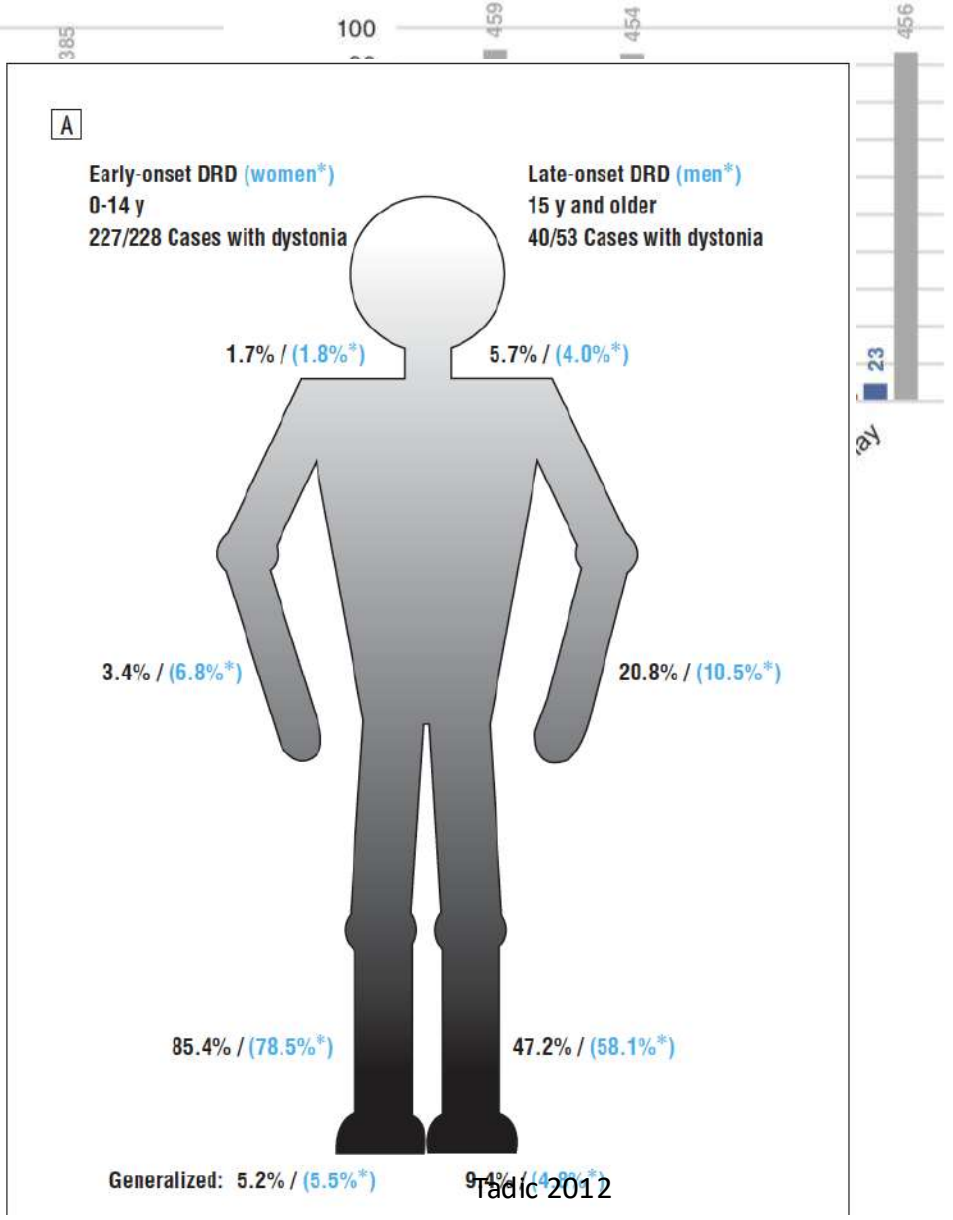
Every dystonia beginning in childhood should be investigated with an L-DOPA test (up to a maximum daily dose of 3 × 200 mg daily for up to 8 weeks)

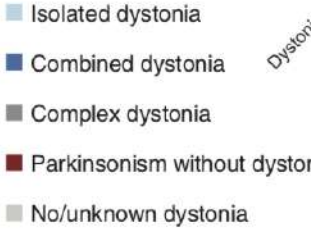
Autosomal dominant DYT/PARK-GCH1

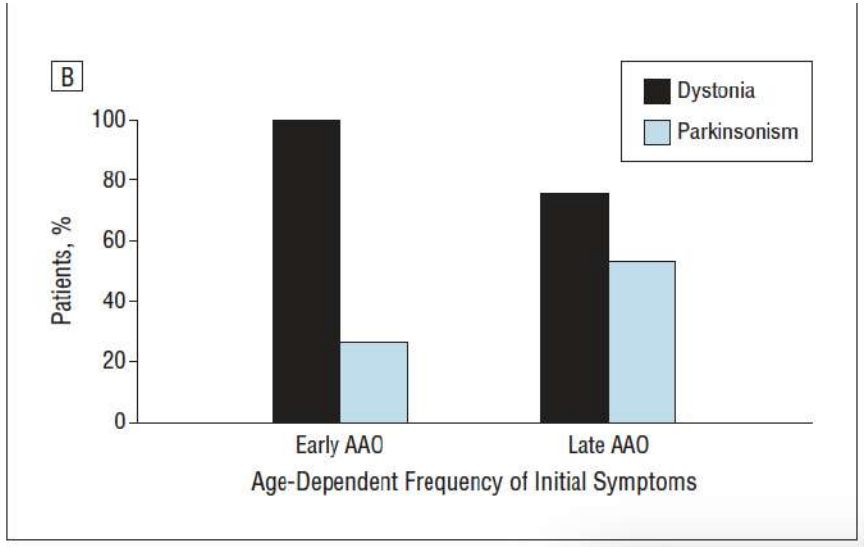
Weissbach, 2021



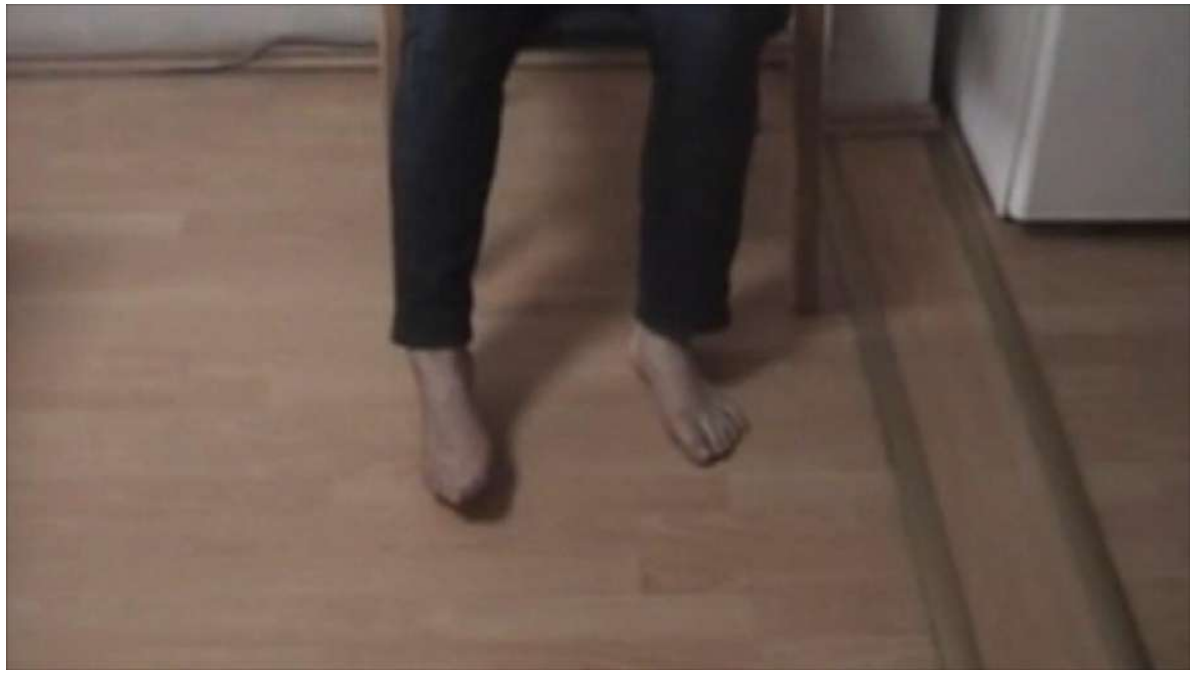








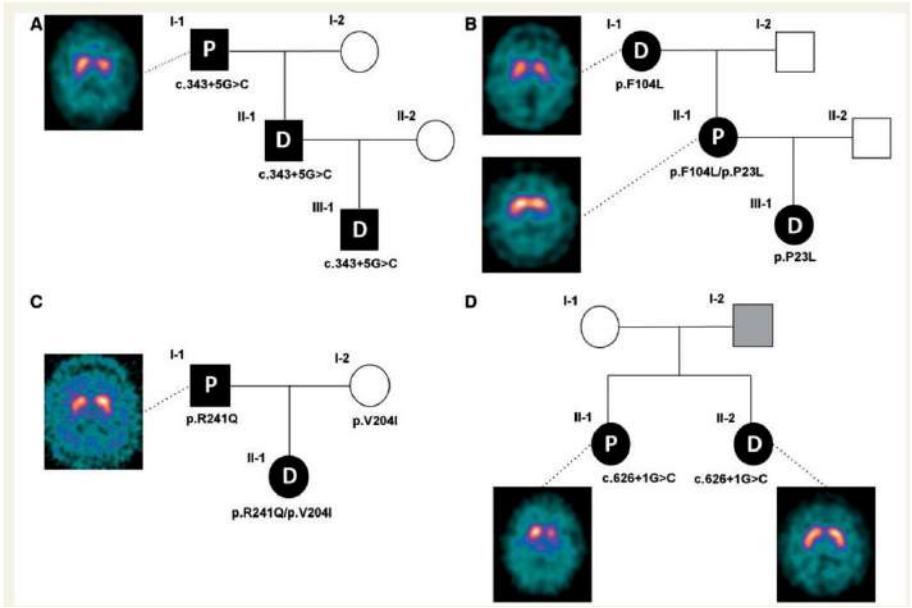
Tadic 2012



Hereditary dystonia and parkinsonism: two sides of the same coin?

