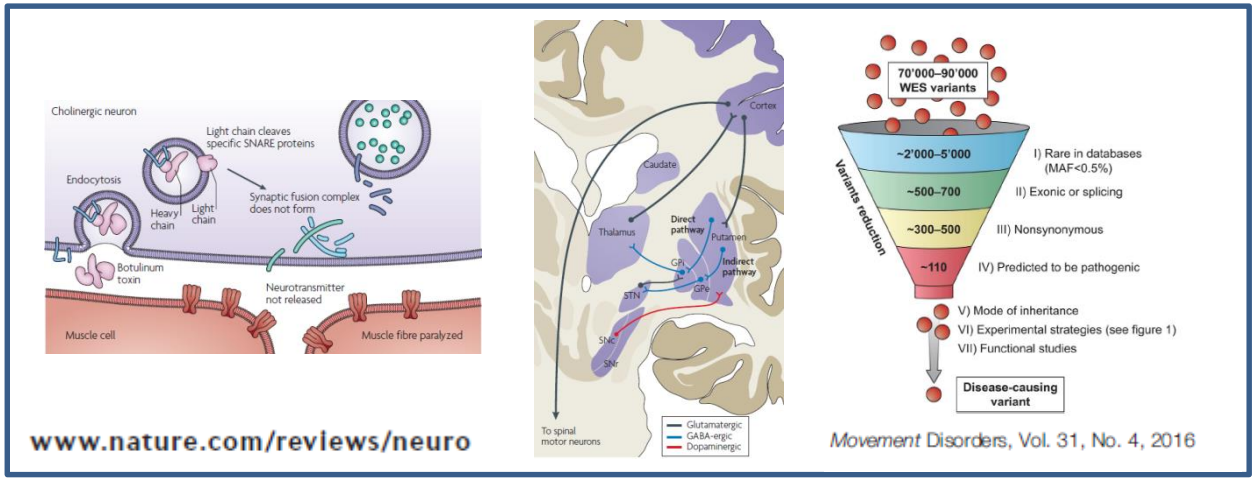
Dystonias: Genetics and Treatment



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learning objectives

- Phenomenology and Classification of Dystonias
- Genetics in Dystonias
- Pathophysiology in genetic/inherited Dystonias
- Treatment options in inherited/genetic Dystonias

European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

webinar outline

- Introduction:

(paroxysmal movement disorders/dyskinesias/dystonias not included)

dystonia/definition
classification
dystonia genetics

- Clinical presentation of inherited dystonias:

case series /phenomenology

- Treatment options in inherited dystonias:

DBS, oral medication, BoNT

REVIEW

CME

Phenomenology and Classification of Dystonia: A Consensus Update

Alberto Albanese, MD,[1,2*] Kailash Bhatia, MD, FRCP,[3] Susan B. Bressman, MD,[4] Mahlon R. DeLong, MD,[5] Stanley Fahn, MD,[6] Victor S.C. Fung, PhD, FRACP,[7] Mark Hallett, MD,[8] Joseph Jankovic, MD,[9] Hyder A. Jinnah, PhD,[10] Christine Klein, MD,[11] Anthony E. Lang, MD,[12] Jonathan W. Mink, MD, PhD,[13] Jan K. Teller, PhD[14]

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

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Axis I. Clinical characteristics

Clinical characteristics of dystonia

Axis II. Etiology

Isolated Dystonias

(Dystonia only, primary dystonia)

Combined Dystonias

(disorders where dystonia frequently co-exists with other movement disorders, dystonia plus syndromes)

Complex Dystonias

(dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders)

○ 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

Idiopathic

- Sporadic
- Familial

CME

Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force

Isolated Dystonias

DYT1	DYT/TOR1A	early onset generalised dystonia	AD
DYT6	DYT/THAP1	adolescent onset dystonia of mixed type	AD
DYT25	DYT/GNAL	adult onset cranio-cervical dytonia	AD

Combined Dystonias

disorders where dystonia frequently co-exists with other movement disorders

DYT5	Dopa-responisve dystonia (DRD)		
	DYT/PARK-GCH1	DRD 5a = GTP cyclohydrolase 1 deficiency	AD/AR
	DYT/PARK-TH	DRD 5b = Tyroxinhydroxylase deficiency	AR
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD

Complex Dystonias

dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders

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

Metabolic Disorder, NBIAs, Spastic Paraplegias, Ataxias, Mitochondrial disease, rare disease with dystonia

Monogenic variants in dystonia: an exome-wide sequencing study

NGS Studies in dystonia up to march 2020:
3 Studies: 2 studies had used whole-exome sequencing (WES) and 1 study had used whole-genome sequencing (WGS) in a small cohort of individuals with dystonia.

- The first WES study detected disease-causing variants in 6 of **16 cases** (38%) with early-onset generalized dystonia.
- The second WES reported a diagnostic yield of 20% in **189 individuals** with dystonia.
- The third WGS study in a cohort of mostly isolated dystonia-affected **probands (111 families),** established a molecular diagnosis in 13 (12%) cases.

No study comprehensively investigated the role of monogenic disorders in the aetiology of dystonia, provided a framework for translating findings into genetic testing recommendations, or prioritised novel disease-causing genes.

This study: 708 patients from 33 movement disorder and neuropaediatric specialty centres across Europe (Austria, Czech Republic, France, Germany, Poland, Slovakia, and Switzerland). Each individual with dystonia was diagnosed in accordance with the dystonia consensus definition.
Index cases were eligible for this study if they had no previous genetic diagnosis and no indication of an acquired cause of their illness.

	Subcohort by dystonia clinical category*		Entire dystonia cohort (N=708)
	Isolated dystonia (N=459)	Combined dystonia (N=249)	
Demographics			
Sex			
Female	269 (59%)	137 (55%)	406 (57%)
Male	190 (41%)	112 (45%)	302 (43%)
Ancestry			
European	450 (98%)	213 (86%)	663 (94%)
Middle Eastern	4 (<1%)	20 (8%)	24 (3%)
Turkish	3 (<1%)	6 (2%)	9 (1%)
Asian	2 (<1%)	6 (2%)	8 (1%)
South American	0	4 (2%)	4 (<1%)
Age			
0–12 years	44 (10%)	72 (29%)	116 (16%)
13–20 years	32 (7%)	34 (14%)	66 (9%)
≥21 years	383 (84%)	143 (57%)	526 (74%)
Positive family history†	138 (30%)	47 (19%)	185 (26%)
Dystonia clinical characteristics			
Age at onset			
0–12 years	115 (25%)	163 (65%)	278 (39%)
13–20 years	69 (15%)	28 (11%)	97 (14%)
≥21 years	275 (60%)	58 (23%)	333 (47%)
Body distribution			
Generalised	112 (24%)	137 (55%)	249 (35%)
Segmental	105 (23%)	64 (26%)	169 (24%)
Focal	242 (53%)	48 (19%)	290 (41%)
Diagnosed with idiopathic dystonic cerebral palsy‡	7 (2%)	49 (20%)	56 (8%)
Additional clinical characteristics			
Other movement disorder(s)			
Myoclonus	..	68 (27%)	68 (10%)
Parkinsonism	..	36 (14%)	36 (5%)
Choreiform movements	..	37 (15%)	37 (5%)
Ataxia	..	73 (29%)	73 (10%)
Spasticity	..	92 (37%)	92 (13%)
Non-movement disorder-related symptoms			
Developmental delay or hypotonia	58 (13%)	125 (50%)	183 (26%)
Intellectual disability	43 (9%)	75 (30%)	118 (17%)
Speech disorder	19 (4%)	70 (28%)	89 (13%)
Seizures or epilepsy	22 (5%)	40 (16%)	62 (9%)
Other neurological features	43 (9%)	83 (33%)	126 (18%)
Leading motor phenomenology§			
Dystonia-predominant manifestation	56/71 (79%)	158/249 (63%)	214/320 (67%)
Brain MRI abnormality¶	50/348 (14%)	106/219 (48%)	156/567 (28%)
Previous genetic testing			
Single-gene analysis	177 (39%)	56 (22%)	233 (33%)
Gene-panel analysis	37 (8%)	40 (16%)	77 (11%)
Chromosomal microarray analysis	31 (7%)	62 (25%)	93 (13%)
Unknown	74 (16%)	67 (27%)	141 (20%)

(Table continues on next page)

Lancet Neurol 2020; 19: 908–18

Monogenic variants in dystonia: an exome-wide sequencing study

Molecular diagnostic results for the dystonia cohort

A) **Proportions of individuals with diagnostic gene variants** for different dystonia clinical categories, represented by 388 (isolated dystonia), 98 (combined dystonia), and 222 (isolated or combined dystonia with coexisting non-movement disorder-related neurological symptoms) individuals. Known gene with novel variant includes genes with compound heterozygous variants if at least one identified variant was novel.

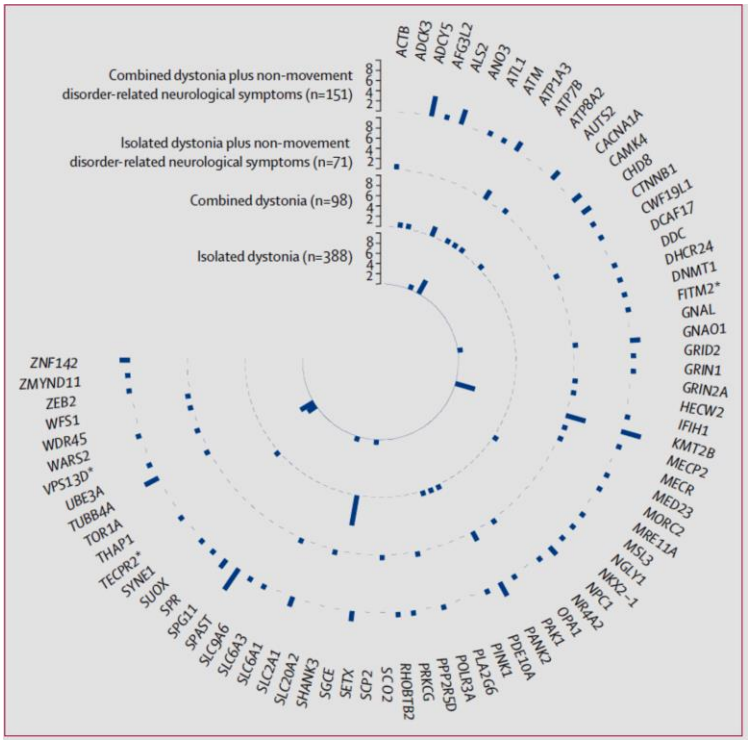
B) **Distribution of variants by inheritance pattern**.

