

The Aspen Course

International Parkinson and Movement Disorder Society Pan American Section

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Comprehensive Review of Movement Disorders for the Clinical Practitioner

Ataxia

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Medicine UNIVERSITY OF TORONTO

U of T NEUROLOGY

UHN Krembil Brain Institute

Disclosures

- Advisor for AbbVie, AFFiRis, Alector, Amylyx, Aprinoia, Biogen, BioAdvance, Biohaven, BioVie, BlueRock, BMS, Cavion, CoA Therapeutics, Denali, Janssen, Jazz, Lilly, Novartis, Paladin, Pharma 2B, PsychoGenetics, Roche, Sun Pharma, and UCB.
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Nothing relevant to this lecture

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- Lauren Jackson (Mayo, Rochester Minn)
- Mark Hallett (NIH, Bethesda)

Topics

- Definition
- Anatomical and functional background (pdf)
- Phenomenology & semiology (pdf)
- Classification (pdf)
- Picture Quiz
- Etiologies (Selected Acquired and Genetic Ataxias)
- 2 Cases from Video Challenge

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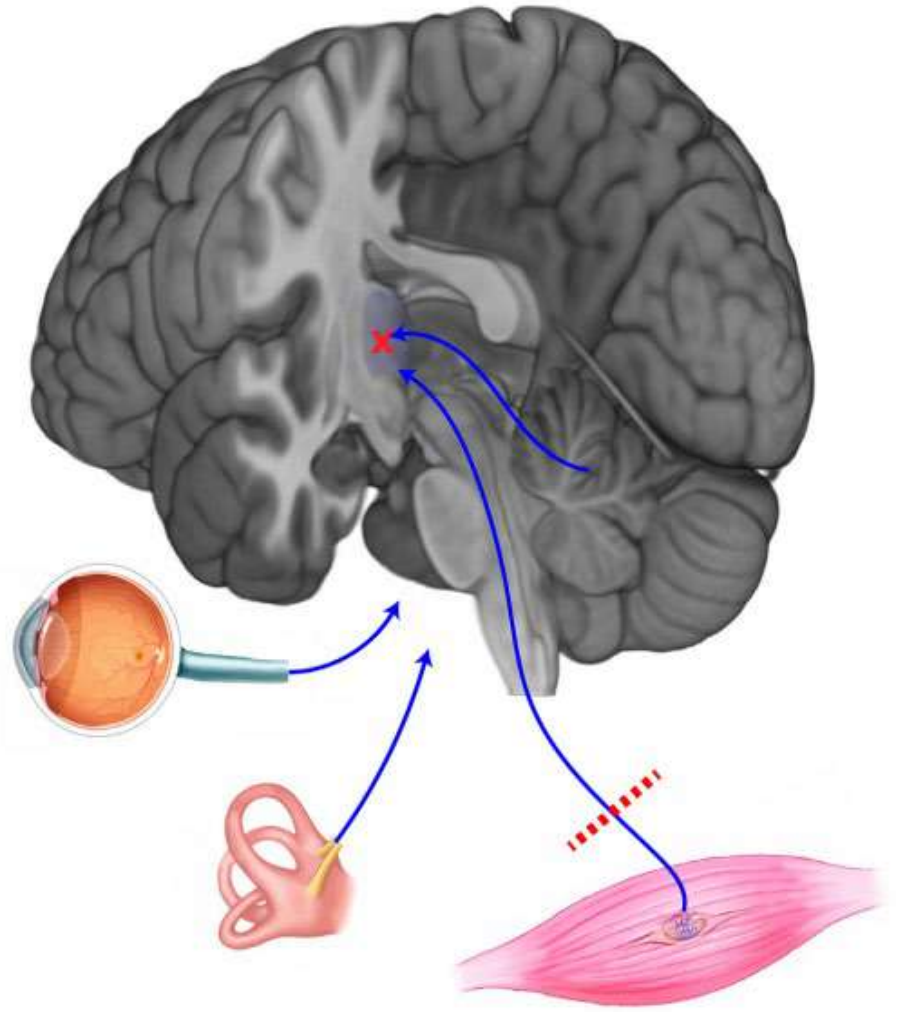
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Showing 1 to 1 of 1 entries

Definition

- Ataxia: lack of "*taxis*" (order, control)
- Involves cerebellar, sensory, and vestibular systems
- Results in incoordination:
  - Eye movements
  - Speech
  - Limbs
  - Gait