Anne Weissbach and Christine Klein
Institute of Neurogenetics, University of Lübeck, Germany

Brain, 2014



- Rare GCH1 variants are associated with an increased risk for PD, 0.38% vs 0.1%
- Other monogenic dystonias may also be accompanied by signs of parkinsonism- DYT-TOR1A and MYOC-DYT-SGCE
- **Hypothesis:** GCH1 mutation carriers may be able to compensate for the effect of the mutation, i.e.haploinsufficiency of GCH1, for decades but later go on to develop neurodegeneration??

DYT/PARK-GCH1 (biallelic)

- Age at onset usually below 1 year (0-8 years)
- Truncal hypotonia, dystonia, with/without parkinsonism, autonomic dysfunction, seizures and developmental delay,
- Dystonia involves lower limbs (52%), trunk (40%) or upper limbs (20%)
- Dystonia is generalized (40%)
- Diurnal variation (+)
- Good response to L-dopa but may be delayed/incomplete, L-dopa induced dyskinesias may be observed in quarter of patients

Weissbach, 2021

DYT/PARK-TH

- AR, homozygous or compound heterozygous
- More severe condition associated with dopamine and norepinephrine deficiency
- Age at onset between 5 weeks after birth and 5 years
- Oculogyric crises, ptosis, hypersalivation, tremor, focal or generalized dystonia with crises, autonomic disturbance
- Diurnal variation (+)
- Good response to L-dopa but may be delayed/incomplete, frequent L-dopa induced dyskinesias
- Progressive hypokinetic-rigid syndrome with dystonia (type A), complex encephalopathy (type B), tremor, ptosis, spasticity, hypotonia, delayed motor developmental milestones, intellectual disability (proposed to be abandoned by iNTD registry study group in 2021 Nature Commun. Paper)

DYT/PARK-SPR (sepiapterin reductase)

- AR
- Motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises
- Diurnal fluctuations +
- L-DOPA response +

DYT/PARK-PTPS (*6-pyruvoyl tetrahydrobiopterin synthase deficiency)*

- Hypokinesia, ridigity, chorea, dystonia and oculogyric crisis
- Severe disease is associated with learning disabilities, epilepsy and psychiatric symptoms
- Detection of HPA may help early diagnosis
- Tx: BH4, levodopa and 5-hydroxytryptophan supplementation

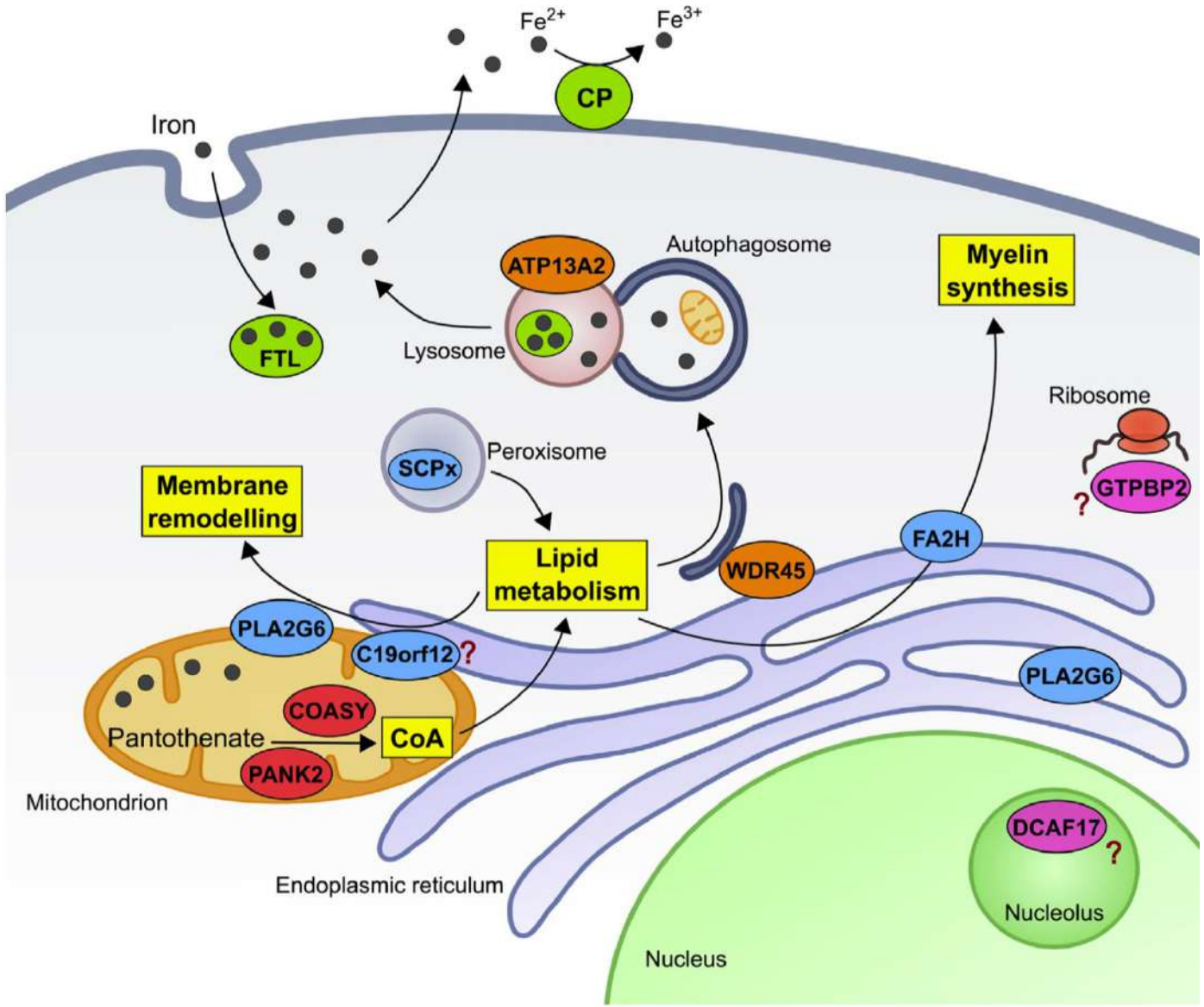
Dystonias combined with parkinsonism

Gene (previous DYT symbol)	Inheritance	Age at onset	Body region involved at onset	Distribution	Body parts involved	Additional features
ATP1A3 (DYT12)	AD and/or de novo	Btw 1st-4th decades	Oromandibular region and upper ext	Generalized/ segmental	Orofacial region, larynx, upper ext, neck, lower ext	• Rapid onset • Fluctuating course • Parkinsonism • Postural instability • Psychiatric symptoms
TAF1(DYT3)	X-linked	Btw 3rd-4th decades	Neck and oromandibular region	Generalized	Orofacial region, neck, upper ext, lower ext, body	• Parkinsonism • Striatal atrophy on MR
PRKRA (DYT16)	AR	Inbtw. 1st and 2nd decade	Lower ext, upper ext and larynx	Generalized	Orofacial region, larynx, neck, upper and lower ext, trunk	• Parkinsonism • Hyperreflexia

DYT/PARK-ATP1A3

- AD, 90% penetrance, de novo mutations are common
- Onset at in adolescence and early adulthood (4-58)
- **The condition manifests within minutes to days**
- Physical and psychological stressors may provoke (e.g., fever, childbirth, alcohol binging, fall, excessive exercise, heat exposure, and psychological stress)
- Rostrocaudal involvement is a hallmark: *orofacial dystonia, dysarthria, hypophonia, and dysphagia are more severe than upper limb dystonia, and the latter worse than the leg symptoms*
- Hemidystonia without bulbar involvement, paroxysmal dystonia, seizures, and nonmotor features (cognitive dysfunction, mood disorders, social phobia, psychosis)
- Parkinsonism (bradykinesia and postural instability)
- Plateau within 30–60 days after disease onset and persist thereafter with no or minimal improvement
- Few patients may experience a second exacerbation 1-9 years later

ATP1A3 c.1135G>C p.Asp379His variant (heterozygous)



- Mutations frequently affect the transmembrane N-terminal region
- The catalytic unit of the Na+/K+ pump, which breaks down ATP, is affected
- Neuronal loss in GP, STN, red nucleus, inferior olivary nuclei, cerebellum (Purkinje cell as well as granule cell layer), and in subcortical white matter tracts, SN is spared (Oblak et al. 2014)

Jinnah HA & Sun YV Neurobiol Dis 2019

DYT/PARK-TAF1

- **X-linked recessive** neurodegenerative dystonia-parkinsonism disorder (1976)
- Seen in people with Filipino ancestry, prevalent in Panay island, females are rarely affected
- Variable number of repeats of **hexameric sequence (CCCTCT)n in TAF1** gene encoding TATA-binding protein (TBP)-associated factor-1, a subunit that mediates transcription by RNA polymerase II
- Start as focal/segmental dystonia then transforms into generalized dystonia
- Dystonia predominant in the **cranio-cervical** region and in the limbs
- Parkinsonian symptoms are characterized by axial rigidity, bradykinesia and postural instability
- FDG-PET shows bilateral metabolic reductions in caudate/putamen, frontal operculum, and cingulate cortex with relative increases in the bilateral somatosensory cortex and cerebellar vermis (Niethammer et al., 2023), usually no abnormality on F-DOPA PET
- Pallidal DBS useful for dystonia but not as much for parkinsonism