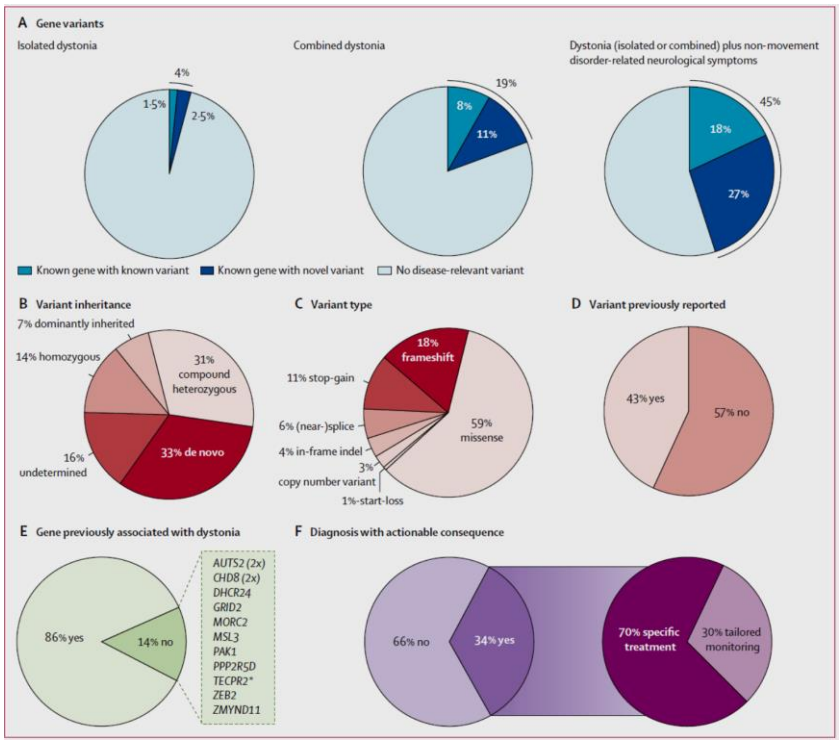
C) **Distribution of variants by variant type.** Percentages shown for variant inheritance and variant type do not total 100 because of rounding.

D) **Numbers of variants previously reported.** Of the 160 variants identified, 91 were not found in ClinVar11 or the published literature. Additional variant characteristics can be found in the appendix (p 16).

E) **Proposed novel associations between known disease genes and dystonia.** 13 individuals had diagnostic variants in 11 genes (green box) whose dystonia manifestations were interpreted as expansions of the previously appreciated gene-specific phenotypes. For the remaining 66 variant-harboring genes, dystonia or (dystonic) tremor has already been documented to be part of the associated disease spectra.

F) **Fraction of 135 whole-exome sequencing-based diagnoses that pointed towards a clinical management or treatment implication.**





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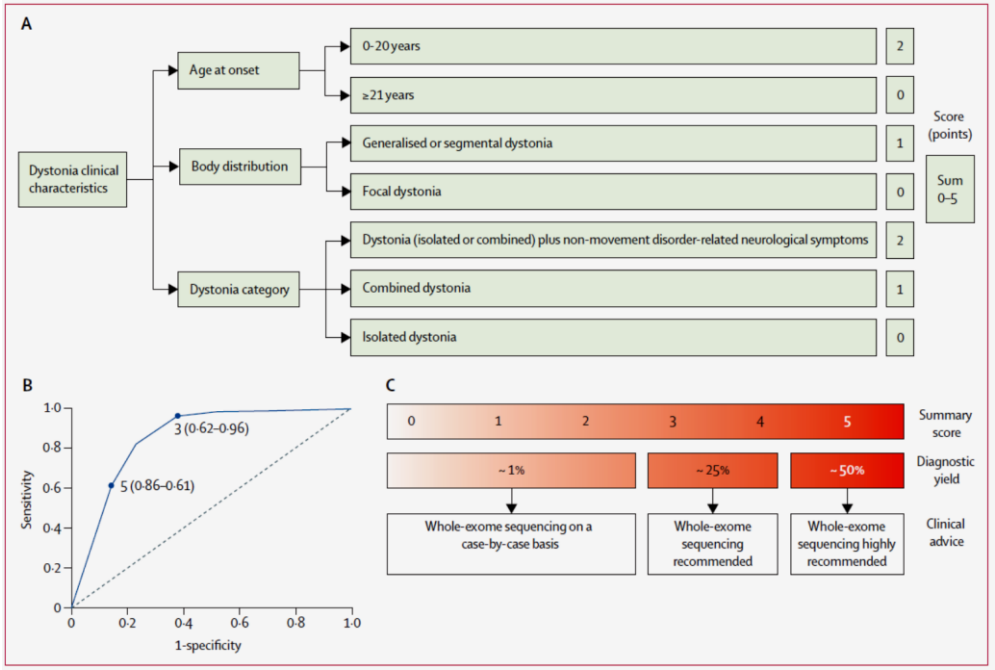
Michael Zech, Robert Jech, Sylvia Boesch, Matej Škorvánek, Sandrina Weber, Matias Wagner, Chen Zhao, Angela Jochim, Ján Necpál, Yasemin Dincer, Katharina Vill, Felix Distelmaier, Malgorzata Stoklosa, Martin Krenn, Stephan Grunwald, Tobias Bock-Bierbaum, Anna Fečíková, Petra Havránková, Jan Roth, Iva Příhodová, Miriam Adamovičová, Olga Ulmanová, Karel Bechyně, Pavlína Danhofer, Branislav Veselý, Vladimír Haň, Petra Pavelekova, Zuzana Gdovinová, Tobias Mantel, Tobias Meindl, Alexandra Sitzberger, Sebastian Schröder, Astrid Blaschek, Timo Roser, Michaela V Bonfert, Edda Haberlandt, Barbara Plecko, Birgit Leineweber, Steffen Berweck, Thomas Herberhold, Berthold Langguth, Jana Švantnerová, Michal Minár, Gonzalo Alonso Ramos-Rivera, Monica H Wojcik, Sander Pajusalu, Katrin Õunap, Ulrich A Schatz, Laura Pölsler, Ivan Milenkovic, Franco Laccone, Veronika Pilshofer, Roberto Colombo, Steffi Patzer, Arcangela Iuso, Julia Vera, Monica Troncoso, Fang Fang, Holger Prokisch, Friederike Wilbert, Matthias Eckenweiler, Elisabeth Graf, Dominik S Westphal, Korbinian M Riedhammer, Theresa Brunet, Bader Alhaddad, Riccardo Berutti, Tim M Strom, Martin Hecht, Matthias Baumann, Marc Wolf, Aida Telegrafi, Richard E Person, Francisca Millan Zamora, Lindsay B Henderson, David Weise, Thomas Musacchio, Jens Volkmann, Anna Szuto, Jessica Becker, Kirsten Cremer, Thomas Sycha, Fritz Zimprich, Verena Kraus, Christine Makowski, Pedro Gonzalez-Alegre, Tanya M Bardakjian, Laurie J Ozelius, Annalisa Vetro, Renzo Guerrini, Esther Maier, Ingo Borggraefe, Alice Kuster, Saskia B Wortmann, Annette Hackenberg, Robert Steinfeld, Birgit Assmann, Christian Staufner, Thomas Opladen, Evžen Růžička, Ronald D Cohn, David Dyment, Wendy K Chung, Hartmut Engels, Andres Ceballos-Baumann, Rafal Ploski, Oliver Daumke, Bernhard Haslinger, Volker Mall, Konrad Oexle, Juliane Winkelmann



Proposed algorithm to predict diagnostic success rate of whole-exome sequencing in individuals with dystonia

(A) **Schematic overview of the proposed scoring system.** We selected as scoring parameters clinical predictors of a diagnostic whole-exome sequencing finding, as determined by multiple logistic regression analysis. The assigned scoring points add up to yield a summary score, ranging from 0 to 5.

(B) **Receiver operating characteristic curve plot** for the proposed score with indication of the specificities and sensitivities at the thresholds postulated in part C. A summary score threshold of 3 points implies a small number (4%) of individuals are erroneously excluded from whole-exome sequencing and an acceptable number (38%) are erroneously included.

(C) **Summary scores (0–5), proportions of the subgroups with a diagnostic variant (diagnostic yield),** and proposed recommendations for the clinical application of whole-exome sequencing in individuals with dystonia.

Lancet Neurol 2020; 19: 908–18

Dystonias
Clinical presentation and treatment options

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CME

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DYT-*GNAL*[66]	Adult onset cranial-cervical dystonia	615073	AD	*DYT25*

TOR1A dystonia (DYT1)
Prevalence: 1:160.000 (1:9.000 Ashkenazi)
Disease-causing mutation: TOR1A (torsin family 1, member A). Deletions impair TOR1A activity, may produce a mutant protein that lacks a single glutamic acid residue (then: potential gain-of function or dominant negative interactions).
Genetic modifiers for incomplete penetrance and symptom variability are unknown.
Phenotype: symptoms begin in a single limb and tend to generalize throughout the body, although they may remain focal.

Ozelius, L.J. et al. (1997) The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat. Genet. 17, 40–48. Goodchild, R.E. et al. (2005) Loss of the dystonia-associated protein TorsinA selectively disrupts the neuronal nuclear envelope. Neuron 48, 923–932, Opal, P. et al. (2002) Intrafamilial phenotypic variability of the DYT1 dystonia: from asymptomatic TOR1A gene carrier status to dystonic storm. Mov. Disord. 17, 339–345

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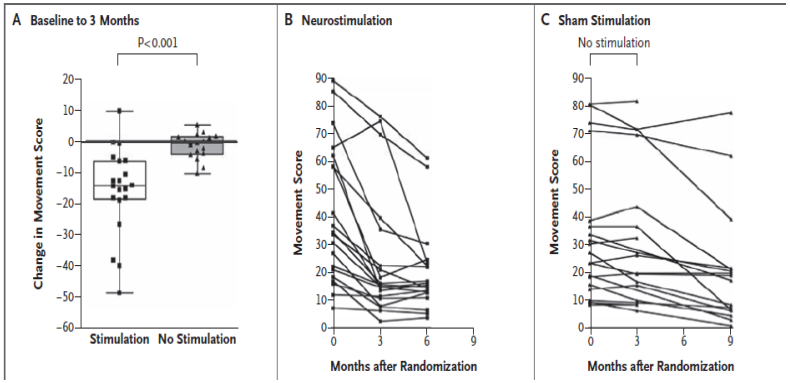
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia



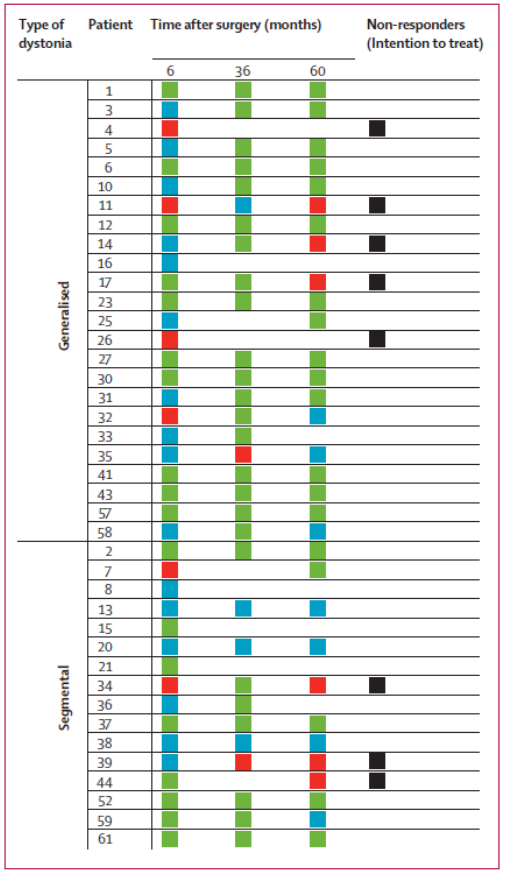
N Engl J Med 2006;355:1978-90.