Anatomical / Phylogenetic / Functional Background

Phylogenetic Classification

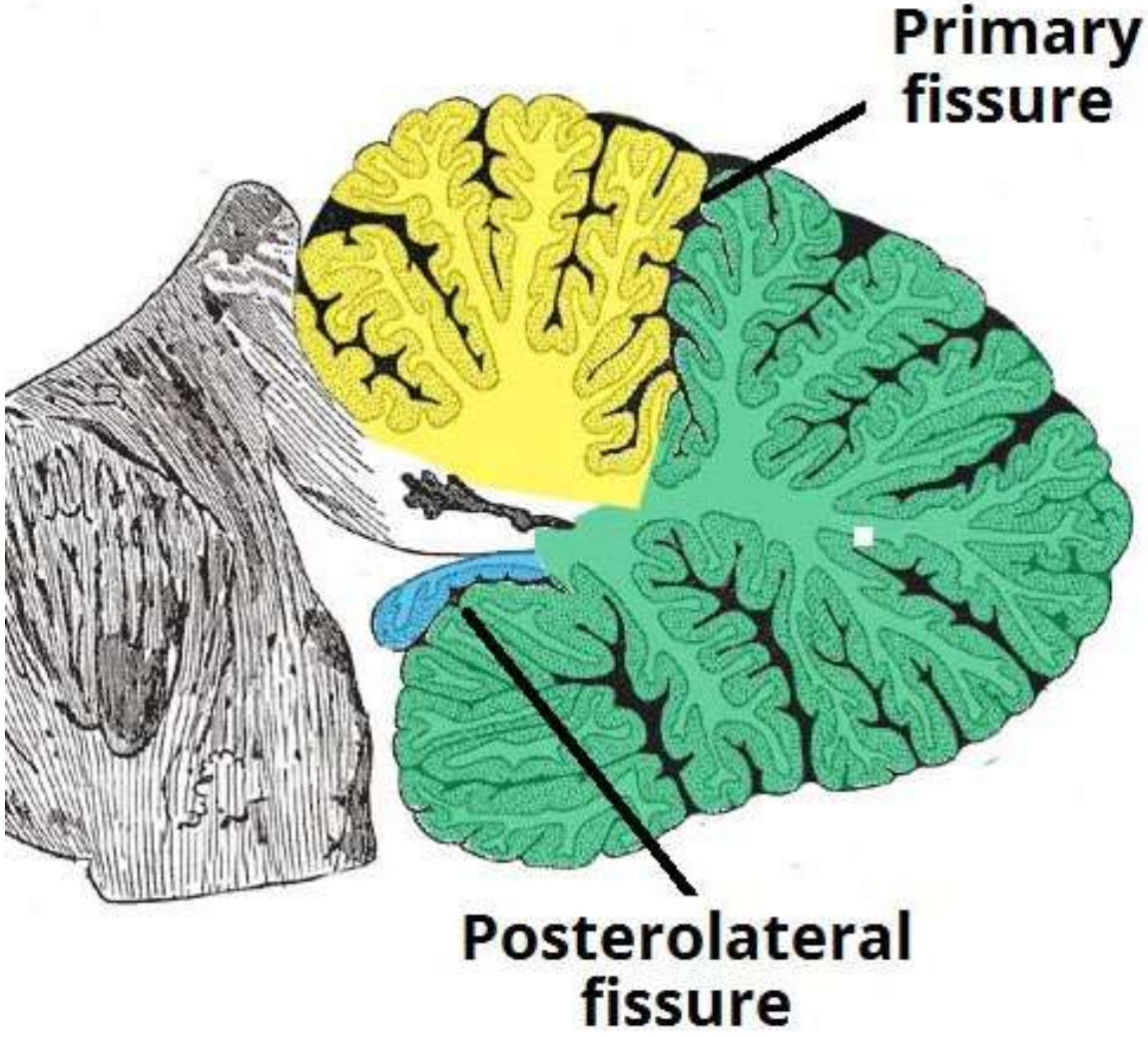
- Archicerebellum
- Paleocerebellum
- Neocerebellum