Alonto&Jamora, 2024

DYT-PRKRA (Protein kinase, interferon-inducible double-stranded RNA-dependent activator)

- First defined in patients from southeast central Brasil, then also in patients from outside Brasil, rare
- AR, variants may lead to **altered endoplasmic reticulum stress,** characterized by delayed phosphorylation of eIF2-alpha
- **Young onset** progressive **generalized dystonia combined with parkinsonism**
- Dystonia is severe, with a sardonic smile, laryngeal involvement and opisthotonos
- On the other hand, **parkinsonian symptoms are mild**, non-responsive to L-DOPA and may be absent

Gene (previous DYT symbol)	Inheritance	Age at onset	Body region involved at onset	Distribution	Body parts involved	Additional features
SGCE(DYT11)	AD	1st-2nd decade	Neck and upper ext.	Focal and segmental	Neck, upper ext and orofacial region	• Marked myoclonic jerks involving the shoulder girdle • Motor symptoms improve with alcohol consumption • Psychiatric symptoms (depression, anxiety, and OCD)
KMT2B (DYT28)	AD and/or de novo	1st decade (inbtw. 1st and 2nd decade)	Upper and lower ext.	Mostly generalized, rarely focal	Orofacial region, larynx, neck, upper and lower ext, trunk	• Microcephalus • Short stature • Cognitive dysfunction • Disturbance in eye movements • Myoclonus • Dysmorfisms • Psychiatric signs • Systemic features
ADCY5	AD and/or de novo (rarely AR)	1st decade	Lower ext	Generalized	Orofacial region, neck, upper ext, lower ext, body	• Axial hypotonia • Growth retardation • Facial twitchings • Chorea • Myoclonus • Occulomotor apraxia • Intermittant worsening of symptoms with falling asleep and waking up

DYT/Myoc-SGCE

- The most common form of combined dystonia (2/million in Europe)
- AD, reduced penetrance, maternal imprinting
- Mutation in the epsilon-sarcoglycan gene affects the extracellular component of the protein
- Onset in childhood, average age 6
- Myoclonus primarily affecting the neck, shoulders, trunk, and upper extremities
- Focal or segmental dystonia appears later (in 2/3 of patients), mostly restricted to the upper part of the body (cervical dystonia and writer's cramp most common)
- Psychiatric comorbidities: anxiety, depression, alcohol dependency, and obsessive–compulsive disorders

DYT-KMT2B (*Lysine-Specific Histone Methyltransferase 2B)*

- Childhood-onset (typically before 10 years of age), AD
- Mostly *de novo* mutations, truncating and loss of fxn
- Onset usually with ***lower limb dystonia*** progressing into ***generalized dystonia***
- Adult-onset cases with hearing loss and intellectual diasability
- Varying combinations of dystonia, ***psychomotor developmental delay***, mild-to-moderate ***intellectual disability and short stature***
- Oculomotor abnormalities, microcephaly, characteristic facies
- Choreoathetosis, myoclonus and seizures

Onset at 8 yrs of age with inward twisting of left foot
Speech difficulty
Twisting of right foot
Learning difficulties (had difficulty in gainin literacy)
Short stature, microcephaly

- Heterozygous pathogenic frameshift deletion in KMT2B gene (c.3646_3653del variant)

Case No.	*KMT2B* Variant	Age at Symptoms Onset	Age at Surgery	Distribution of Dystonia Before Surgery	Improvement After Surgery
1[1]	Deletion: chr.19:35,017,972-36,307,788; de novo	2.5	7	Neck, larynx, BiLL, BiUL	Improvement of cervical and limb dystonia; loss of efficacy when off DBS for almost a year and functional recovery when switched on again
2[1]	Deletion: chr.19:35,414,997-37,579,142; de novo	4	6	Face, neck, larynx, BiLL, BiUL	Marked global improvement
3[1]	Deletion: chr.19:35,967,904-37,928,373; de novo	4	14	Face, larynx, BiLL, BiUL	Marked global improvement with independent walking
4[1]	c.6515_6518 delinCCCAA p.Val2172 Alafs*11; de novo	1	16	Face, larynx, BiLL, BiUL	Marked global improvement with independent walking
5[1]	c.8079del p.Ile2694Serfs*44; de novo	2	27	Face, neck, larynx, BiLL, BiUL	Improvement of cranial and cervical dystonia
6[1]	c.3528 + 2T > A; unknown	4	32	Face, neck, larynx, BiLL, BiUL	Sustained improvement in foot posture but only transient benefit to cervical and limb dystonia
7[1]	c.4955G > A p.Gly1652Asp; de novo	6	15	Face, neck, larynx, BiLL, BiUL	Marked global improvement with independent walking
8[1]	c.4986C > A p.Phe1662Leu; maternal	5	20	Face, neck, larynx, BiLL, BiUL	Marked global improvement with independent walking
9[1]	c.5114G > A p.Arg1705Gln; de novo	3	7	Face, neck, BiLL, BiUL	Marked global improvement
10[1]	c.5342T > C p.Leu1781Pro; de novo	8	19	Face, neck, larynx, BiLL, BiUL	Marked global improvement with independent walking
11[2]	c.6406delC p.Leu2136 Serfs*17; de novo	7	23	Face, neck, larynx, BiLL, BiUL	Marked global improvement
12[9]	c.4622C > T p.Ala1541Val; unknown	43	53	Face, neck, larynx, trunk, BiUL	Marked global improvement
13[9]	c.5336G > A p.Arg1779Gln; unknown	7	43	Face, neck, larynx, trunk, BiLL, BiUL	Marked global improvement
14[5]	c.309delG; de novo	7	16	Face, neck, larynx, trunk, BiLL, BiUL	Marked global improvement
15[5]	c.1656dupC; de novo	7	17	Neck, larynx, trunk, BiLL, BiUL	Marked global improvement; no improvement of laryngeal dystonia
16[5]	c.3325dupC; de novo	5	13	Neck, larynx, trunk, BiLL, BiUL	Partial improvement; no improvement of laryngeal and axial dystonia

Variable expressivity of *KMT2B* variants at codon 2565 in patients with dystonia and developmental disorders

Antonia M. Stehr[a,1], Jan Fischer[b,1], Nazanin Mirza-Schreiber[a,c,1], Katerina Bernardi[d,e], Joseph Porrmann[b], Philip Harrer[a,f], Frank Kaiser[g], Rami Abou Jamra[h], Juliane Winkelmann[a,f,i,j], Robert Jech[k], Anne Koy[e,l], Konrad Oexle[a,c,f], Michael Zech[a,f,m,*]

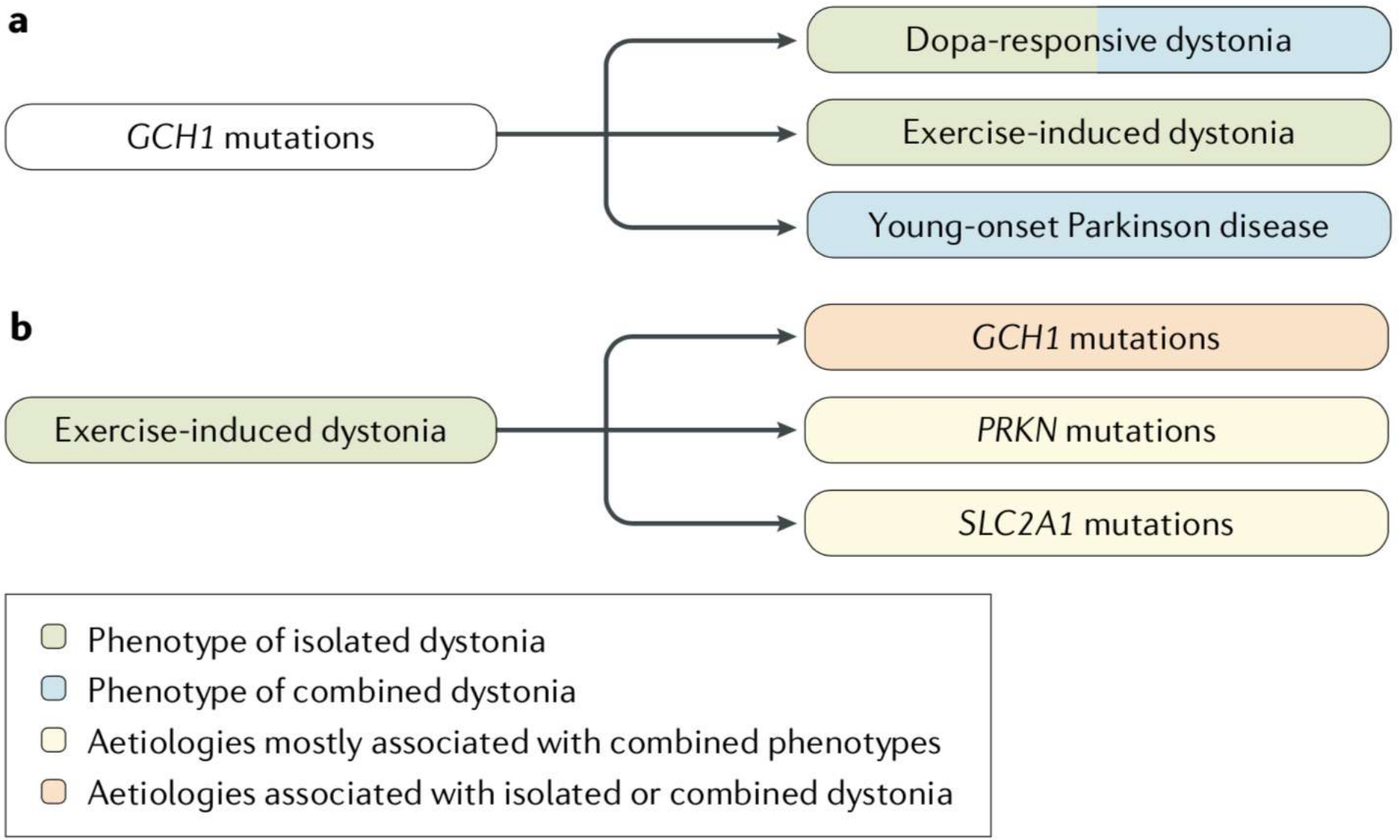
Represents 10% of childhood onset dystonia