Study design:
Study population: 40 patients with primary segmental/generalized dystonia; DBS; randomly assigned to DBS or sham stimulation for 3 months.
Primary end point: Change from baseline to 3 months in the severity of symptoms (subscore on the Burke–Fahn–Marsden Dystonia Rating Scale).
Two investigators unaware of treatment status assessed the severity of dystonia by reviewing videotaped sessions.
All patients received open-label neurostimulation; blinded assessment was repeated after 6 months of active treatment.

Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial

*Jens Volkmann, Alexander Wolters, Andreas Kupsch, Jörg Müller, Andrea A Kühn, Gerd-Helge Schneider, Werner Poewe, Sascha Hering, Wilhelm Eisner, Jan-Uwe Müller, Günther Deuschl, Marcus O Pinsker, Inger-Marie Skogseid, Geir Ketil Roeste, Martin Krause, Volker Tronnier, Alfons Schnitzler, Jürgen Voges, Guido Nikkhah, Jan Vesper, Joseph Classen, Markus Naumann, Reiner Benecke, for the DBS study group for dystonia**

	Before surgery		6 months		3 years	
	Total, N	n (%)	Total, N	n (%)	Total, N	n (%)
Anticholinergics	40	9 (23%)	40	3 (8%)	31	1 (3%)
Benzodiazepines	40	14 (35%)	40	11 (28%)	31	7 (23%)
Antispastics	40	4 (10%)	40	2 (5%)	31	0
Neuroleptics	40	4 (10%)	40	0 (0%)	31	0
Tetrabenazine	40	5 (13%)	40	2 (5%)	31	1 (3%)
Levodopa/dopa decarboxylase inhibitor	40	2 (5%)	40	1 (3%)	31	0 (0%)
Analgesics	40	4 (10%)	40	1 (3%)	31	1 (3%)
Antidepressants	40	7 (18%)	40	1 (3%)	31	3 (10%)
Intrathecal baclofen	40	2 (5%)	40	0 (0%)	31	0
Botulinum toxin injection within past 4 months	40	14 (35%)	40	5 (13%)	31	3 (10%)



The response is denoted for each patient by a colour-coded symbol. Green indicates an improvement of more than 50%, blue 25–50%, and red less than 25% or worsening on the Burke–Fahn–Marsden dystonia rating scale motor score compared with baseline. A non-responder was defined as a patient showing less than 25% improvement or worsening on the motor score at the last available visit.

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15 years after Gpi - DBS

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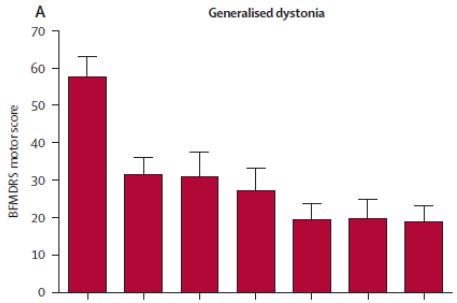

Treatment Failure DBS-Gpi in Dystonias

Pallidal deep brain stimulation (GPi-DBS) is effective for isolated dystonia, but 10-20% of patients show improvement below 25-30%.

Causes of insufficient response to GPi-DBS in isolated dystonia/cross-sectional study:

22 patients from 11 centres were included (8 men, 14 women; 9 generalized, 9 segmental, 3 focal, 1 bi-brachial dystonia; mean (range): age 48.7 (25-72) years, disease duration 22.0 (2-40) years, DBS duration 45.5 (6-131) months). Mean BFMDRS-score was 31.7 (4-93) preoperatively and 32.3 (5-101) postoperatively. Half of the patients (n=11) had poor lead positioning alone or in combination with other problems (combined with: other disease n=6, functional dystonia n=1, other problems=2).

Other problems were disease other than isolated inherited or idiopathic dystonia (n=5),fixed deformities (n=2), functional dystonia (n=3), and other causes (n=1). Excluding patients with poor lead location from further analysis, non-isolated dystonia accounted for 45.5%, functional dystonia for 27.3%, and fixed deformities for 18.2%.

In patients with true isolated dystonia, lead location was the most frequent problem.

After exclusion of lead placement and stimulation programming issues, non-isolated dystonia, functional dystonia and fixed deformities account for the majority of GPi-DBS failures in dystonia.

http://dx.doi.org/10.1016/j.parkreldis.2017.06.023

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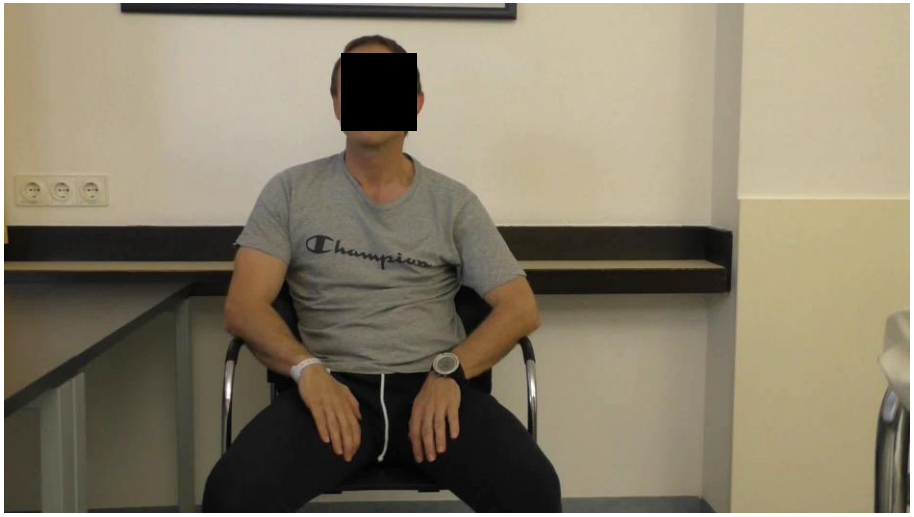

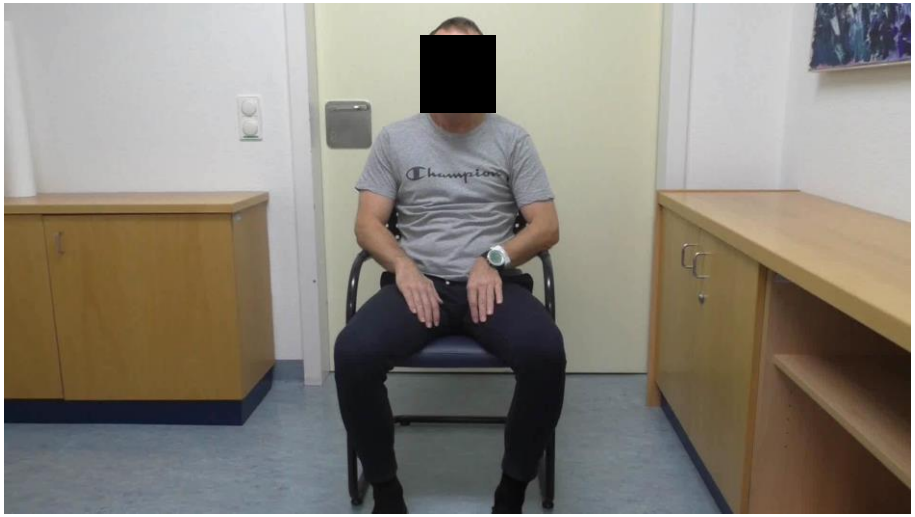

AE, *1966; 49 years
Disease onset: 11.yrs., UEx right; initial symptom:“Irregular tremor“ UEx right, ~20.Lj. „tremor“ right LEx, since ~ 35.Lj.;
BoNT without satisfying results (cervical dystonia), Anticholinergics not tolerated.
No other complaints or symptoms
Medical history: normal delivery, normal development, motor milestones
Med./Allergies: none
Family history: no movement disorders

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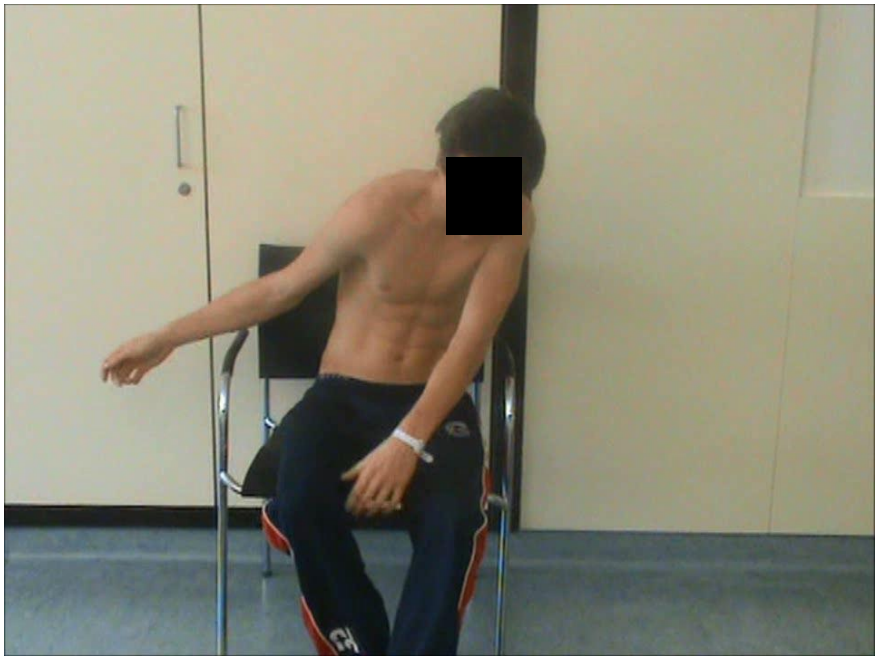

DYT6 dystonia

autosomal dominant inherited, reduced penetrance (40%).

Mutational spectrum: >100 different mutations including missense, nonsense, and frameshift mutations in Thanatos associated domain containing, apoptosis associated protein 1 (THAP1).

Phenotype: dystonia / tremor

dystonia usually manifests in childhood or early adulthood, mean age at onset 9 years.

Tendency to generalize, broad phenotypic spectrum.

DYT6 dystonia often involves the upper half of the body, including laryngeal adductor-type dystonia, which occasionally culminates in aphonia.

Djarmati A, Schneider SA, Lohmann K, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. Lancet Neurol 2009;8:447–452. Fuchs T, Gavarini S, Saunders-Pullman R, et al. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. Nat Genet 2009;41:286–288. Klein C. Genetics in dystonia. Parkinsonism Relat Disord 2014;20(suppl 1):S137–S142. Blanchard A, Ea V, Roubertie A, et al. DYT6 dystonia: review of the literature and creation of the UMD Locus Specific DataBase (LSDB) for mutations in the THAP1 gene. Hum Mutat 2011;32:1213–1224.