Functional / Aferent Classification

- Vestibulocerebellum
- Spinocerebellum
- Cerebrocerebellum

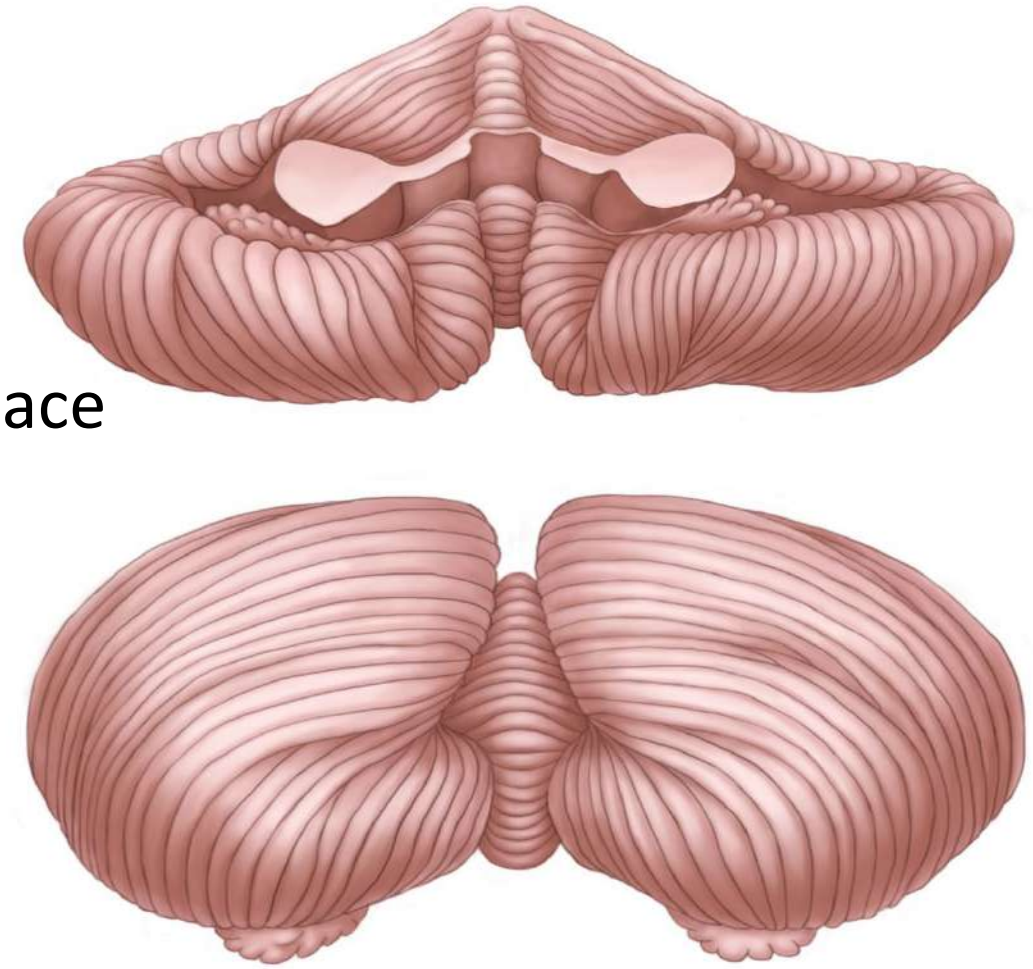
Anatomical Divisions

- Flocularnodular lobe
- Vermis/paravermis
- Hemispheres



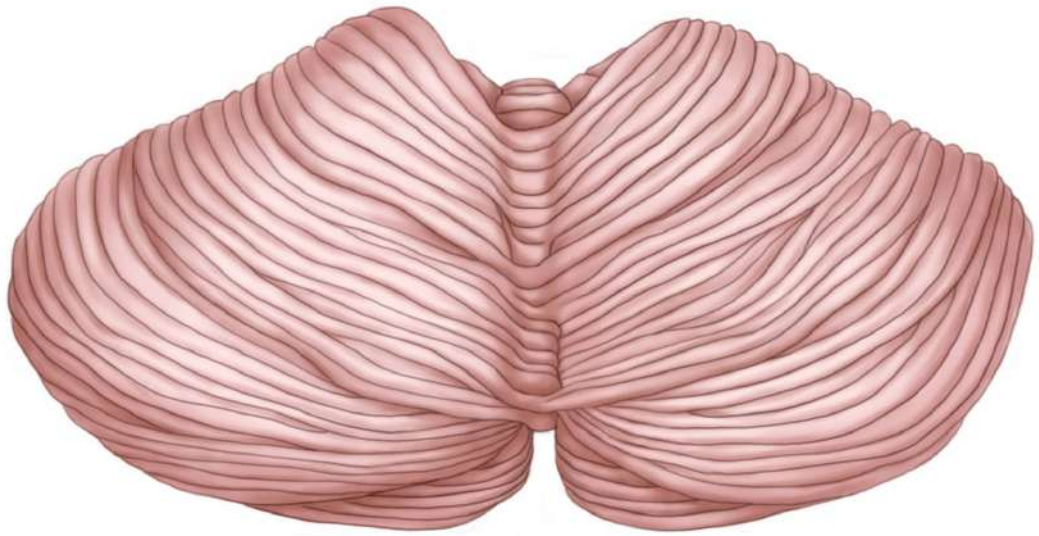
Vestibulocerebellum

- Flocculonodular lobe
- Proprioceptive fibers from vestibular nuclei
- Recognition of **head and neck position** in space
- Adjustment of the **eyes position** and gaze



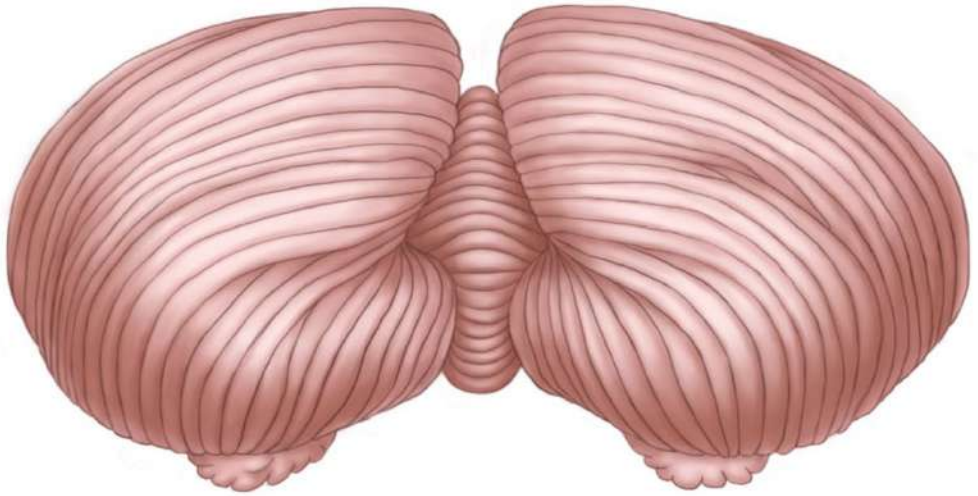
Spinocerebellum

- Anterior lobes, paravermal areas and part of the vermis
- Proprioceptive fibers from the muscles and tendons of the limbs via spinocerebellar tracts
- **Body position (posture), muscle tone, axial muscle control and locomotion**



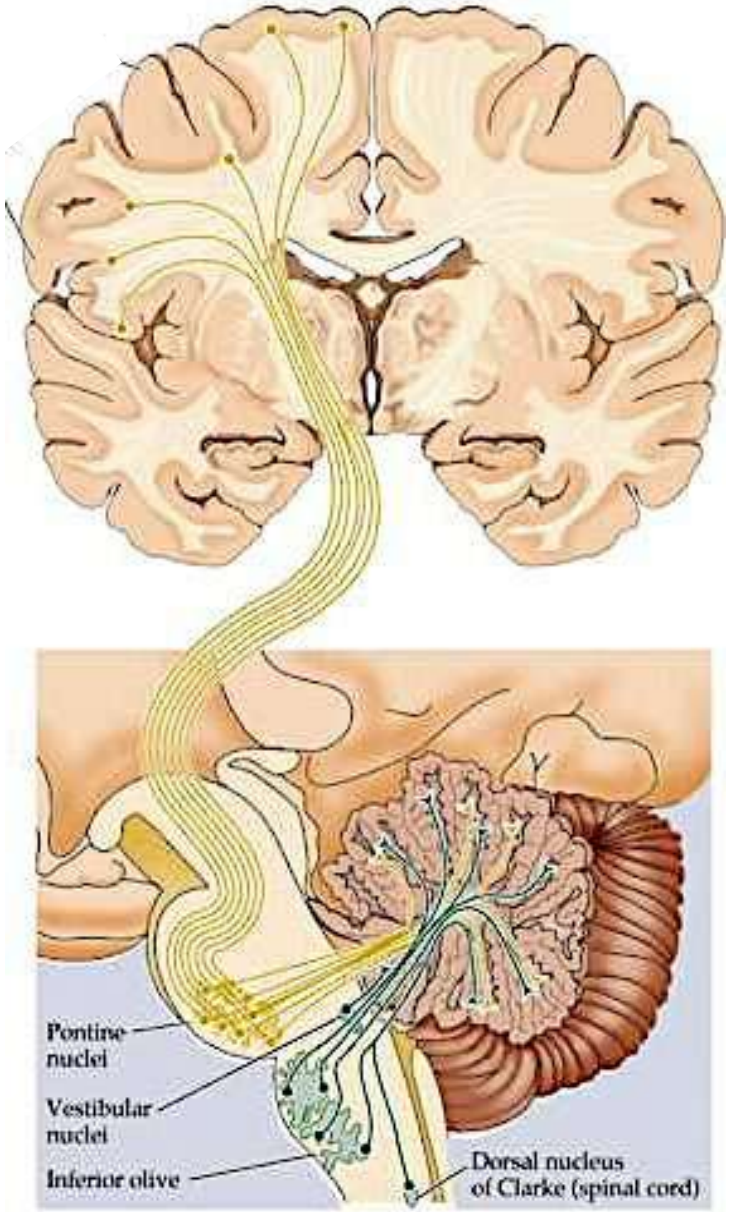
Cerebrocerebellum

- Lateral cerebellar hemispheres
- Afferents from the cerebral cortex via pontine nuclei
- **Coordination of skilled movements** initiated at the cerebral cortex.