Cao et al., 2019

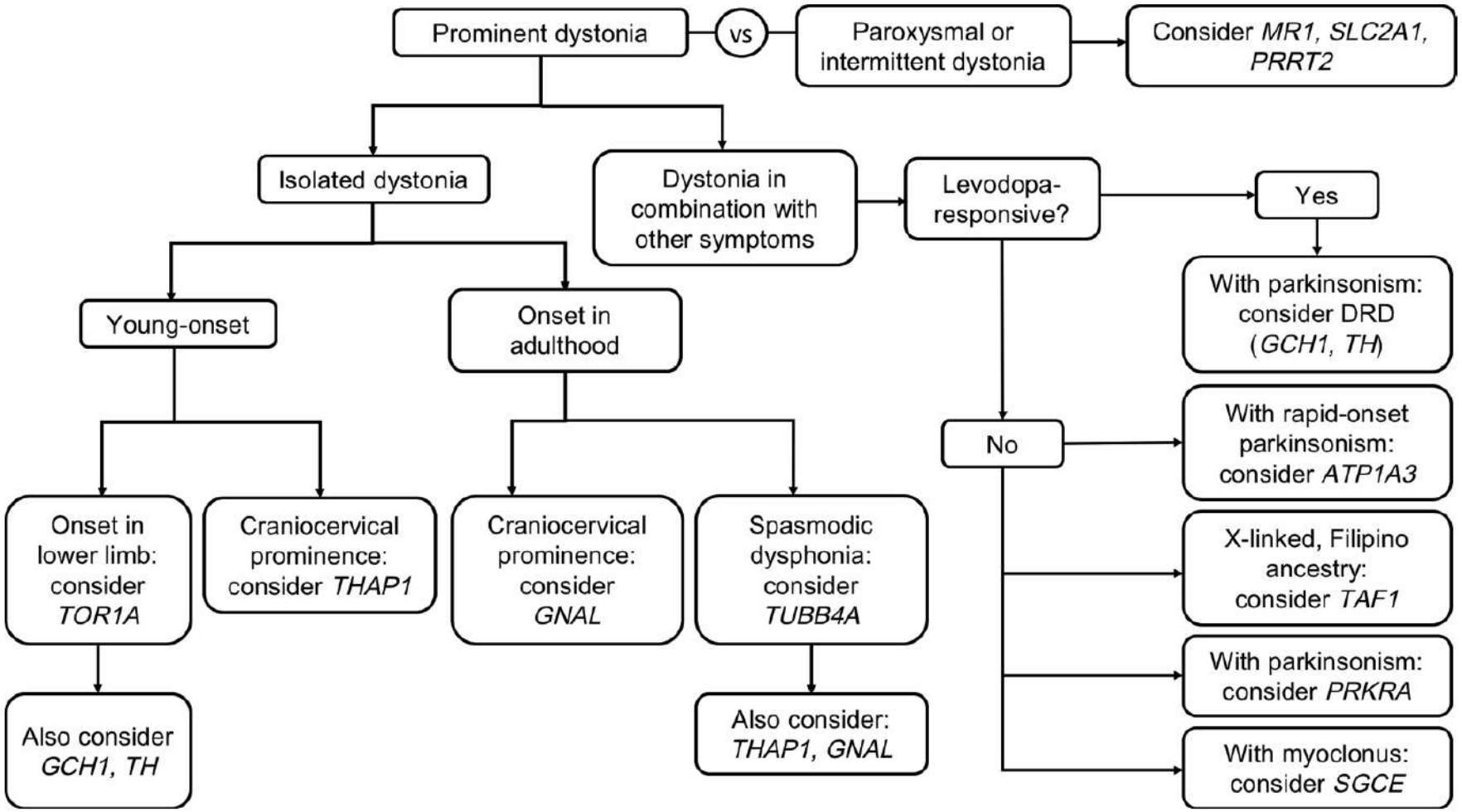
Paroxysmal dyskinesia/dystonia

- Paroxysmal non-kinesigenic dyskinesia/ dystonia (MR1 mutation)
- Paroxysmal kinesigenic dyskinesia/ dystonia (PRRT2 mutation)
- Paroxysmal exercise-induced dyskinesia/ dystonia (SLC2A1 mutation)

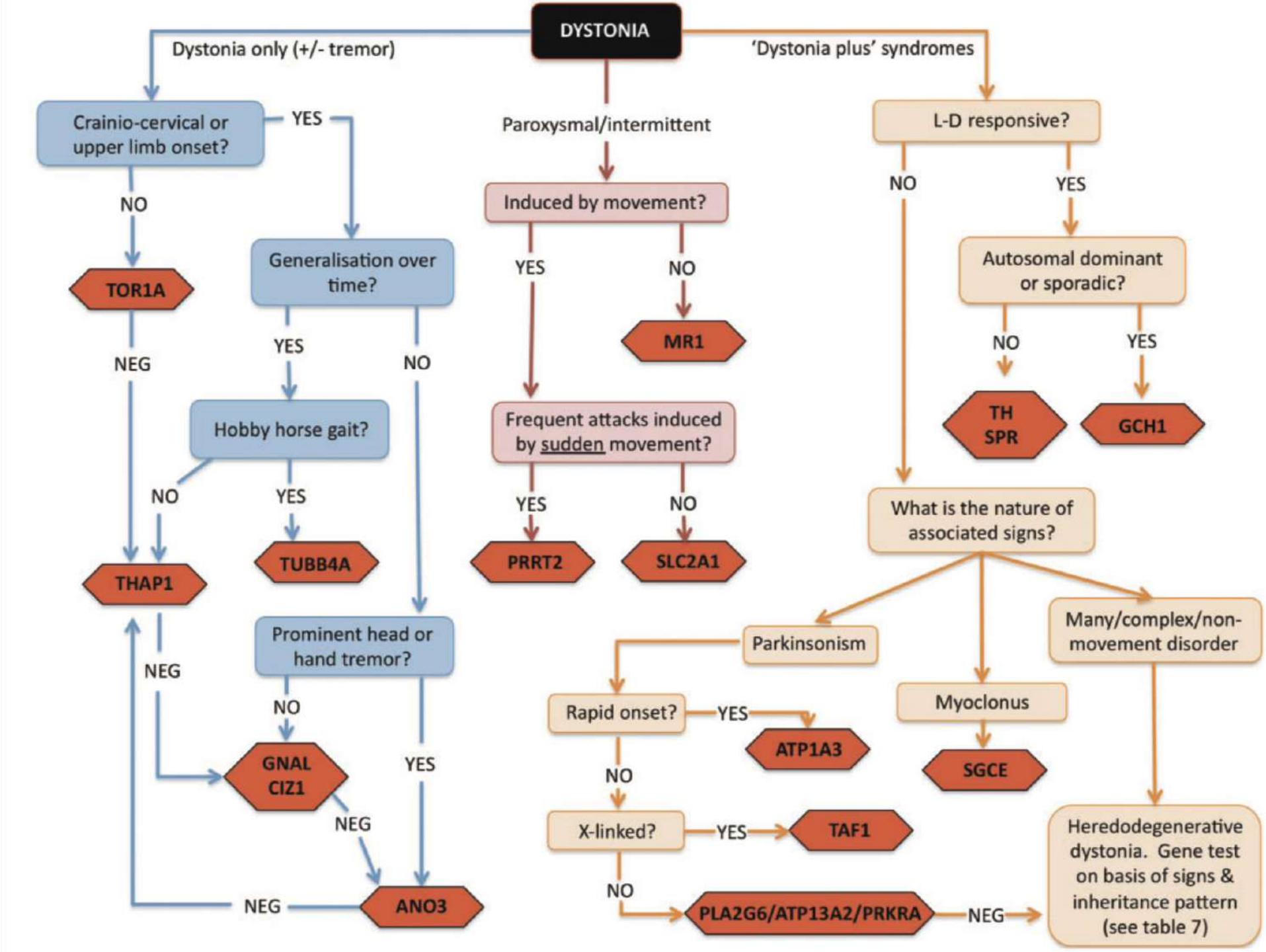
	Paroxysmal kinesigenic dyskinesia (PKD)	**Paroxysmal non-kinesigenic dyskinesia (PNKD)**	**Paroxysmal exercise-induced dyskinesia (PED)**
Trigger	Sudden movement	Alcohol, coffee, tea, spontaneous	Long duration exercise
Duration	Seconds to few minutes	Minutes to days	5–30 minutes
Typical movement pattern	Dystonic, choreatic, ballistic	Dystonic	Dystonic
Frequency	Several per day	Few per day to some per year	1/day to 2/month
Age at onset	7th–4th year of age	Earlier than PKD	9th–15th year of age
Gender ratio	Male ≫ female	Male > female	Male > female
Treatment	Antiepileptic drugs	Avoidance of triggers	Avoidance of long duration exercise