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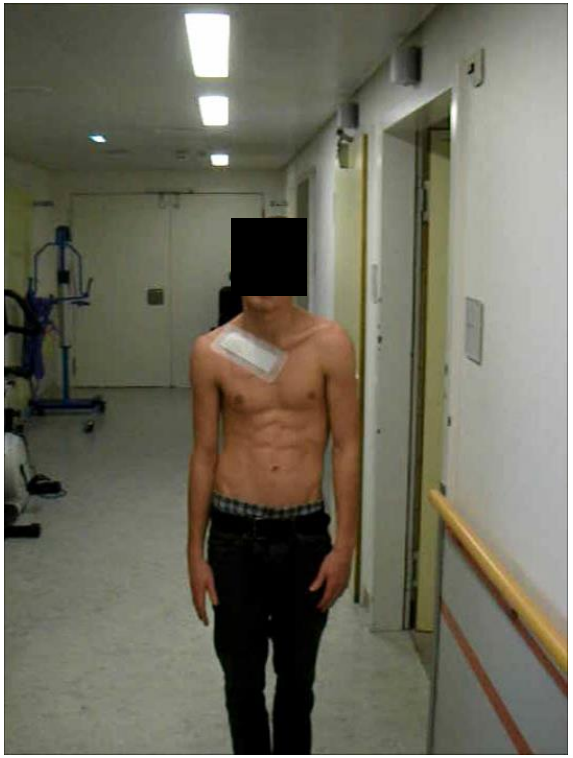
DYT-*THAP1*[65]	Adolescent-onset dystonia of mixed type	602629	AD	*DYT6*
DYT-*GNAL*[66]	Adult onset cranial-cervical dystonia	615073	AD	*DYT25*

Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia

	DYT6	DYT1
No.	8	9
Distribution, generalized/segmental/focal	5/3/0	8/0/1
Sex, M/F	7/1	3/6
Family history, positive/negative/unknown	4/3/1	5/4/0
Age at onset, y		
Mean (SD)	10.0 (3.3)	11.2 (6.6)
Range	6-15	2-23
Years until first DBS		
Mean (SD)	27.0 (10.8)	20.1 (11.1)
Range	11-46	5-41
BFMDRS scores, preoperative		
Motor, mean (SD) (n = 55)	37.0 (15.9)	43.8 (30.7)
Disability, mean (SD) (n = 30)	7.8 (2.7)	14.3 (7.8)
Responder rate motor BFMDRS, n (%)		
Early follow-up (1-16 mo)	4/7 (57.1)	7/7 (100)
Late follow-up (22-92 m)	6/7 (85.7)	5/8 (62.5)

Abbreviations: BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; DBS = deep brain stimulation.
[a] Significant values.

Brüggemann et al., Neurology 2015



DBS in patients with DYT 6 dystonia

2010 Groen et al.,	n=4, FU=6 Monate,	Improvement=33%
2010 Zittle et al.,	n=2, FU=2-7 Jahre,	Improvement=Moderate
2011 Jech et al.,	n=1, FU=32 Monate,	Improvement=85%
2012 Panov et al.,	n=3,FU=3 Jahre,	Improvement=48%
2012 Franca et al.,	n=1, FU=2 Monate,	Improvement=59%
2012 Miyamoto et al.,	n=1, FU=years,	Improvement=Moderate
2013 Miri et al.,	n=1,FU= 1 year,	Improvement=78%

Isolated Dystonia

Isolated dystonias				
DYT-*TOR1A*[64]	Early-onset generalized dystonia	128100	AD	*DYT1*
DYT-*THAP1*[65]	Adolescent-onset dystonia of mixed type	602629	AD	*DYT6*
DYT-*GNAL*[66]	Adult onset cranial-cervical dystonia	615073	AD	*DYT25*

GNAL gene mutation (DYT25)

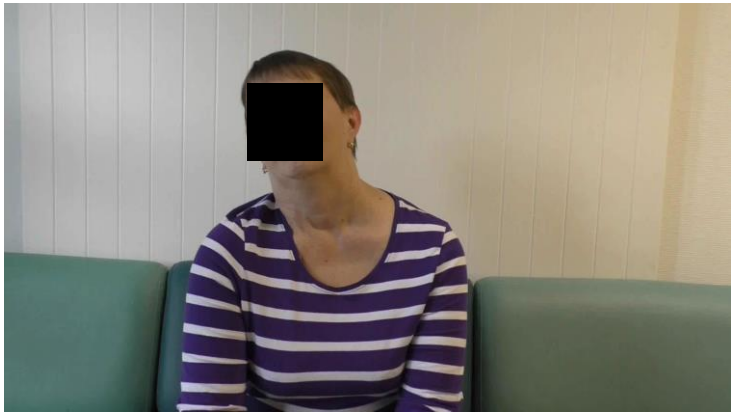
Rare cause of dystonia (app. 0.5 – 1%); onset : 7 - 63 yrs.

Phenotype: cranio-cervical region affected (generalization in 10%); dystonic head tremor, laryngeal onset or development of spasmodic dysphonia. Useful diagnostic clue: hyposmia

Genetics: >30 different GNAL mutations, highly but not fully penetrant; GNAL encodes guanine nucleotide-binding protein, alpha activating activity polypeptide, olfactory type Ga(olf), a protein involved in olfactory signal transductions and in dopamine (D1) signaling. Gαolf is enriched in the striatum where it couples D1 dopamine (D1R) and A2A adenosine (A2AR) receptors to downstream effector molecules.

Coupling to A2AR leads to activation of adenylyl cyclase type 5 (AC5) encoded by ADCY5;

Mice deficient in GNAL are anosmic and displayed motor hyperactivity.



Zech M, Gross N, Jochim A, et al. Rare sequence variants in ANO3 and GNAL in a primary torsion dystonia series and controls. Mov Disord 2014; 29:143– 147. Fuchs T, Saunders-Pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2012; 45:88–92. Vemula SR, Puschmann A, Xiao J, et al. Role of G((olf) in familial and sporadic adult-onset primary dystonia. Hum Mol Genet 2013; 22:2510–2519. Dufke C, Sturm M, Schroeder C, et al. Screening of mutations in GNAL in sporadic dystonia patients. Mov Disord 2014. Kumar KR, Lohmann K, Masuho I, et al. Mutations in GNAL: a novel cause of craniocervical dystonia. JAMA Neurol 2014; 71:490–494.

Isolated Dystonia

Isolated dystonias				
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DYT 24

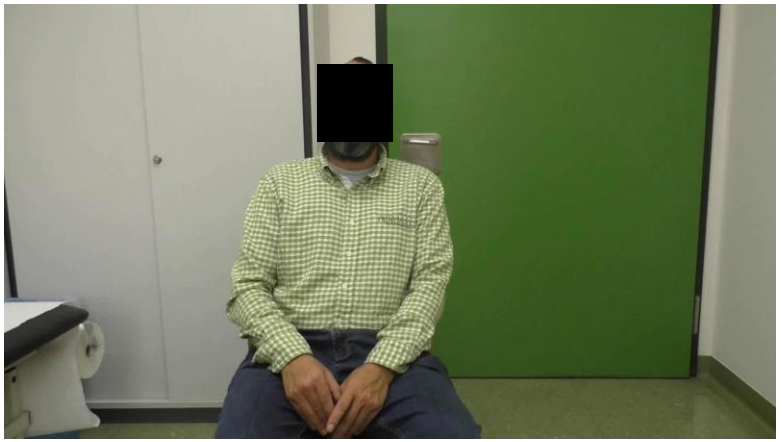
Mutations in the Anoctamin 3 gene (ANO3): gene is highly expressed in the striatum; role in calcium signaling and mediating neuronal excitability.

Age at onset: from early childhood to the forties.

Predominant phenotype: tremulous cervical dystonia (cranial and laryngeal dystonia to a variable degree); mild dystonia of the arms in some cases; generalized dystonia never observed until todate.

Tremor: present in all identified patients, mostly as head and arm tremor; sometimes myoclonic jerks of the head or the arms (electrophysiological studies-subcortical).

DYT24 may be distinguished by crancio-cervical onset from DYT1 and by tremor from DYT6.



CME

Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force

Isolated Dystonias

DYT1	DYT/TOR1A	early onset generalised dystonia	AD
DYT6	DYT/THAP1	adolescent onset dystonia of mixed type	AD
DYT25	DYT/GNAL	adult onset cranio-cervical dytonia	AD

Combined Dystonias

disorders where dystonia frequently co-exists with other movement disorders

DYT5	Dopa-responisve dystonia (DRD)		
	DYT/PARK-GCH1	DRD 5a = GTP cyclohydrolase 1 deficiency	AD/AR
	DYT/PARK-TH	DRD 5b = Tyroxinhydroxylase deficiency	AR
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD

Complex Dystonias

dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders

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

Metabolic Disorder, NBIAs, Spastic Paraplegias, Ataxias, Mitochondrial disease, rare disease with dystonia

Combined Dystonia

defined: disorders where dystonia frequently co-exists with other movement disorders

Combined dystonias (disorders where dystonia frequently coexists with other movement disorders)				
DYT-*PRKRA*[67]	Rare form of usually generalized dystonia, parkinsonism inconsistent	612067	AR	*DYT16*
DYT/PARK-*GCH1*[24]	GTP cyclohydrolase I deficiency (mild form)25: childhood-onset dopa-responsive dystonia, adult-onset dystoniaparkinsonism Additional clinical manifestations: diurnal fluctuation.	128230	AD	*DYT5a*

DYT5	Dopa-responisve dystonia (DRD)		
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	DYT/PARK-TH	DRD 5b = Tyroxinhydroxylase deficiency	AR
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD

	Very severe form: infantile-onset dystonia and parkinsonism, oculogyric crises, severe global developmental delay, truncal hypotonia, limb spasticity, autonomic dysfunction		AR	None
DYT/PARK-*ATP1A3*[22]	Rapid-onset dystonia-parkinsonism, chorea in later life[b]	128235	AD	*DYT12*
DYT/PARK-*TAF1*[23a]	Dystonia-parkinsonism	314250	X-linked	*DYT3*
DYT-*SGCE*[69]	Myoclonus-dystonia	159900	AD	*DYT11*
CHOR/DYT-*ADCY5*[70]	See Table 5	600293	AD	None

Combined Dystonia

defined: disorders where dystonia frequently co-exists with other movement disorders

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	DYT/PARK-TH	DRD 5b = Tyroxinhydroxylase deficiency	AR
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD