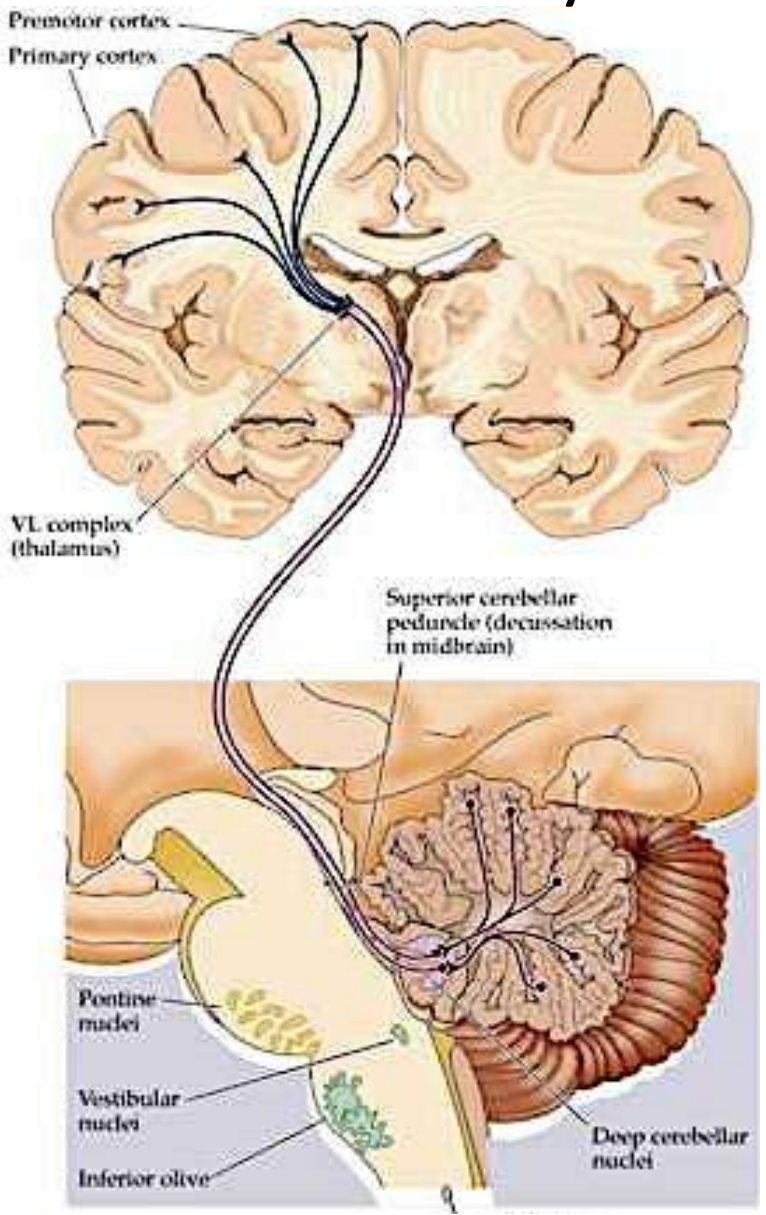


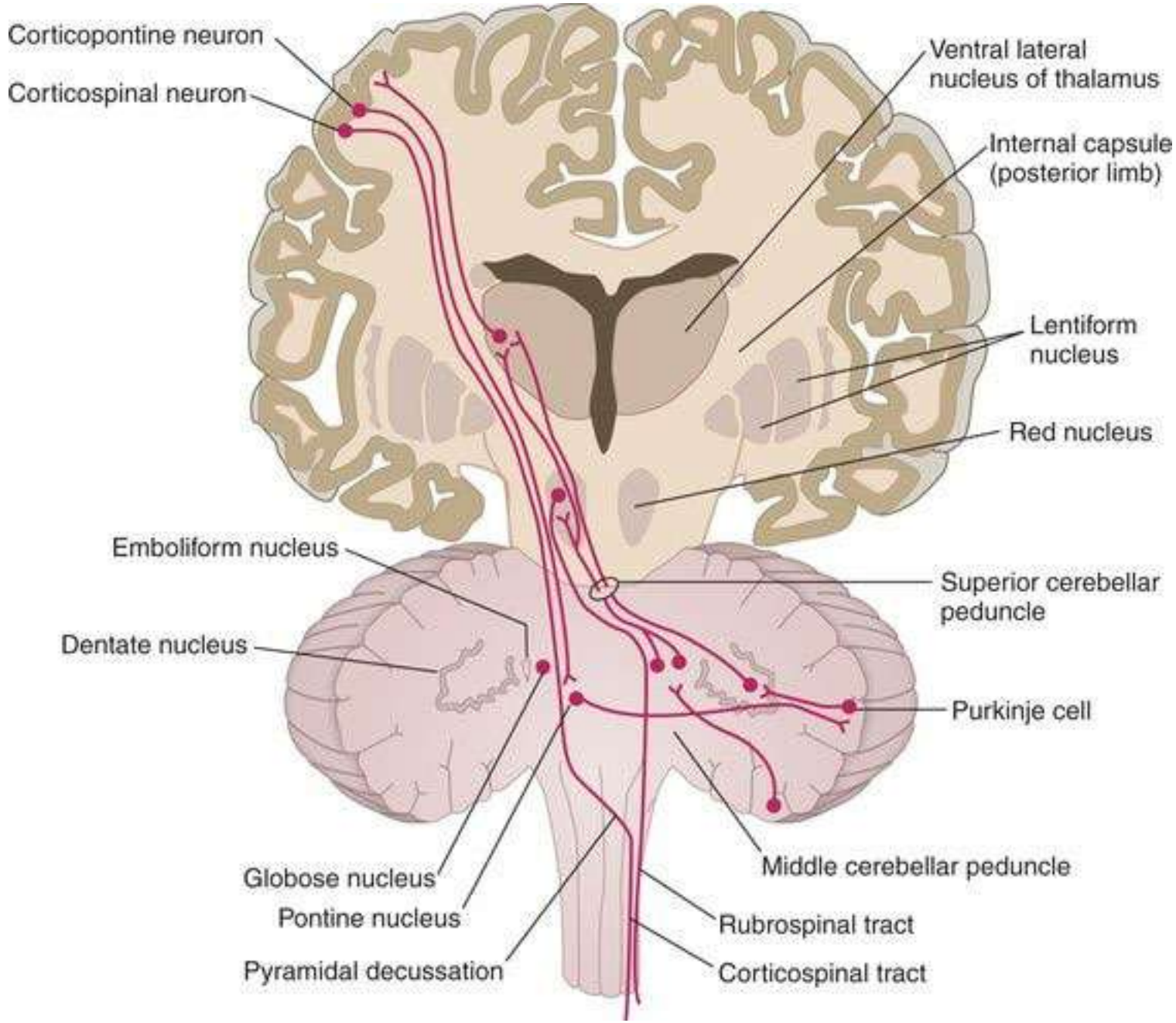
Cerebellar System

Afferent Pathway



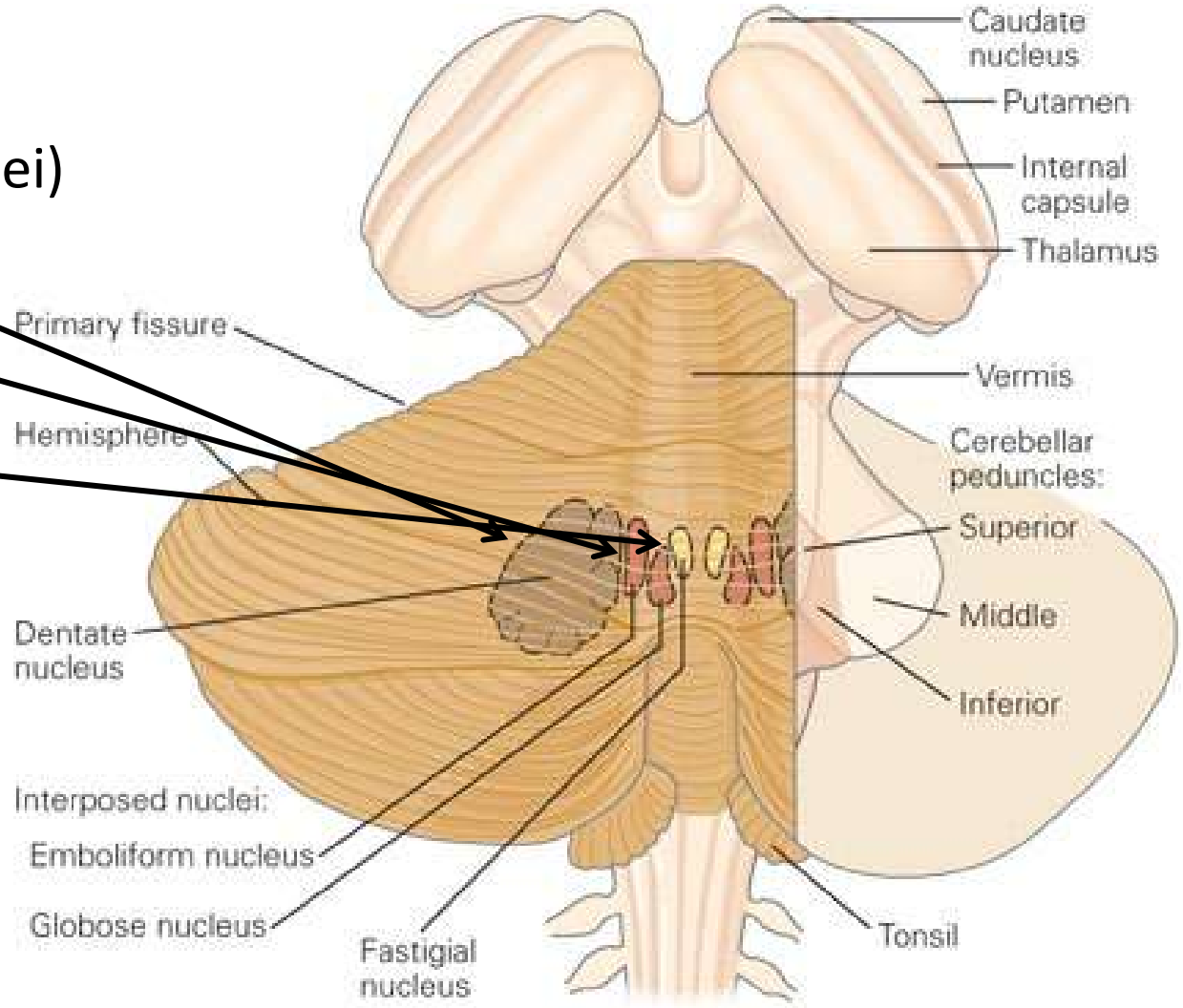
Efferent Pathway




Corticopontine neuron
Corticospinal neuron
Ventral lateral nucleus of thalamus
Internal capsule (posterior limb)
Lentiform nucleus
Red nucleus
Emboliform nucleus
Superior cerebellar peduncle
Dentate nucleus
Purkinje cell
Middle cerebellar peduncle
Globose nucleus
Pontine nucleus
Rubrospinal tract
Pyramidal decussation
Corticospinal tract