Balint B. 2018 Nat Rev



Grütz&Klein, 2021



Charlesworth ve ark. Brain 2013

Complex dystonia

- Sustained dystonia at rest
- Prominent tongue, perioral involvement
- Developmental delay or cognitive impairment
- Spasticity, ataxia, bulbar involvement including anarthria
- Visual impairment, oculomotor disturbances, hearing loss, or seizures

- Dystonia in children is complex in about 50% of cases and tends to generalize (Marsden and Harrison 1974)
- In 80% of patients w. generalized dystonia, onset <15 yr.s of age
- Clinical red flags for neurodegenerative complex dystonia:
  - Prominent bulbar involvement
  - Rapid progression of dystonia
  - Oculomotor signs
  - Associated hearing problems/vision loss
  - Cognitive decline and behavioral abnormalities
- Often **acute onset after metabolic decompensation** leading to basal ganglia damage
- More insidious and progressive course is also possible
- In most cases **continuous temporal pattern**, but can also very well be paroxysmal or influenced by intercurrent illnesses, fatigue, exercise, or eating/fasting

Kuiper et al., 2016

Disease	Gene	Major features besides dystonia
Autosomal dominant		
Autosomal recessive		
Ataxia-telangectasia	*ATM*	Ataxia, oculomotor apraxia, telangiectasia, susceptibility to malignancy.
Choreoacanthocytosis	*VPS13A*	Chorea, orofacial dyskinesias, cognitive decline, axonal neuropathy
Ceroid-lipofuscinosis	*Multiple genes*	Visual failure, cerebral atrophy and seizures
Dystonia with brain manganese deposition	*SLC30A10*	Hepatic cirrhosis, polycythemia and hypermanganesaemia.
Fucosidosis	*FUCA1*	Mental retardation, growth retardation, dysostosis multiplex,
X-Linked		
Dystonia-deafness syndrome	*TIMM8A*	Progressive hearing loss, spasticity, cortical blindness
Lesch-Nyhan syndrome	*HPRT*	Choreoathetosis, ballismus, cognitive and attentional deficits, self-injurious behaviours
Lubag disease (DYT3)	*TAF1*	Parkinsonism
Pelizaeus-Merzbacher disease	*PLP1*	Pyramidal dysfunction, cerebellar ataxia, head tremor
Rett syndrome	*MECP2*	Mental retardation, motor regression, autistic behaviours, seizures
Static encephalopathy of childhood with neurodegeneration in adulthood	*WDR45*	*De novo* inheritance pattern, global developmental delay, parkinsonism and dementia
Mitochondrial		
Leber's optic neuropathy	*ND1, ND4, ND6*	Bilateral or sequential visual failure
Leigh syndrome	Multiple genes	Optic atrophy, ophthalmoplegia, ataxia, spasticity and developmental delay/regression. May also be autosomale recessive inheritance.
Myoclonic Epilepsy with Ragged Red Fibres (MERRF)	Mainly *tRNA(lys)* but others reported	Epilepsy, short stature, hearing loss

Balint et al., 2018

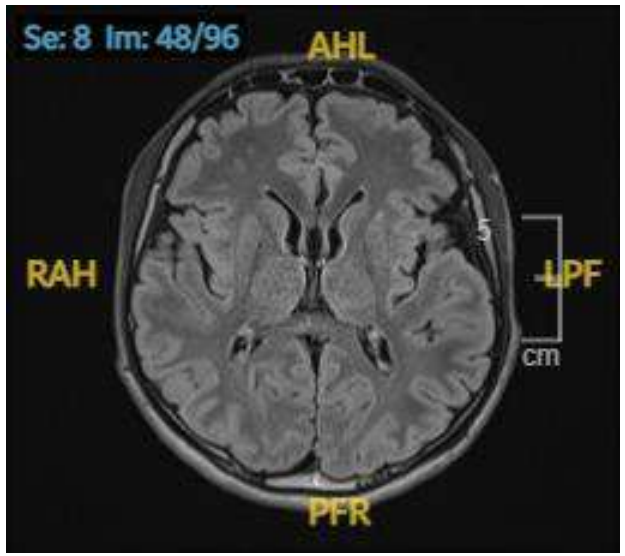
	Disease	Gene (MOI)	Characteristics / diagnostic clues
Typically adult-onset	Neuro-acanthocytosis	*VPS13A1* (AR, possibly AD)	Lingual dystonia; intermittent head drop; acanthocytes in blood smear, elevated CK
	Primary familial brain calcification	*PDGFB* (AD), *PDGFRB* (AD), *SLC20A2* (AD), *XPR1* (AD), *MYORG* (AR)	Calcifications in basal ganglia, white matter, and cerebellum
	Wilson's disease	*ATP7B* (AR)	Hepatobiliary disease, Kaiser-Fleischer corneal ring, low ceruloplasmin plasma level
	NBIAs (see Table 2)	*FTL* (AD), *CP* (AR)	MRI-abnormalities predominantly in the basal ganglia
	Leber's hereditary optic neuropathy "plus"	Pathogenetic variants in mtDNA (*MT-ND1, MT-ND2, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-CYB, MT-CO1, MT-CO3, MT-AP6*)	Optic nerve changes in fundoscopy
	POLG-related disorders	*POLG* (AD/AR)	Progressive external ophthalmoplegia, ataxia, neuropathy; hepatobiliary disease
Variable onset	DRPLA	*ATN1* (AD)	Juvenile: myoclonic epilepsy and intellectual deficits Adult: ataxia, chorea, myoclonus, dementia Symmetrical, diffuse white matter, thalamic and pallidal lesions on T2-weighted images; atrophy of cerebellum and pontine tegmentum
	NBIAs (see Table 2)	*CP* (AR), *FLT1* (AD), *PANK2* (AR), *COASY* (AR), *PLA2G6/iPLA2* (AR), *C19orf12* (AR), *FA2H* (AR), *WDR45* (XL), *CRAT* (AR), *REPS1* (AR), *AP4M1* (AR), *GTPBP2* (AR)	Iron accumulation predominantly in the basal ganglia
	Niemann-Pick type C	*NPC1, NPC2* (AR)	Supranuclear gaze palsy, splenomegaly, increased oxysterol blood levels
	GM1/GM2-Gangliosidosis	*GLB1, GM2A* (AR)	Infantile/juvenile: severe mental retardation, seizures, spastic tetraparesis Adult: dysarthria, gait disturbance MRI: hyperintensity of caudate nucleus and putamen

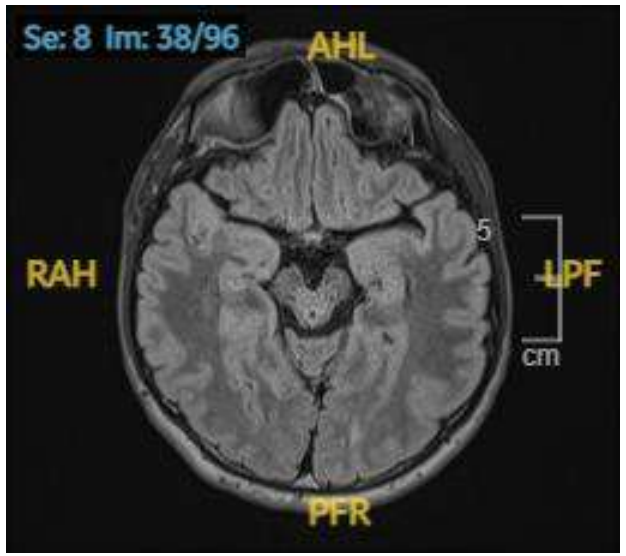
Complex dystonias: an update on diagnosis and care

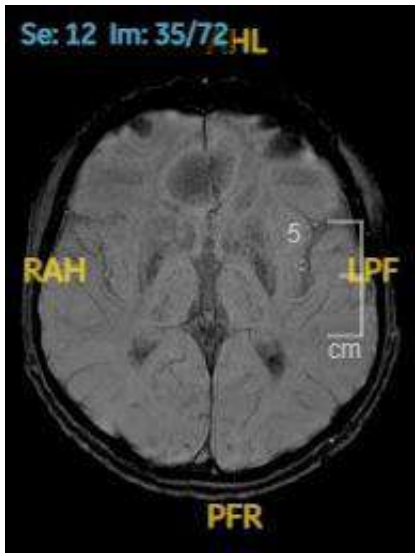
Rebecca Herzog[1] · Anne Weissbach[1] · Tobias Bäumer[1] · Alexander Münchau[1]

Journal of Neural Transmission (2021) 128:431–445

45 yr.s old
Diagnosed at age 8
Neurological symptom onset at age 31, with speech impairment, drooling, difficulty lifting a spoon to the mouth and unsteady gait
Parents are first degree relatives
Two siblings died at early ages
Ceruloplasmin 2.89 mg/dL, last 24-hour urine copper 370 µg/day
Previously treated with D-penicillamine
Trientine 3x250 mg and zinc 3x1
Speech-language therapy and clonazepam were recommended