REVIEWS

Dopa-responsive dystonia—clinical and genetic heterogeneity

Subhashie Wijemanne and Joseph Jankovic

Cause of dystonia	Inheritance	Age at onset	Site of dystonia onset	Distribution of dystonia	Diurnal variation	Levodopa response	Additional clinical features
GTP-CH-I deficiency[19]	Autosomal dominant with low penetrance	Mean 8.5 years, range 0.2–48 years	Lower limbs	Generalized	Yes	Excellent and sustained response to low doses; minimal wearing off or levodopa-induced dyskinesia	Normal initial motor development, parkinsonism, brisk lower limb reflexes, scoliosis, anxiety, depression, obsessive–compulsive disorder and sleep disturbances
GTP-CH-I deficiency[101]	Autosomal recessive	Can manifest at <6 months	Legs	Generalized	Yes, but might not be obvious	Excellent sustained response, but high doses required	Spasticity, excessive drooling, oculogyric crises, poor sleep, neonatal hyperphenylalaninaemia
Tyrosine hydroxylase deficiency[3]	Autosomal recessive homozygotic or compound heterozygotic	Between a few weeks after birth and 5 years	Lower limbs	Segmental or generalized	Yes	Good response but can be delayed or incomplete; frequent levodopa-induced dyskinesia	Progressive hypokinetic–rigid syndrome with dystonia (type A), complex encephalopathy (type B), tremor, ptosis, autonomic disturbance, spasticity, hypotonia, delayed motor developmental milestones, intellectual disability
Sepiapterin reductase deficiency[4]	Autosomal recessive	Between birth and 6 years	Lower limb and trunk	Generalized	Yes	Good response but can be only partial; possible levodopa-induced dyskinesia	Oculogyric crises, symptoms of dysautonomia symptoms (such as hypersalivation), developmental delay, microcephaly or growth retardation, hypotonia, intellectual disability, sleep disorders, parkinsonism, hyperreflexia
PTP synthase deficiency[68]	Autosomal recessive	Birth to early childhood	Legs	Generalized	Yes	Marked and sustained positive response to levodopa; no levodopa-induced dyskinesia	Early childhood seizure, spasticity, mild cognitive deficits

Abbreviations: GTP-CH-I, GTP cyclohydrolase 1; PTP, 6-pyruvoyl tetrahydropterin.

Wijemanne, S. & Jankovic, J. *Nat. Rev. Neurol.* advance online publication 23 June 2015; doi:10.1038/nrneurol.2015.86

Classic DRD

Presentation:
- Levodopa-responsive limb-onset dystonia
- Diurnal variation

Differential diagnoses:
- GTP-CH-I deficiency (autosomal dominant and recessive forms)
- Tyrosine hydroxylase deficiency
- Sepiapterin reductase deficiency
- PTP synthase deficiency (rare)
- Spinocerebellar ataxia type 3 (single case reported)

DRD with parkinsonism

Presentation:
- Levodopa-responsive dystonia
- Parkinsonism
- With or without diurnal variation

Differential diagnoses:
- GTP-CH-I deficiency (autosomal dominant and recessive forms)
- Tyrosine hydroxylase deficiency
- Sepiapterin reductase deficiency
- PTP synthase deficiency
- Hereditary spastic paraplegia (*SPG11* mutation, single case reported)
- Ataxia telangiectasia (single case reported)
- Young-onset PD
- Genetic forms of PD with dystonia: *Parkin*-associated PD (PARK2), *LRRK2*-associated PD (PARK8), *PINK1*-associated PD (PARK6), *DJ1*-associated PD (PARK7), *SNCA*-associated PD (PARK1, PARK4), rapid onset dystonia parkinsonism (DYT12), rare (PARK9, PARK14)

Early-onset atypical DRD

Presentation:
- Onset in infancy or early childhood
- Oculogyric crisis
- Hypotonia
- Focal or generalized dystonia
- Parkinsonism

Differential diagnoses:
- GTP-CH-I deficiency (autosomal recessive)
- Tyrosine hydroxylase deficiency
- Sepiapterin reductase deficiency
- PTP synthase deficiency
- Aromatic L-amino acid decarboxylase deficiency
- Seizure disorder
- Metabolic disorder
- Mitochondrial disorder
- Hypoxic–ischaemic encephalopathies
- Cerebral palsy

Abbreviations: DRD, dopa-responsive dystonia; GTP-CH-I, GTP cyclohydrolase 1; PTP, 6-pyruvoyl-tetrahydropterin.

Combined Dystonia

defined: disorders where dystonia frequently co-exists with other movement disorders

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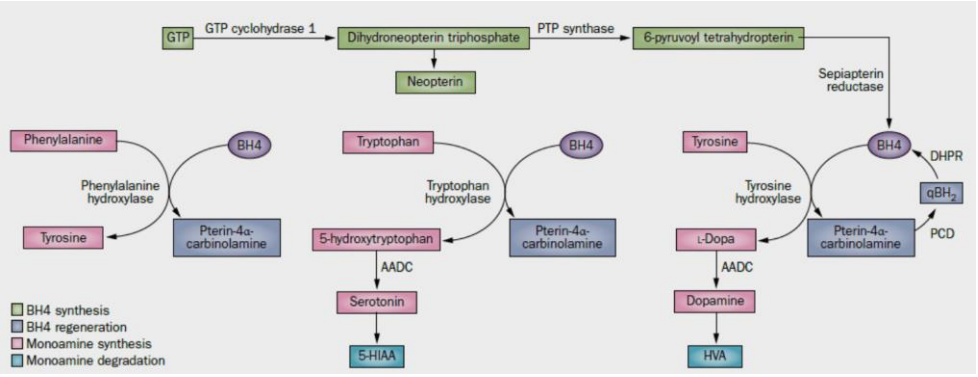
	DYT/PARK-TH	DRD 5b = Tyroxinhydroxylase deficiency	AR
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD

Dopa-responsive dystonia (DRD; DYT5a)
Childhood-onset with diurnal fluctuation/SEGAWA:
heterozygous mutations GCH1 gene (GTP cyclohydrolase 1), encoding the rate-limiting enzyme in the biosynthesis of dopamine via the biopterin pathway; >100 different mutations (missense, nonsense, frameshift, and splice-site) all over the gene, and whole-exon or whole-gene deletions. Penetrance: ~50% (higher in women than in men).
Phenotype: dystonia and/or parkinsonian features (rarely associated with a dopaminergic deficit in DAT SPECT). Non-motor features (e.g. sleep disturbances, mood disorders, or migraine) are frequent. GCH1 variants: risk factor for PD.
Recessively inherited (biallelic) mutations in GCH1, infantile onset: more severe motor phenotype and developmental delay.
Treatment: Enzymatic defect in the levodopa biosynthesis, life-long response to levodopa. *Prenatal treatment* with levodopa in a homozygous GCH1 mutation carrier prevented severe phenotype (dopamine signaling important for intra-uterine (brain) development).



Wijemanne, S. & Jankovic, J. *Nat. Rev. Neurol.* advance online publication 23 June 2015; doi:10.1038/nrneurol.2015.86

V. Tadic, M. Kasten, N. Bruggemann, S. Stiller, J. Hagenah, C. Klein, Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs, Arch Neurol (2012) 1-5. Lewthwaite AJ, Lambert TD, Rolfe EB, Olgiati S, Quadri M, Simons EJ, et al. Novel GCH1 variant in dopa-responsive dystonia and Parkinson's disease. Parkinsonism Relat Disord. 2015;21: 394–7. Mencacci NE, Isaias IU, Reich MM, Ganos C, Plagnol V, Polke JM, et al. Parkinson's disease in GTP cyclohydrolase 1 mutation carriers. Brain. 2014;137:2480–92. Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet. 2014;46:989–93. Hagenah J, Saunders-Pullman R, Hedrich K, Kabakci K, Habermann K, Wiegers K, et al. High mutation rate in doparesponsive dystonia: detection with comprehensive GCHI screening. Neurology. 2005;64:908–11. Douglas G, Hale AB, Crabtree MJ, Ryan BJ, Hansler A, Watschinger K, et al. A requirement for Gch1 and tetrahydrobiopterin in embryonic development. Dev Biol. 2015;399:129–38.

Combined Dystonia

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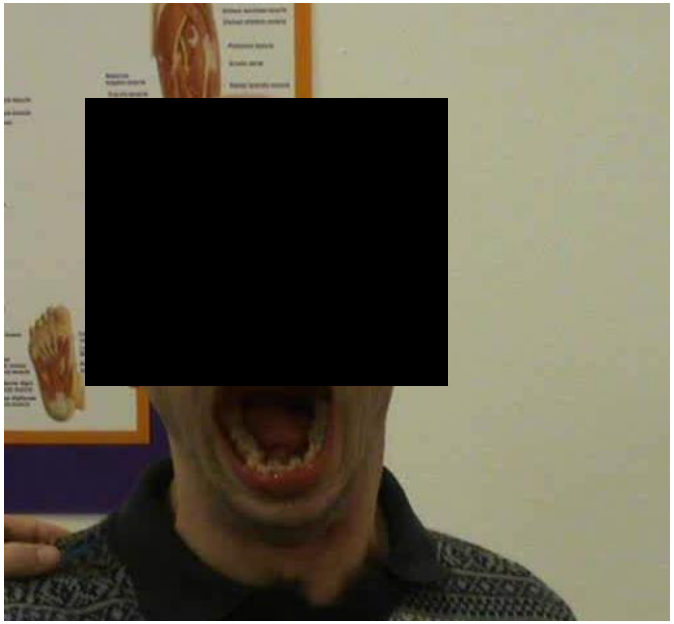
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD



Rapid onset Parkinsonism dystonia (DYT12)

autosomal dominant; reduced penetrance; mutations in ATP1A3 primarily described in rapid-onset dystonia parkinsonism (RODP; DYT12), may cause alternating hemiplegia of childhood (AHC); Mutations in the ATP1A3 gene (ATPase Na+ /K+ transporting subunit alpha 3), encoding an ionic pump. RDP-causing mutations reduce protein levels of ATP1A3 but do not affect the enzymatic activity per se.

Genetics: > 20 different missense mutations; ~ 50% *de novo* or from parents with mosaics; *mutational hot spot* at protein position D801;

Heterozygous missense mutations of the ATP1A3 gene were found to cause CAPOS syndrome.

De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na+ /K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 2003; 33: 192–96. Ambrosini A, D'Onofrio M, Grieco GS, et al. Familial basilar migraine associated with a new mutation in the ATP1A2 gene. Neurology 2005; 65: 1826–28. Bøttger P, Tracz Z, Heuck A, Nissen P, Romero-Ramos M, Lykke-Hartmann K. Distribution of Na/K-ATPase alpha 3 isoform, a sodium-potassium P-type pump associated with rapid-onset of dystonia parkinsonism (RDP) in the adult mouse brain. J Comp Neurol 2011; 519: 376–404.