Cerebellar Nuclei

- **Dentate nucleus**
  - Efferent to thalamus > cerebral cortex
- **Interposed nuclei** (emboliform & globose nuclei)
  - Afferent from D & V SCT
  - Efferent to red nucleus and thalamus
- **Fastigial nucleus**
  - Afferent from vestibular nucleus



Cerebellar System - Functions

- **Coordination and fluency** of voluntary and involuntary movements by comparing...
  - The **expected** movement (where do I want to be / what do I want to do?)
  - The movement **been performed** (where am I / what am I doing **now**?)
- ...resulting in functional and objective movements.
- This is possible because the cerebellum has afferents from:
  - The cerebral cortex (**expected** movement)
  - Peripheral information about position of bodyparts (movement been **performed**).
- Adjustments are performed in real time and improved by repetition (“error-based learning”)

Phenomenology

Lack of **precision** in terms of **rhythm**, **range**, **direction** and **strength**

- **Dysmetria** – imprecision in **space**
  - Overshooting (hypermetria)
    - Finger-nose / heel-shin
    - Finger mirroring test
    - Circular movements (fingers / foot)
- **Dysdiadochokinesia** – imprecision in **time**
  - Inability to start and stop movements at appropriate times
    - Alternating movements of the hands
    - Rhythmic finger / toe tap on a solid surface
    - Heel-knee tapping
- **Dyssynergia** – performance of harmonious multivectorial movements
  - Each vector is “broken” and performed separately

Worse for quick movements and involve multiple joints / body parts.

Phenomenology - Oscillations

- **Postural oscillations**:
  - Head and trunk (titubation) - ~3Hz
  - Upper and lower extremities (postural component of cerebellar tremor)

- **Kinetic oscillations**: finger–nose
  - **Intention tremor**:
    - High amplitude, low frequency
    - Coarse / irregular
    - Worse at end points
  - Intention tremor likely represents a series of **imperfect corrective movements**, resulting from **time-delayed sensory feedback**.
  - Accordingly, intention tremor is reduced when pointing to a target with eyes closed, reducing visually guided corrections.

Phenomenology - Axial

- **Posture:**
  - Stand on a neutral position – “What is a comfortable stance for you?”
  - Look for the distance between feet
  - Stand with progressively narrower base and how uncomfortable that is.
  - “Tendon dance”
- **Gait:**
  - Wide based, staggering, irregular stepping, veering, excessive lifting of the feet above, leg moves at abnormal rates relative to one another.
  - **Tandem gait** accentuates all features, is the most sensitive clinical test.
  - For dubious cases: single leg stance and hop on one foot.
  - Patients often make normal isolated leg movements despite profound gait ataxia, suggesting that cerebellar control of **walking (midline)** is independent from voluntary control of **isolated leg movements (intermediate and lateral areas)**.

Phenomenology – Eye Movements

- Primary position and smooth pursuit (nystagmus / square-wave jerks).
  - **Spontaneous vs. fixation nystagmus**: central nystagmus not suppressed by fixation, peripheral vestibular nystagmus is.
  - **Vertical, torsional and down-beat** nystagmus almost always central
  - **Central nystagmus**: large-amplitude, lower-frequency gaze-evoked
  - **Peripheral nystagmus**: mixed horizontal-torsional, changes depending on the direction of gaze - more when gaze is directed toward the side of the fast-beating component.
- May be described by the patient as blurred vision, diplopia or oscillopsia
- Saccadic dysmetria (overshooting) is best observed when the patient moves the eyes from an eccentric to the primary position of gaze.

Phenomenology - Speech

- Variations in pitch and volume
- Tremor
- “pa, pa, pa”, "la, la, la”, “ma, ma, ma”, “ka, ka, ka”: rapid alternating movements of the tongue, lips and jaw.
- Longer sentences: rhythm, volume, pitch, and enunciation.
  - Scanning speech: slow, labored, uneven stress on syllables

Phenomenology - Cognition

- Less obvious than sensory-motor function.
- Puzzling as the cerebellum projects/receives input from frontal, parietal & temporal cortices; cognitive tasks activate the cerebellum in fMRI studies.
- Heterogeneous descriptions of deficits have been reported in tests of language, executive function, emotion, and attention after cerebellar damage.
- More pronounced with acute lesions, disappear with longer term neocortical compensations for cerebellar loss.
- Movement related cortical areas compensate less than those involved in cognition.

Ataxia - Classification

- **Topography**
- **Clinical course**
- **Etiology**

Ataxia - Classification

Topography

- Peripheral or Sensory
- Vestibular
- Cerebellar
  - Midline
  - Hemispheric
- Thalamic
- Frontal

Sensory* vs Cerebellar Ataxia

Cerebellar ataxia	Sensory ataxia
Scanning speech	Normal speech
Nystagmus and other ocular signs	No nystagmus
Sensory exam and Romberg test normal	Sensory loss, Romberg test abnormal Pseudoathetosis
Pendular reflexes	Hypo – areflexia**
Reeling, ataxic gait	Stamping gait

* Loss of sensory input necessary for movement adjustments
* Sensory neuropathy, ganglinopathy and posterior column lesions e.g. Sjogren syndrome, cisplatin, paraneoplastic sd., SACD (B12), tabes dorsalis

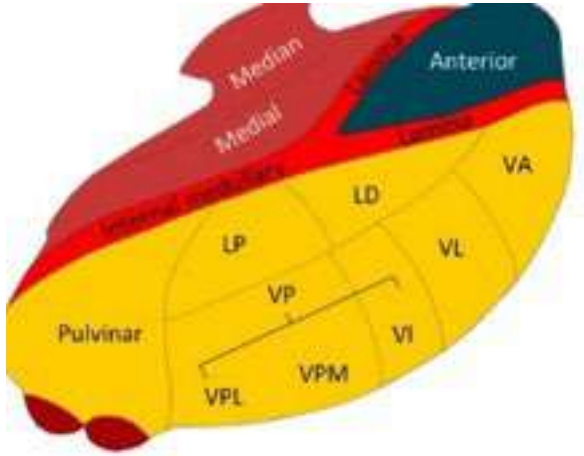
**Hyper in posterior column lesions

Vestibular vs Cerebellar Ataxia

Cerebellar ataxia	Vestibular disorders
Sense of imbalance	Vertigo ± associated tinnitus ± hearing loss Sx worse with changes in body position
Dysmetria in the ipsilateral limb	Mild, bilateral
Gaze evoked nystagmus	Slow phase drifts Increases when eyes are turned in the direction of the quick phases (Alexander law) Suppressed by visual fixation Fast phase opposite to the side of the lesion Exacerbated by change in head position
Scanning speech, intention tremors, dysdiadochokinesia, rebound phenomena, hypotonia and pendular reflexes	Absent