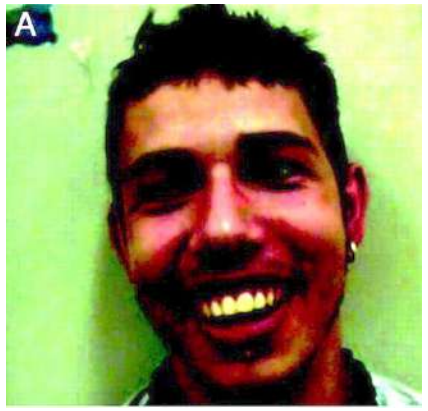






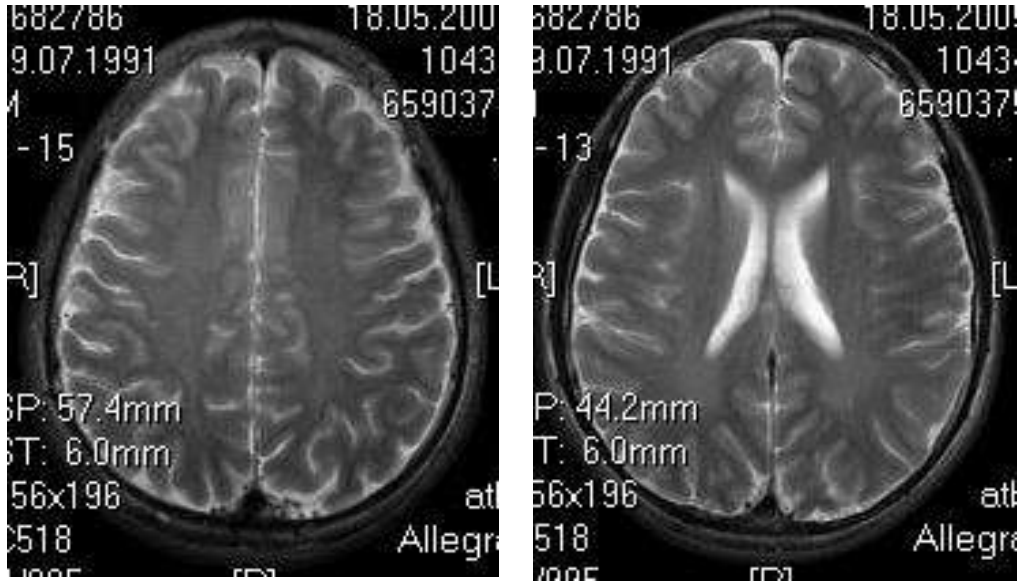
Dystonia in Wilson Disease

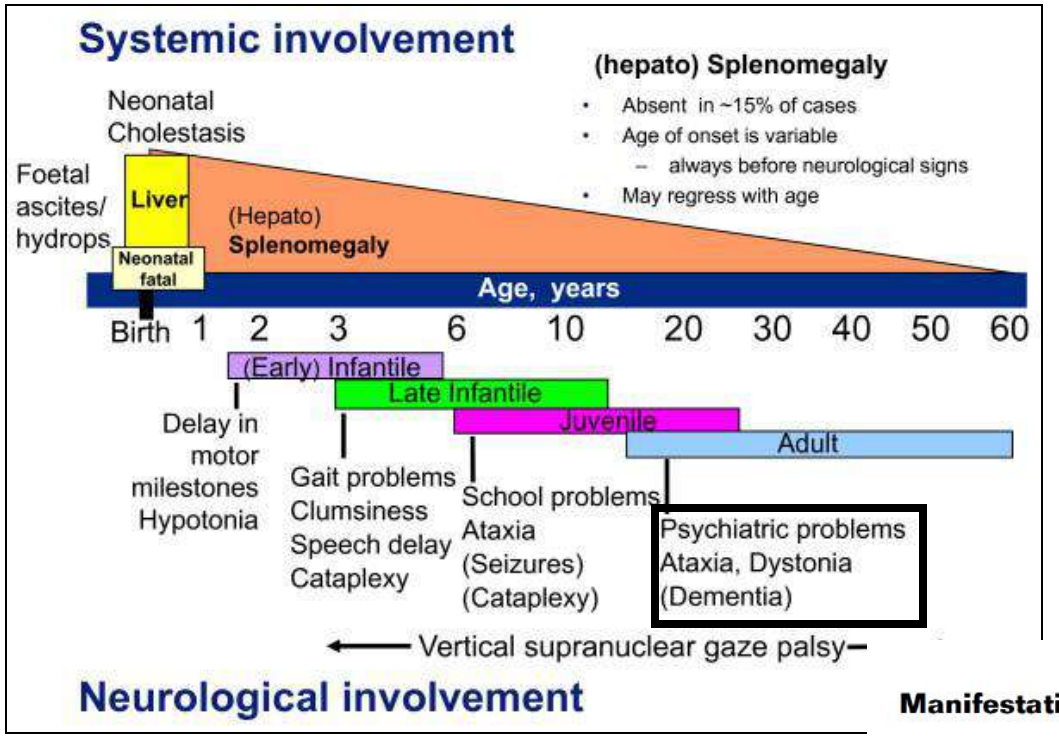
- The most severe, most disabling, and most resistant (to tx) symptom in WD
- **11-65% of the initial** symptoms, **38-65%** prevalence throughout the course of the disease
- Can be focal, segmental, multifocal, and generalized
- The face is the most commonly affected region (risus sardonicus—a sardonic facial expression resulting from dystonic contraction of the facial muscles).
- Neck, hands (writer's cramp), legs, tongue, and upper face (blepharospasm)
- Respiratory muscles, tongue, lips, and throat may be affected—dysarthria, sialorrhea
- Drug-induced dystonia is also more common



Cetlin, Neurology 2009

- 31 years old
- Age at symptom onset : 13.5 (dx at 18 yr.s)
- No consanguinity
- Vertical supranuclear gaze palsy, ataxia, pyramidal signs, seizures, insomnia, dysphagia
- Organomegaly absent
- Genotype *NPC1*
- *Treatment: Miglustat, LEV*





Patterson MC et al.Orphanet J Rare Dis. 2013; 8: 12

- Among adults, movement disorders have been reported in **58–62%** of patients.
- **Dystonia**, the most common movement disorder in NPC, is reportedly more commonly in adults than children.

Bonnot, et al., 2018, Sevin, et al., 2007

Neurological features in NPC cohorts

Manifestation (%)	Cohort (N)			
	Patterson et al. 2020,[25] all NPC (448)	Nadjar et al. 2018,[38] adult NPC (47)	Pineda et al. 2019,[39] all NPC (63)	RUMC cohort,* all NPC (53)
Ataxia	68	91	70	50
VSGP	67		80	90
Dysarthria	65	87	76	62
Cognitive/learning impairment	63	87	57	81
Dysphagia	49	80		58
Dystonia	40		41	38
Seizures	26	9	41	36
Clumsiness	21		75	25
Cataplexy	19	11	28	21
Behavioral issues	14		14	8
Psychiatric symptoms	11	34	24	11
Hearing Loss		33		26
Sleep disturbance	8			19

*All patients seen at Rush University Medical Center at baseline visit prior to entering treatment studies or for clinical management from 2013 to 2020.

Adult-onset NP-C cases presenting with movement disorders

References	Number of patients	Gender (n)	Age of Onset (years)	Movement phenotypes (n)
Wherett and Rewcastle [1]	2	M (2)	4	Ataxia (2)
Horoupian and Yang [2]	1	F (1)	18	Ataxia (1)
Breen et al. [3]	1	M (1)	20	Ataxia (1), Dystonia (1)
Longstreth et al. [4]	1	M (1)	23	Ataxia (1), Dystonia (1)
Elleder et al. [5]	1	F (1)	26	Ataxia (1), Dystonia (1) and Parkinsonism (1)
Yan-Go et al. [6]	1	F (1)	18	Ataxia (1), Chorea (1) and Parkinsonism (1)
Vanier et al. [7]	2	NA	28, 59	Ataxia (2)
Fink et al. [8]	1	M (1)	18	Ataxia (1), Dystonia (1)
Vanier et al. [9]	2	F (2)	34, 36	Ataxia (2), Chorea (1)
Hulette et al. [10]	1	F (1)	32	Ataxia (1), Parkinsonism (1)
Shulman et al. [11]	1	M (1)	30	Ataxia (1), Dystonia (1), Chorea (1), Parkinsonism (1)
Love et al. [12]	4	M (4)	25, 33, 33, 25	Ataxia (1), Chorea (1), Parkinsonism (3)
Grau et al. [13]	1	F (1)	30	Ataxia (1)
Lossos et al. [14]	3	M (2), F (1)	28, NA, NA	Ataxia (3)
Campo et al. [15]	1	M (1)	16	Ataxia (1)
Yamamoto et al. [16]	1	M (1)	25	Ataxia (1), Dystonia (1)
Imrie et al. [17]	12	M (5), F (7)	22, 20, 18, 18, 24, 19, 16, 17, 18, 22, 25, 38	Ataxia (11), Dystonia (7), Chorea (2)