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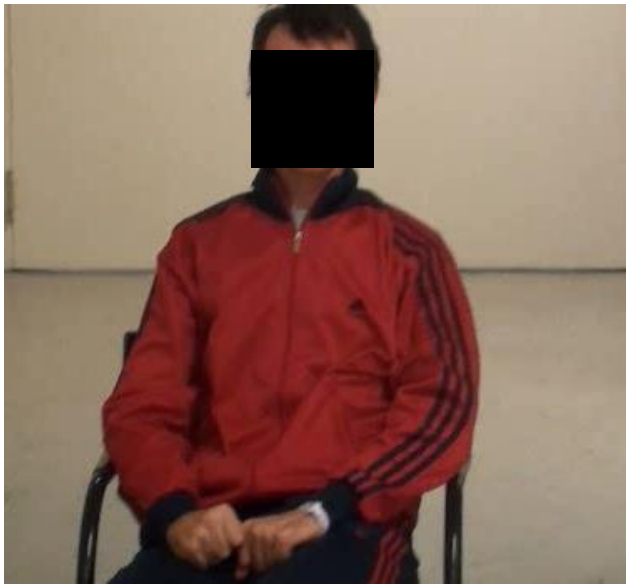
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/Sdefined: disorders where dystonia frequently co-exists with other movement disordersGCE		
	Myoclonus-dystonia	AD	
ADCY5	CHOR/DYT-ADCY5	???	AD



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D. Freudenstein, MD
T. Gasser, MD

NOVEL *ATP1A3* MUTATION IN A SPORADIC RDP PATIENT WITH MINIMAL BENEFIT FROM DEEP BRAIN STIMULATION

Neurology 70 April 15, 2008

Rapid onset dystonia-parkinsonism (RDP) is a rare, autosomal dominantly inherited movement disorder, characterized by abrupt or subacute onset of both dystonic symptoms and parkinsonism

Scale	Possible range	Baseline	Post-surgery 7 d	Post-surgery 3 mo	Post-surgery 12 mo
Eyes	0-8	0.5	0	0	0
Mouth	0-8	1	1	0.5	0.5
Speech/swallowing	0-16	6	2	3	2
Neck	0-8	3	1	0.5	0.5
Right arm	0-16	12	12	9	9
Left arm	0-16	9	9	9	9
Right leg	0-16	9	9	9	9
Left leg	0-16	9	6	6	9
Trunk	0-16	6	9	2	2
Total	0-120	55.5	49	39	41

Phenotype: acute onset is usually associated with a trigger such as fever, physical exertion, or emotional stress. Dystonic symptoms - rostro-caudal gradient, asymmetry of symptoms; strong involvement of the bulbar region; often accompanied by bradykinesia as a parkinsonian feature. Additional features: developmental delay, cognitive and psychiatric disturbances, epilepsy and unusual manifestations like adult-onset limb dystonia or exercise-induced dystonia.
Treatment: minor response to levodopa; to a certain degree to benzodiazepine and clonazepam therapy.

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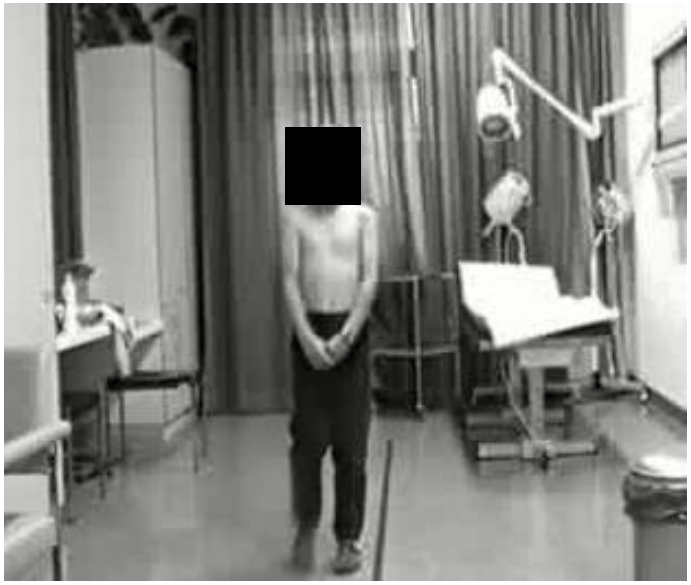

Myoclonus dystonia syndrome (MDS)

Disease onset: 1.-2. decade.

Phenotype: alcohol responsive truncal and upper limb myoclonus with cervical dystonia and/or writer's cramp; evidence of prominent co-morbid psychiatric disorders, specifically compulsivity, anxiety disorders and excessive alcohol use.

Genetics: Mutations in the epsilon-sarcoglycan gene (SGCE); autosomal dominant; variable penetrance due to *maternal imprinting*; >80 different mutations (loss of-function mutations due to frameshift, splice site, nonsense mutations, or deletions of whole exons or even the entire gene);

SGCE encodes the epsilon-sarcoglycan protein, a single pass transmembrane protein forming part of the dystrophin-associated glycoprotein complex.

Asmus F et al (2002) Myoclonus-dystonia syndrome: epsilonsarcoglycan mutations and phenotype. Ann Neurol 52(4):489– 492 Raymond D et al (2008) Phenotypic spectrum and sex effects in eleven myoclonus-dystonia families with epsilon-sarcoglycan mutations. Mov Disord 23(4):588–592 Chung EJ et al (2007) Novel SGCE gene mutation in a Korean patient with myoclonus-dystonia with unique phenotype mimicking Moya-Moya disease. Mov Disord 22(8):1206–1207 Chen XP et al (2008) A novel mutation of the epsilon-sarcoglycan gene in a Chinese family with myoclonus-dystonia syndrome. Mov Disord 23(10):1472–1475 Neurology 59(8):1187–1196 Hess CW et al (2007)

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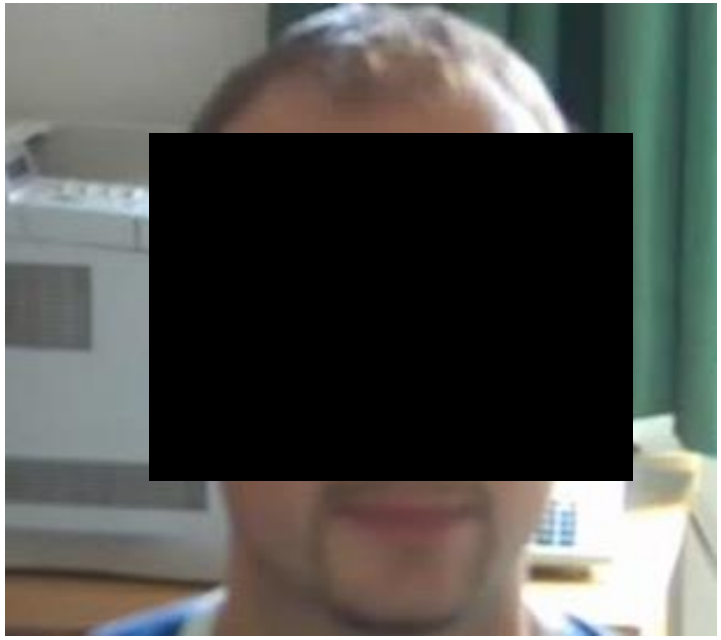
ADCY5	CHOR/DYT-ADCY5	???	AD



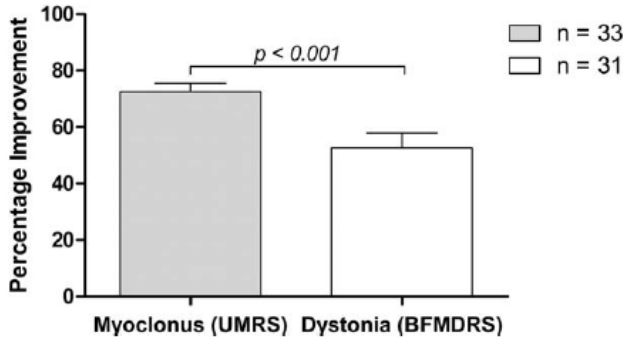
REVIEW

Surgical Treatment of Myoclonus Dystonia Syndrome

Anand I. Rughani, MD,* and Andres M. Lozano, MD

Division of Neurosurgery, University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada.

Relative Improvements in Myoclonus and Dystonia In Patients Treated with Deep Brain Stimulation



Movement Disorders, Vol. 28, No. 3, 2013

Myoclonus-dystonia, obsessive-compulsive disorder, and alcohol dependence in SGCE mutation carriers. Neurology 68(7):522–524 Peall KJ et al (2013) SGCE mutations cause psychiatric disorders: clinical and genetic characterization. Brain 136(Pt 1):294–303 Zimprich A et al (2001) Mutations in the gene encoding epsilonsarcoglycan cause myoclonus-dystonia syndrome. Nat Genet 29(1):66–69 Schule B et al (2004) Genetic heterogeneity in ten families with myoclonus-dystonia. J Neurol Neurosurg Psychiatry 75(8):1181– 1185 Grabowski M et al (2003) The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. Eur J Hum Genet 11(2):138–144

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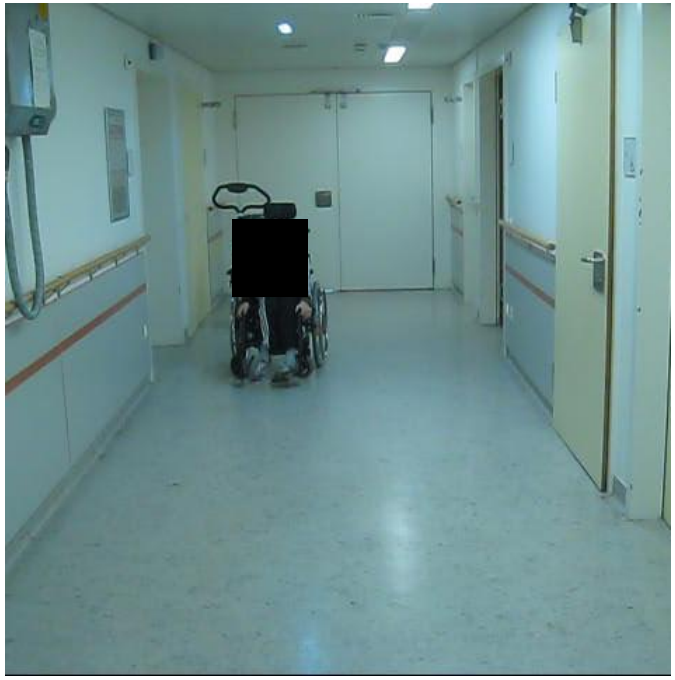
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD



Autosomal Dominant Familial Dyskinesia and Facial Myokymia

Arch Neurol. 2012;69(5):630-635

Single Exome Sequencing Identifies a Mutation in Adenylyl Cyclase 5

Ying-Zhang Chen, MD, PhD; Mark M. Matsushita, BS; Peggy Robertson, PhD; Mark Rieder, PhD; Santhosh Girirajan, MBBS, PhD; Francesca Antonacci, PhD; Hillary Lipe, MN, ARNP; Evan E. Eichler, PhD; Deborah A. Nickerson, PhD; Thomas D. Bird, MD; Wendy H. Raskind, MD, PhD

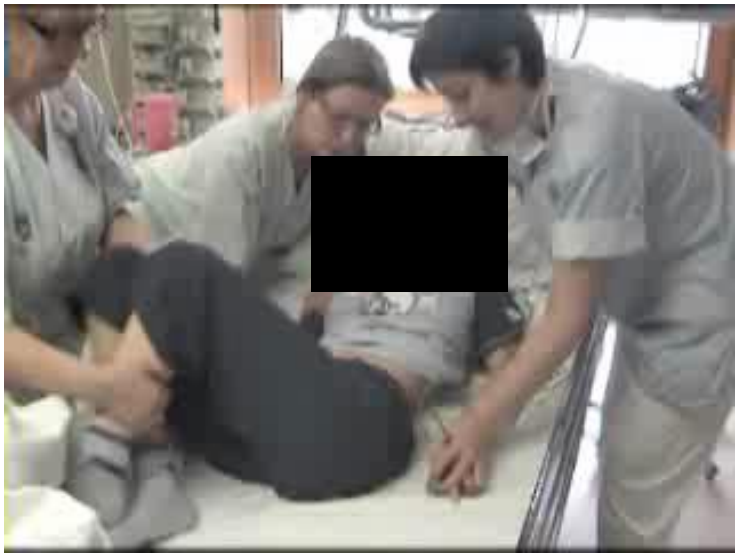
Genetics: familiar cases rare, often *de novo* mutations;
ADCY5 encodes an enzyme that is responsible for the synthesis of cAMP (plays a role in signaling, functionally linked to Gαolf).
Mutations in ADCY5 cluster within regions encoding the C1 or C2 domain of the protein.
Phenotype: wide range of clinical manifestations including childhood-onset paroxysmal or persistent choreatic and/or dystonic features, developmental delay in some cases.