Thalamic Ataxia

- **Hemiataxia** similar to cerebellar but…
- …never occurs in isolation:
  - Ipsilateral **sensory** disturbance (hemiataxia hypoesthesia)
  - **Hemiparesis** (ataxic hemiparesis)
  - Sensory disturbance and hemiparesis (hypoesthetic ataxic hemiparesis)
- Hemiataxia: VPL thalamus lesions, adjacent to the corticospinal tract (hemiparesis) and the VP thalamus (hypoesthesia).
- Recovery: sensory / motor deficits improve before and better than ataxia.

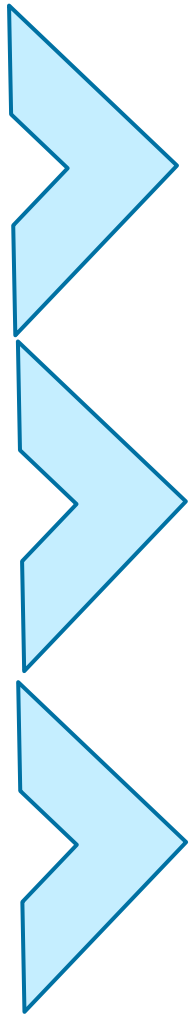


Cerebellar vs Frontal Ataxia

	Cerebellar Ataxia	Frontal Ataxia
Base of support	Wide based	Wide based
Velocity	Variable	Very slow
Stride	Irregular, lurching	Short, shuffling
Heal-shin	Abnormal	Normal
Initiation	Normal	Hesitant
Turns	Unsteady	Hesitant, Multistep
Postural instability	**	****
Falls	Late	Frequent

ATAXIA DISORDERS

- Vascular
- Infectious
- Traumatic
- Autoimmune
- Metabolic/toxic
- Iatrogenic
- Neoplastic
- Congenital
- Degenerative
- Endocrine



Acute

Subacute

Chronic

Work up

- Imaging (MRI, head/spine)
- Blood work
- Spinal fluid
- Autonomic testing
- Vestibular testing
- Genetic testing

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Time Course	Cause	Syndromes/Diseases
Acute	Stroke	Brainstem stroke syndromes (posterior circulation stroke)
	Toxic/Metabolic	Alcohol, hypoxia, vitamin deficiencies, zinc deficiency, endocrine causes (hypothyroidism), drug induced
	Infections	Rubella, Hemophilus influenza, post-infectious cerebellitis (most commonly varicella zoster), Creutzfeldt-Jakob disease
Subacute	Tumors	Medulloblastoma, Astrocytoma, Ependymoma, Hemangioblastoma, Metastatic tumor, Meningioma, Schwannoma
	Autoimmune & Paraneoplastic	Paraneoplastic (breast, lung, testicular, and Hodgkin lymphoma), GAD antibody ataxia, celiac diseases
Chronic	Degenerative Ataxia	Multiple System Atrophy (MSA), late onset genetic causes of ataxia
	Demyelinating	Multiple sclerosis, acute disseminated encephalomyelitis, Miller Fisher syndrome
	Other Syndromes	Superficial siderosis, Chiari malformation, abscesses, hydrocephalus

MDS Web-based education: Ataxia

Important Points from Clinical History

- **Age at onset** of any sign/symptom of the syndrome
- Ethnic **background** (patient and most remote ancestors)
- Mode of **onset** (sudden, insidious)
- Precipitating factors
- Rate of **progression** (insidious, aggressiveness, paroxysmal)
- Presence of **non-motor and systemic** symptoms
- **Exposure** to drugs or toxins
- **Family history** of motor or systemic signs of the syndrome

Approach to the Patient with Ataxia

IMPORTANT POINTS IN THE HISTORY

- **HPI**
  - Age at Onset
  - Progression of the disease- EPISODIC?
  - Other neurologic symptoms - RBD
  - Systemic symptoms – CHRONIC COUGH
- **Comorbidities**
  - Malignancies
  - Thyroid disorders
  - Infections
  - Drugs
- **Detailed Family History**
  - Parents? Siblings? Relatives?
  - Consanguinous marriage?
  - Ethnic origin?
- **Personal/Social History**
  - Alcohol consumption

Approach to the Patient with Ataxia

IMPORTANT PARTS OF THE PE

- **Cerebellar examination**
  - Localize- which part of the cerebellum?