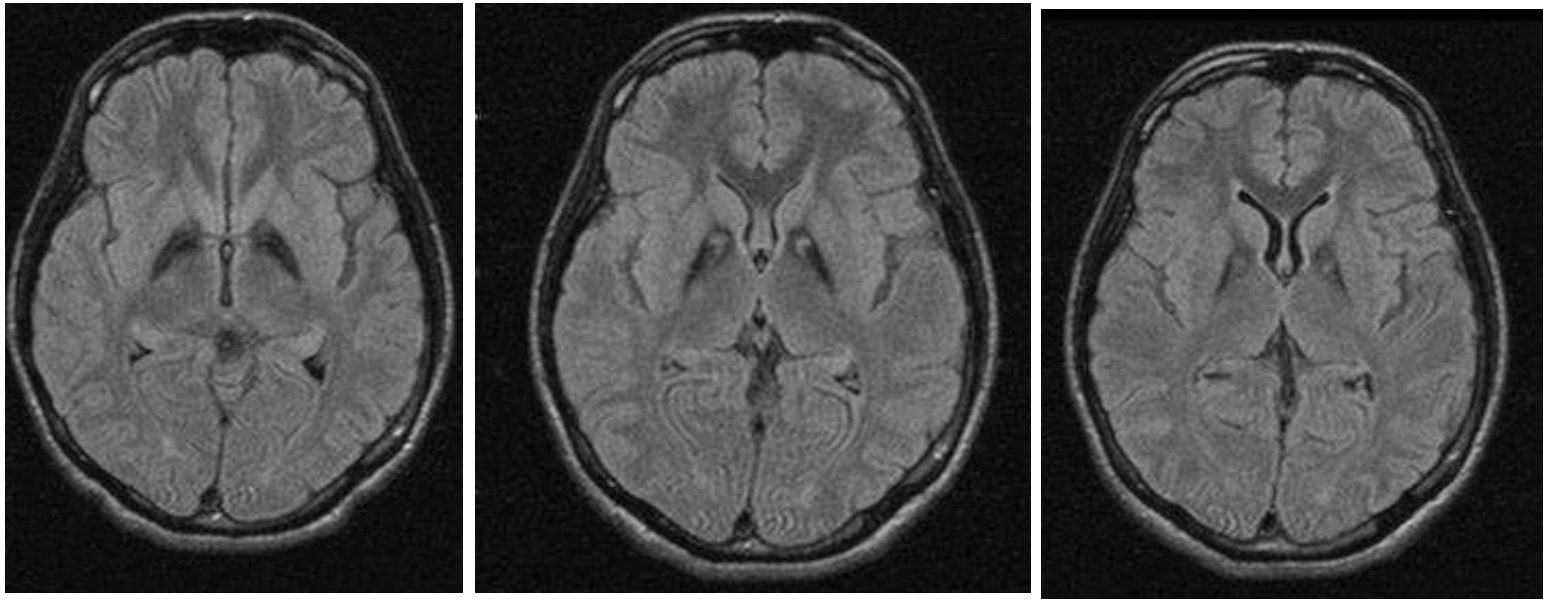
Klu¨nemann et al. [18]	2	F (2)	40, 35	Ataxia (2), Chorea (1)
Josephs et al. [19]	2	F (2)	29, 27	Ataxia (2), Dystonia (2), Parkinsonism (1)
Lachmann et al. [20]	1	F (1)	25	Ataxia (1), Dystonia (1)
Sullivan et al. [21]	1	M (1)	25	Dystonia (1)
Trendelenburg et al. [22]	1	F (1)	53	Dystonia (1)
Walterfang et al. [23]	3	M (3)	15, 16, 18	Ataxia (2), Dystonia (2)
Sevin et al. [24]	12	M (7), F (5)	16, 30, 15, 16, 34, 28, 16, 17, NA, 17, 19, 17	Ataxia (10), Dystonia (6), Chorea (1), Myoclonus (1)
Anheim et al. [25]	1	F (1)	50	Ataxia (1), Myoclonus (1)
Abela et al. [26]	4	F (4)	27, 22, 46, 19	Ataxia (4), Dystonia (1)
Koens et al. [27]	3	M (2), F (1)	18, 52, 40	Ataxia (3), Dystonia (2), Myoclonus (2)
Eggink et al. [28]	1	M (1)	52	Myoclonus (1)
Rodriguez-Quiroga et al. [29]	2	M (1), F (1)	40, 17	Chorea (2)
Devaraj et al. [30]	3	M (2), F (1)	25, 38, 20	Ataxia (3), Dystonia (3)
Mohamed et al. [31]	1	M (1)	34	Ataxia (1), Tremor (1)

Movement disorders in cerebrotendinous xanthomatosis

Bianca M.L. Stelten[a,b,*], Bart P.C. van de Warrenburg[c], Ron A. Wevers[d], Aad Verrips[b]

Demographic characteristics	
M/F/unknown	30/29/3
Mean age CTX diagnosis	35 ± 11 years (median 36, range 14–67 years)
Mean age diagnosis movement disorder	40 ± 12 years (median 40, range 13–62 years)
Classic systemic CTX features	
Cataract	51 (82%)
Diarrhoea	19 (31%)
Tendon xanthomas	47 (76%)
Classic neurological CTX features	
Cognitive impairment	54 (87%)
Pyramidal signs	46 (74%)
Cerebellar signs	42 (68%)
Polyneuropathy	28 (45%)
Psychiatric signs	23 (37%)
Epilepsy	18 (29%)
Movement disorders	
Dystonia	19 (31%)
Cervical	1
Blepharospasm	2
Oromandibular	5
Limb	15
Myoclonus	11 (18%)
Palatal	5
Limb	6
Postural tremor	6 (10%)
Parkinsonism/Parkinsonian symptoms	32 (52%)
Symmetric/Asymmetric	6/16
Rigidity	23
Bradykinesia/Hypokinesia/Akinesia	26
Hypophonia	9
Hypomimia	15
Rest tremor	11
Postural instability	7
Extrapyramidal signs, not specified	10 (16%)
Gait disturbances	28 (45%)
Falls	11 (18%)

- Speech difficulty since the age of 7, due to difficulty in producing sound
- Widespread painful spasms that have increased in recent years
- Pronounced spasms in the right arm, torso, and neck
- Difficulty in gait
- Difficulty eating due to involuntary opening of the jaw (especially chewing difficulties)
- Struggling to sit unsupported due to backward spasms



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ORIGINAL ARTICLE

Long-Term Outcomes of Deep Brain Stimulation in Pantothenate Kinase-Associated Neurodegeneration-Related Dystonia

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Table 1. Demographics and clinical characteristics of the patients

	Patients									
	A	B	C	D	E	F	G	H	I	J
Sex	F	F	M	M	M	F	M	M	M	M
Onset age (yr)	9	1	2	2	2	11	15	21	25	45
DBS age (yr)	10	7	9	10	13	18	16	26	54	47
PKAN type	Classic	Classic	Classic	Classic	Classic	Unknown	Atypical	Atypical	Atypical	Atypical
Family history	None	Sister of C	Brother of B	Younger brother with *PANK2* mut	Younger brother died of HSD	None	Younger brother with *PANK2* mut	None	Unclear	None
Clinical course (age, yr)	Falling → generalized dystonia, bedridden (10)	Dev delay → tiptoeing (5) → generalized dystonia, bedridden (6)	Dev delay → tiptoeing (6) → generalized dystonia (8)	MR → tiptoeing (8) → generalized dystonia (10)	Language delay, falling → generalized dystonia (9)	Rt. hand dystonia → craniocervical & limbs dystonia over years	Rt. hand dystonia → generalized dystonia (16)	Rt. arm dystonia Mild dystonia in both legs	Writer's cramp → propagation to all limbs over 20 years	Rt. arm dystonic tremor, jaw dystonia, slowly progressive
Limb/Truncal dystonia	+/+	+/+	+/+	+/+	+/+	+/-	+/+	+/-	+/+	+/-
Dysphagia	+	+	+	+	+	+	+	-	+	-
Cognitive impairment	+	+	+	+	+	+	+	-	-	-
Other findings	Respiratory failure, retinopathy	Severe retrocollis	Scoliosis	Status dystonicus	Choreoathetosis	Severe dystonic posturing	Impulse control disorder	Rt. arm myoclonus, tremor	Weakness, both legs	Both hands tremor
Medical treatments	TBZ, DZP	THX, DZP	THX, DZP	MDZ div, DZP, QTP, THX, HPD	DZP, THX, ZNS, BCF, CNZ, HPD	CNZ, THX	THX, CNZ, BCF	DZP, THX, BCF	ALP, BCF, CNZ, THX, Levodopa	CNZ, THX, ECT
DBS date	Sep 2010	Jul 2015	Sep 2015	Oct 2012	Dec 2007	Jan 2015	Jul 2009	Nov 2011	May 2009	Feb 2019
Length of follow-up										
BFMDRS (mo)	120	60	60	45	12	6	84	72	24	24
Clinical follow-up (mo)	128 (FU+)	71 (FU+)	69 (FU+)	56 (FU lost)	27 (Expired)	75 (FU+)	100 (FU lost)	78 (FU lost)	62 (FU lost)	24 (FU+)
Last status	Bedridden	Assisted gait	Wheelchair ambulation	Assisted gait	Expired	Assisted gait	Assisted gait	Independent	Assisted gait	Independent
Major clinical events and surgery-related adverse events (mo)	Status dystonicus (1 mo) Respiratory failure (22 mo)	Wound dehiscence and infection (1 mo) s/p wound revision, Rt. hip subluxation s/p operation (34 mo)	Brain abscess s/p Lt. electrode removal (5 mo) Recurrent seizure with polyspike-and-waves, both frontotemporal (43 mo)	Recurrent wound dehiscence and MRSA infection s/p wound revision, s/p DBS removal (19 mo) s/p GKS, both GPi (20 mo)	Pneumonia (23 mo) followed by sepsis and status Dystonicus (27 mo)	Hospitalized due to painful dystonia (62 mo) Improved after battery change	Blepharospasm (4 day, reversed) Jaw opening dystonia and falling (54 mo) Improved after battery change	None	Aggravation of dystonia (40 mo) Improved after battery change, hospitalized due to limb tremor aggravation (62 mo)	None
Stimulation parameters (Rt.)*	4.3 V, 120 μs/60 Hz	3.0 V, 60 μs/130 Hz	3.3 V, 60 μs/90 Hz	-	2.6 V, 120 μs/185 Hz	4.1 V, 60 μs/130 Hz	3.5 V, 60 μs/130 Hz	3.2 V, 90 μs/130 Hz	2.6 V, 90 μs/130 Hz	2.0 V, 60 μs/130 Hz
Stimulation parameters (Lt.)*	4.5 V, 120 μs/60 Hz	3.5 V, 60 μs/130 Hz	-	-	2.8 V, 120 μs/185 Hz	4.2 V, 60 μs/130 Hz	3.5 V, 60 μs/130 Hz	3.2 V, 90 μs/130 Hz	3.6 V, 120 μs/130 Hz	2.1 V, 60 μs/130 Hz