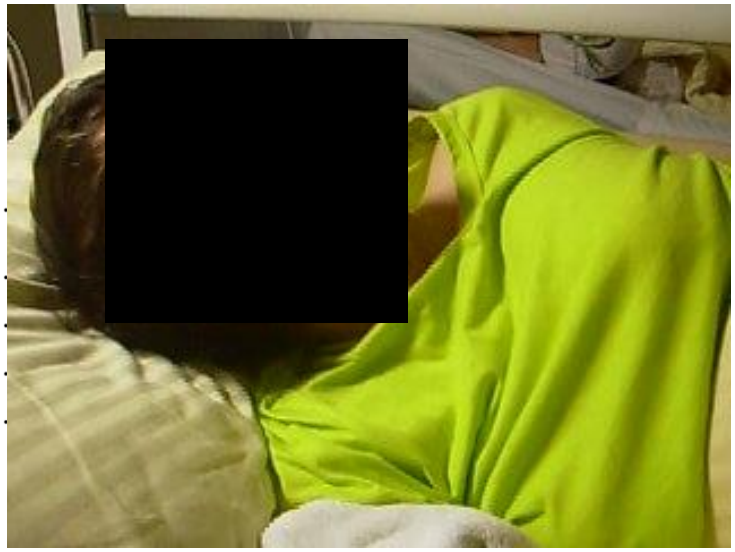
Chen YZ, Matsushita MM, Robertson P, Rieder M, Girirajan S, Antonacci F, et al. Autosomal dominant familial dyskinesia and facial myokymia: single exome sequencing identifies a mutation in adenylyl cyclase 5. Arch Neurol. 2012;69:630–5.
Carapito R, Paul N, Untrau M, Le Gentil M, Ott L, Alsaleh G, et al. A de novo ADCY5 mutation causes early-onset autosomal dominant chorea and dystonia. Mov Disord. 2015;30:423–7.
F.C. Chang, A. Westenberger, R.C. Dale, M. Smith, H.S. Pall, B. Perez-Duenas, et. al, C. Klein, V.S. Fung, Phenotypic insights into ADCY5-associated disease, Mov Disord (2016).

Combined Dystonia

defined: disorders where dystonia frequently co-exists with other movement disorders

DYT5	Dopa-responisve dystonia (DRD)		
	DYT/PARK-GCH1	DRD 5a = GTP cyclohydrolase 1 deficiency	AD(SEGAWA) /AR
	DYT/PARK-TH	DRD 5b = Tyroxinhydroxylase deficiency	AR
DYT12	DYT/PARK-ATP1A3	Rapid-onset parkinson-dystonia	AD
DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD





CME

Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force

Isolated Dystonias

DYT1	DYT/TOR1A	early onset generalised dystonia	AD
DYT6	DYT/THAP1	adolescent onset dystonia of mixed type	AD
DYT25	DYT/GNAL	adult onset cranio-cervical dytonia	AD

Combined Dystonias

disorders where dystonia frequently co-exists with other movement disorders

DYT5	Dopa-responisve dystonia (DRD)		
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DYT 11	DYT/SGCE	Myoclonus-dystonia	AD
ADCY5	CHOR/DYT-ADCY5	???	AD

Complex Dystonias

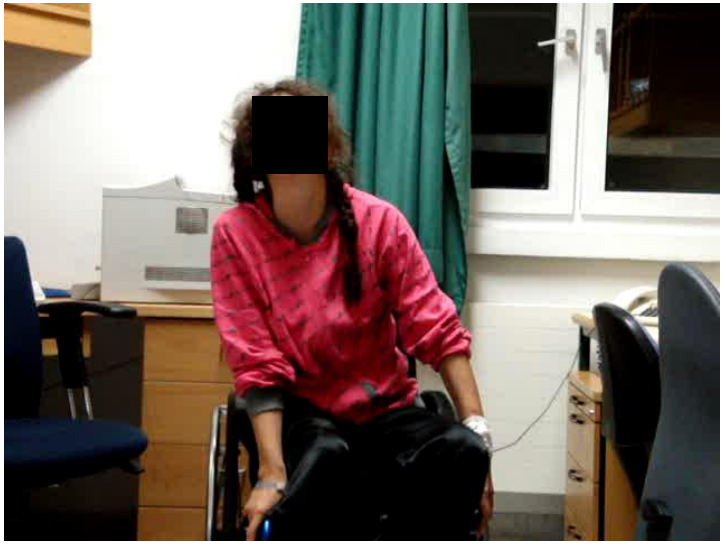
dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders

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

Metabolic Disorder, NBIAs, Spastic Paraplegias, Ataxias, Mitochondrial disease, rare disease with dystonia

Isolated Dystonia?

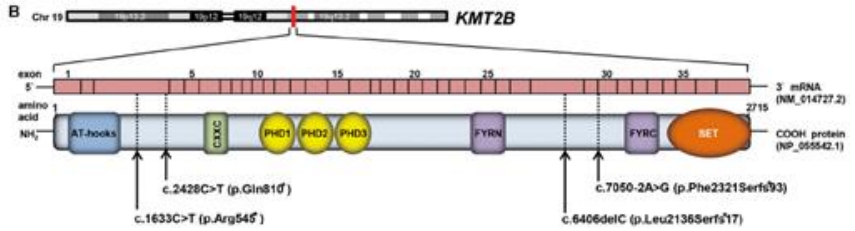
Isolated dystonias				
DYT-*TOR1A*[64]	Early-onset generalized dystonia	128100	AD	*DYT1*
DYT-*THAP1*[65]	Adolescent-onset dystonia of mixed type	602629	AD	*DYT6*
DYT-*GNAL*[66]	Adult onset cranial-cervical dystonia	615073	AD	*DYT25*

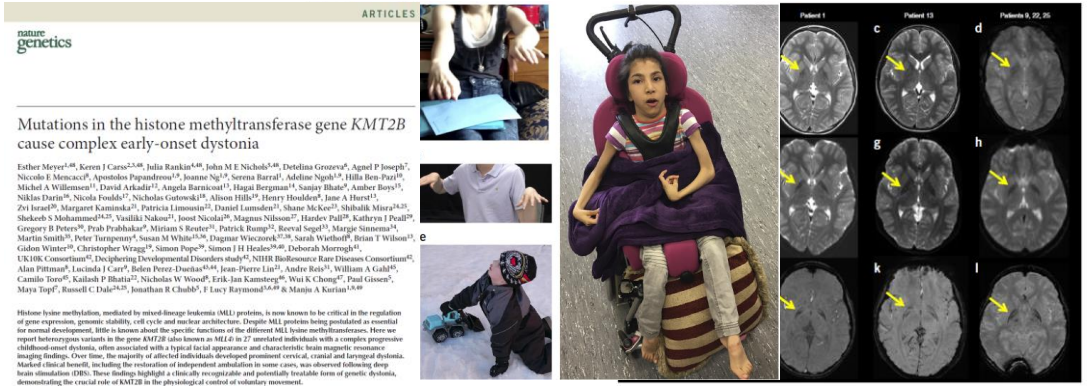


REPORT

Haploinsufficiency of *KMT2B*, Encoding the Lysine-Specific Histone Methyltransferase 2B, Results in Early-Onset Generalized Dystonia

Michael Zech,[1,2] Sylvia Boesch,[3] Esther M. Maier,[4] Ingo Borggraefe,[4] Katharina Vill,[4] Franco Laccone,[5] Veronika Pilshofer,[6] Andres Ceballos-Baumann,[2,7] Bader Alhaddad,[8] Riccardo Berutti,[9] Werner Poewe,[3] Tobias B. Haack,[8,9,10] Bernhard Haslinger,[2] Tim M. Strom,[8,9] and Juliane Winkelmann[1,2,8,11,*]





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REPORT

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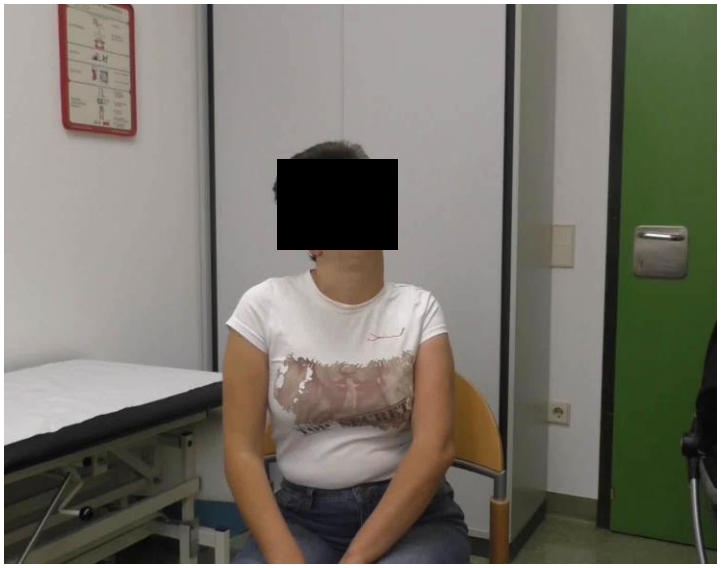
Michael Zech,[1,2] Sylvia Boesch,[3] Esther M. Maier,[4] Ingo Borggraefe,[4] Katharina Vill,[4] Franco Laccone,[5] Veronika Pilshofer,[6] Andres Ceballos-Baumann,[2,7] Bader Alhaddad,[8] Riccardo Berutti,[9] Werner Poewe,[3] Tobias B. Haack,[8,9,10] Bernhard Haslinger,[2] Tim M. Strom,[8,9] and Juliane Winkelmann[1,2,8,11,*]

The American Journal of Human Genetics *99*, 1377–1387, December 1, 2016



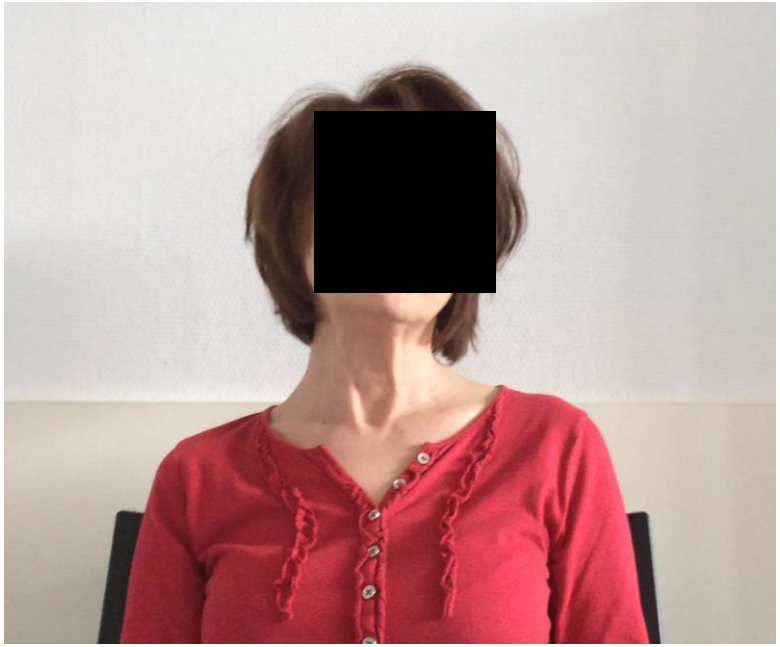
Treatment: DBS – Gpi since 2003 (13 years)
BoNT (adjuvant) cervical and Uex left

Zech M, Boesch S, Maier EM, et al. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in earlyonset generalized dystonia. Am J Hum Genet 2016;99(6):1377–1387. https://doi.org/10.1016/j.ajhg.2016.10.010. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49(2):223–237. https://doi.org/10.1038/ng.3740. Zech M, Lam DD, Winkelmann J. Update on KMT2B-related dystonia. Curr Neurol Neurosci Rep 2019;19(11):92. https://doi.org/10.1007/s11910- 019-1007-y.Ng A, Galosi S, Salz L, et al. Failure to thrive – an overlooked manifestation of KMT2B-related dystonia: a case presentation. BMC Neurol 2020; 20(1):246. https://doi.org/10.1186/s12883-020-01798-x. Artusi CA, Dwivedi A, Romagnolo A, et al. Differential response to pallidal deep brain stimulation among monogenic dystonias: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2020;91(4): 426–433. https://doi.org/10.1136/jnnp-2019-322169.

Complex Dystonia

Defined: dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders

Metabolic disorders with dystonia
Mitochondriopathies
NBIAs
Spastic Paraplegias
Other rare causes for focal or generalized dystonias (z.B. TUBB4A)



Lab-findings
Alpha Fetoprotein **16 ng/ml** (0,0 – 7 ng/ml)
Otherwise unremarkable.

AT (Ataxia Teleangiektasia) Synonym: Louis-Bar Syndrom

Prevalence: ca. 1 : 40 000 – 1 : 100 000, 1-2% of Caucasians are heterozygous, most common childhood-onset ataxia,

Genetics: autosomal recessive, ATM gene, Chrom 11, Serin-Proteinkinase

Phenotype: Ataxia, Teleangiektasias, sensori-motor axonal Neuropathy

Autoimmune Screening: IG subclass deficiency, AFP increased

Immunodefizienz: 60 – 80% , T-Cell deficiency (30%),

Infections: pulmonal/ chron. bronchitis , no oportunistic Infections

Risks for malignancyies 30% cancer (85% Leukaemias/Lymphomas (ALL, CLL), increased risk for brest cancer in heterozygous)

Endokrinology: diabetes mellitus, senilis precox, hypogonadism

Complex Dystonia

Defined: dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders

Metabolic disorders with dystonia
Mitochondriopathies
Rare other conditions that result in dystonia

Patient MK, born 1994, male

Onset of symptoms ~ 2012 (18 years)
Initial symptoms: cervical dystonia,
FU: progression of CD, dystonia LEx (08/2014)

Acute worsening of symptoms 10/2014, involvement of the trunc, massive cervical pain

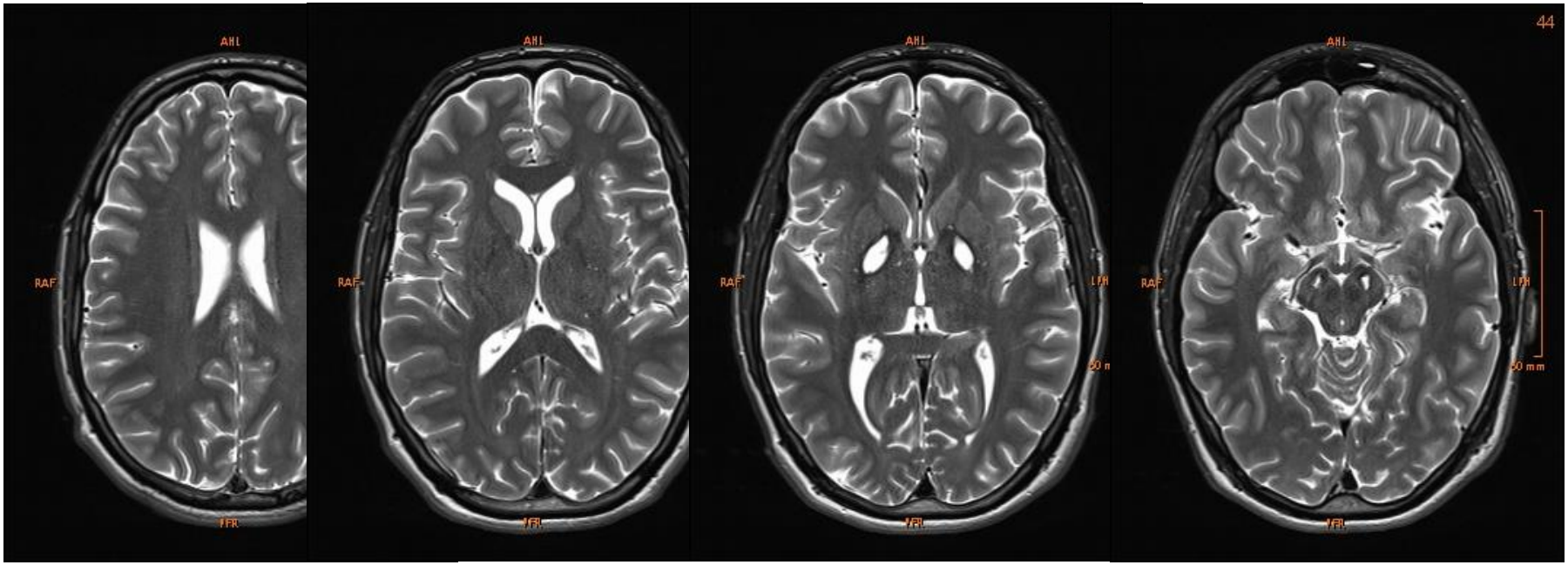
Birth, childhood, motor and cognitive milestones normal,
Infectious disease („flu“ symptoms – serverely sick),
No Hypersensitivity
No illicit drugs, no medication

Co-Morbidity: ITP

Profession: informatics
Family histroy: unremarkable, (parents, 1 sister)

Complex Dystonia

Defined: dystonia dominates the clinical picture but this occurs in the context of complex phenotype including symptoms other than movement disorders



MR-Diagnosis: Leigh or Leigh-like Syndrome

Genetic finding: Mutation in the short-chain enoyl CoA Hydratase (2nd step of the mitochondrial lipid oxidation)
ECHS1 c.[518C>T];[817A>G], p.[Ala173Val];[Lys273Glu]

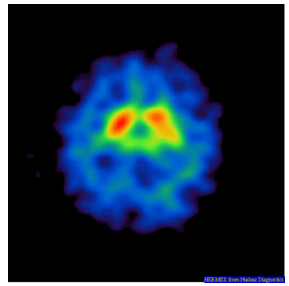
Complex Dystonia

Defined: disorders that usually present with other phenotypes but can have predominant dystonia

Ataxias with dystonia
NBIAs
Spastic Paraplegias (HSP)
Other rare causes of focal/generalized dystonia

Abnormalities of Dopaminergic Neurotransmission in SCA2: A Combined ^{123}I-βCIT and ^{123}I-IBZM SPECT Study

Sylvia M. Boesch, MD,[1*] Eveline Donnemiller, MD,[2] Jörg Müller, MD,[1] Klaus Seppi, MD,[1] Helga Weirich-Schwaiger, MD,[3] Werner Poewe, MD,[1] and Gregor K. Wenning, MD, PhD[1]



Cervical dystonia in spinocerebellar ataxia type 2: clinical and polymyographic findings

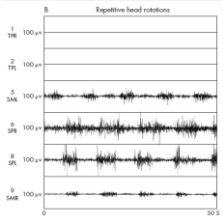
S M Boesch, J Müller, G K Wenning, W Poewe

J Neurol Neurosurg Psychiatry 2007;000:1–4. doi: 10.1136/jnnp.2006.098376

Table 1 Clinical and electrophysiological findings in six SCA2 patients with cervical dystonia

Patient No	CAG repeats	Clinical presentation	EMG activity during spontaneous head position	EMG pattern during head rotation	Geste induced EMG changes	
1	40	Phasic head movements	Tonic activity both SP + SC	Disturbed reciprocal inhibition 4–5 Hz bursts	Tonic both SP	Activation
2	43	Lateroflexion (left) elevation shoulder	Tonic activity both SP + SC	Disturbed reciprocal inhibition	Tonic SCR	Activation
3	40	Rotation (left) and lateroflexion (right)	Tonic activity SPR	Disturbed reciprocal inhibition	Tonic SPL	Activation
4	38	Rotation (left) and lateroflexion (right)	Tonic activity both SP	Disturbed reciprocal inhibition	Tonic SPL	Activation
5	37	Lateroflexion (right)	Tonic activity SPR	Disturbed reciprocal inhibition	Tonic SPL	Activation
6	39	Lateroflexion (right) intermittent head tremor	Tonic-tremulous activation SPR	Disturbed reciprocal inhibition	Tonic both SP	Activation

SC, sternocleidomastoid muscle; SP, splenius capitis muscle; SPL, left splenius capitis muscle; SPR, right splenius capitis muscle.
CAG repeats represent the length of the expanded allele on chromosome 12. Polymyography of the neck included simultaneous recordings of three muscle pairs.



key points/conclusions

Genetic diagnosis should be „state of the art“ in young onset dystonia patients with segmental and generalized dystonia.

Genetic diagnosis in dystonias may result in new treatment options.

Clinical presentation (focal, segmental, multi-focal, generalized) defines therapeutic procedures in most cases.

BoNT remains treatment of choice in focal and most segmental dystonias.