- He injured his left hand while cutting wood with an axe
- He was operated by orthopedics following this injury but his left hand never became functional again
- Later on he had difficulty swallowing
- He had stuttering starting from early childhood, at this stage his speech was also disturbed, started to have articulation problems
- Rapid progression in 2-3 years
- He needed a PEG due to feding problems
- The most disturbing problem is jaw closing dystonia and tongue and cheek biting
- PANK2 homozygous mutation (R278L)

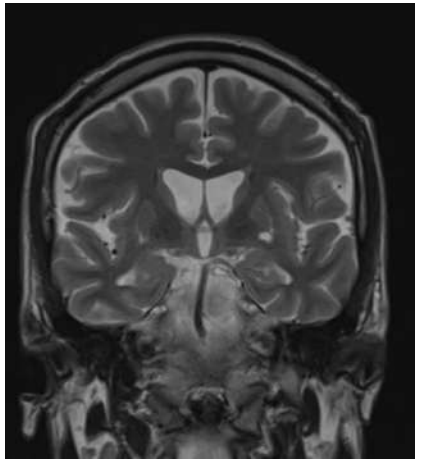
DYT-VAC14

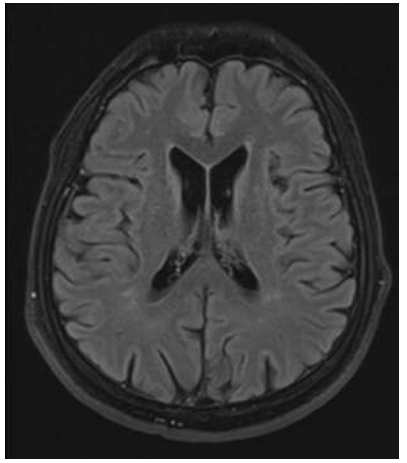
- Childhood onset, AR Generalized dystonia
- Clinically heterogeneous; dystonia, parkinsonism, growth delay, retinitis pigmentosa
- May rapidly generalize, first involve ext
- L-DOPA does not help; DBS may be effective
- Brain MEG reveals iron accumulation in the GP

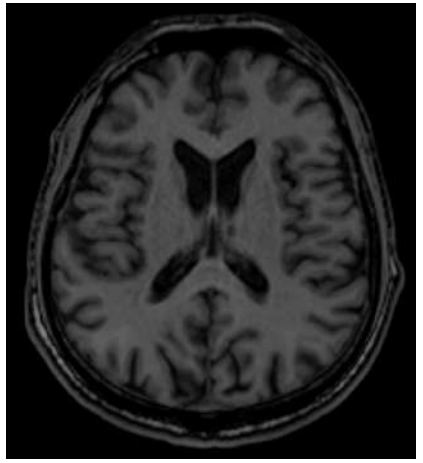
38 years old, male

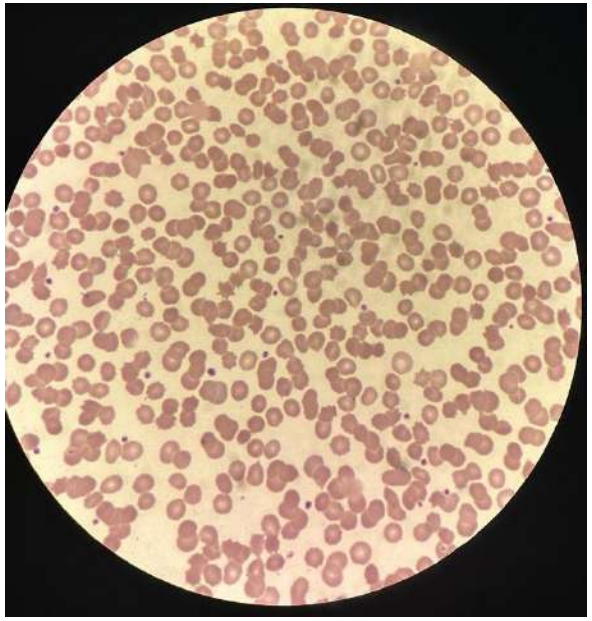
Difficulty in speech and gait, vocal tics like throat clearing and involuntary swearing

Difficulty in feeding









Dysarthria
Tics such as throat clearing
Deep tendon reflexes hypoactive in the lower extremities
Motor impersistence
Bilateral choreic movements in the distal lower extremities
Frequent blinking
Jaw-opening dystonia
Dystonic gait

Homozygous pathogenic variant in VPS13A1 gene

Woodhouse-Sakati Syndrome

- Rare, AR neuroendocrine disorder
- Biallelic pathogenic variants in the DCAF17 gene (at least 13 different variants)
- The most common mutation, c.436delC, is especially prevalent in Arab populations
- Hypogonadism, alopecia, diabetes mellitus, intellectual disability and progressive extrapyramidal symptoms
- Additional features: hearing loss, hypothyroidism, ECG abnormalities and distinctive facial dysmorphism

- 21 years old
- Generalized slowness at age of 16
- Hypophonic, hypokinetic dysarthria, bradymimia
- Rest tremor of left hand
- Bilateral moderate bradykinesia
- Prominent dystonia of both feet (R>L) + cervical dystonia
- CAG repeat number in huntingtin gene: 69
- Westphal variant of Huntington disease

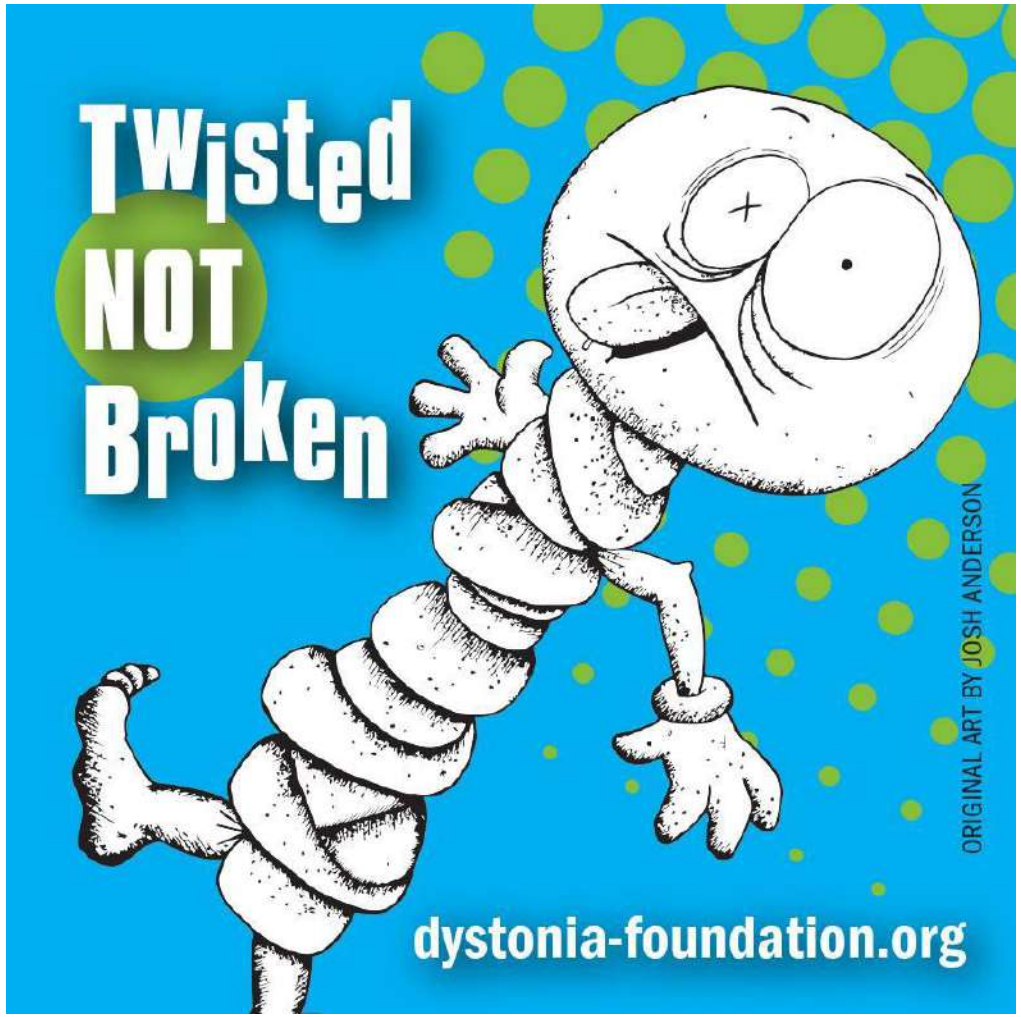
Why is it important to diagnose complex forms of dystonia?

- Not to miss a treatable cause!!

- Unexplained diseases, quality of life of caregivers, particularly mothers of affected children or adolescents, significantly improves by clarifying the etiologic, usually genetic, background of a disabling disease (Lingen et al., 2016)

Hacettepe University, Department of Neurology, Movement Disorders Unit

Dr. Bülent Elibol
Dr. Esen Saka
Dr. Ezgi Yetim Arsava



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