- Ocular motor function
- Speech
- Tone
- Stance and Gait

- Presence of other movement disorders

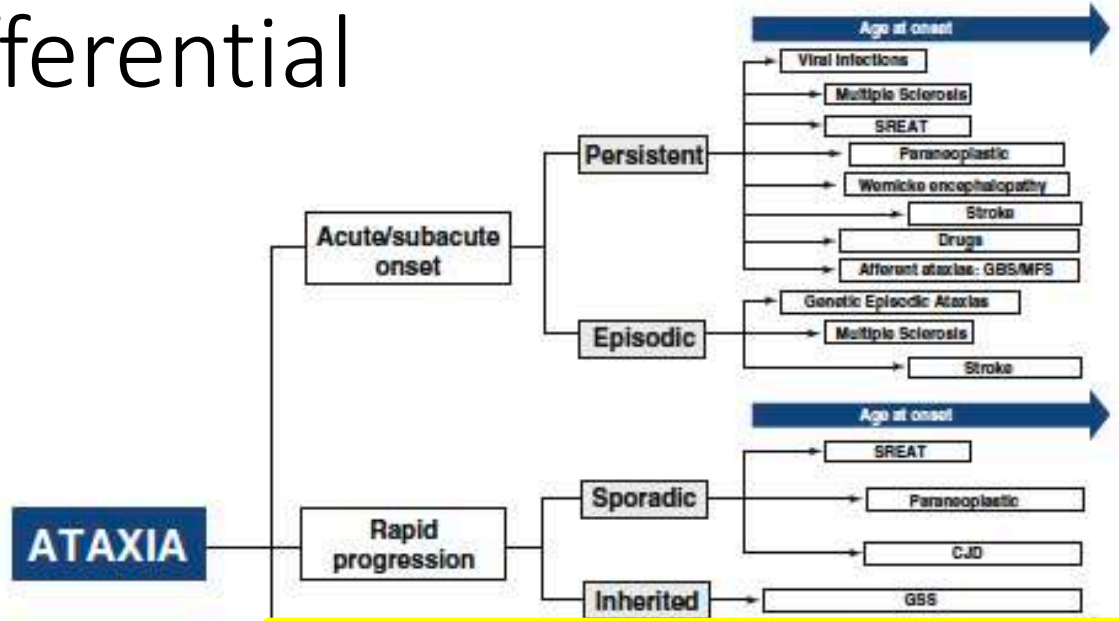
- Presence of other neurologic symptoms

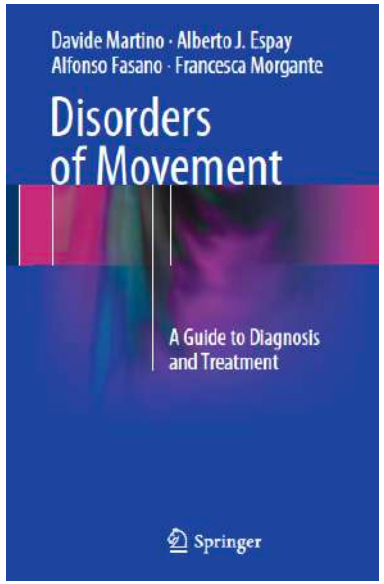
- Systemic signs

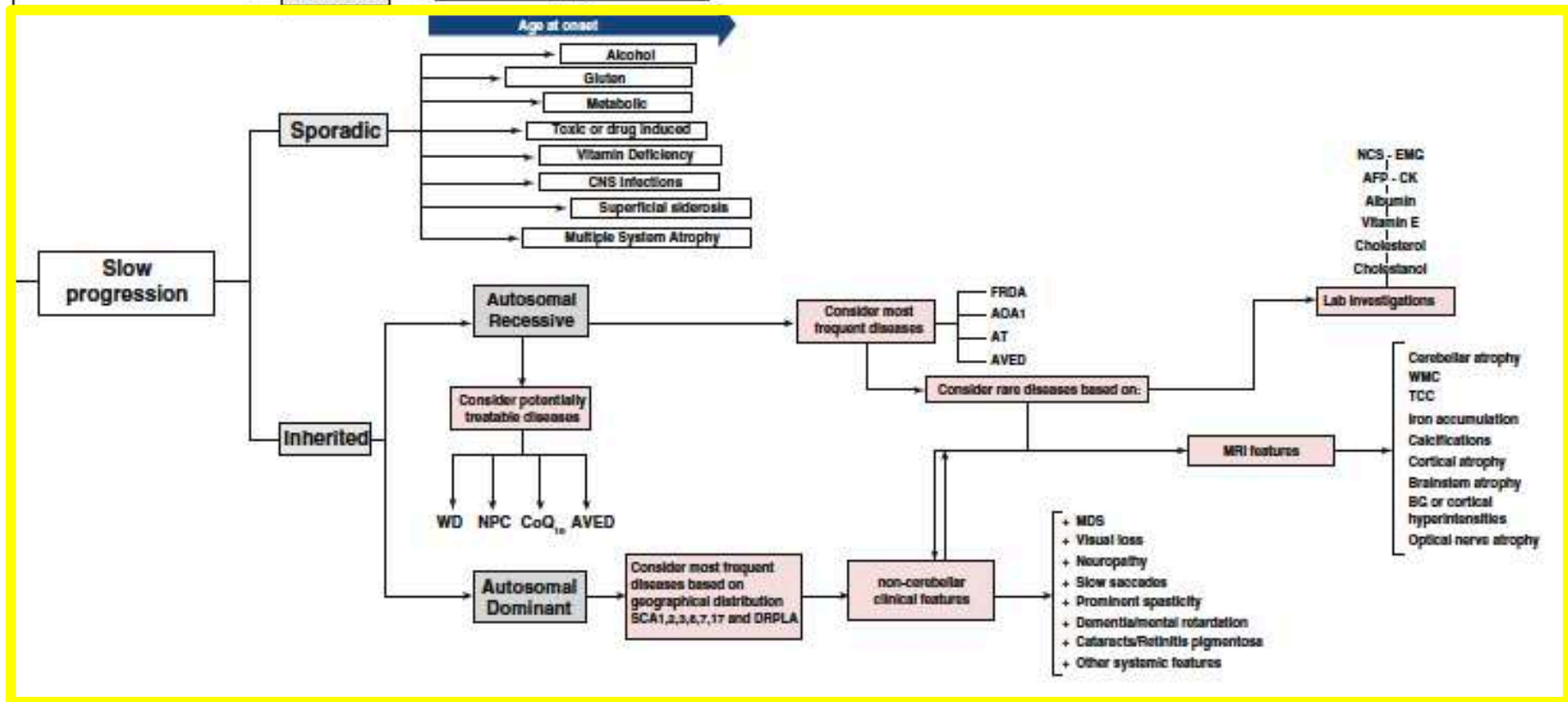
CEREBELLAR LESION AND PHENOMENOLOGY

Lesion	**Clinical Manifestation**
Vermis	Truncal + gait ataxia
Cerebellar hemispheres	Appendicular ataxia
Lateralized	Ipsilateral signs and symptoms
Generalized	Bilateral symmetrical symptomatology
Acute	Severe at onset, good recovery with time *(not if deep nuclei lesions)*
Chronic/degenerative	Gradual progressive decline

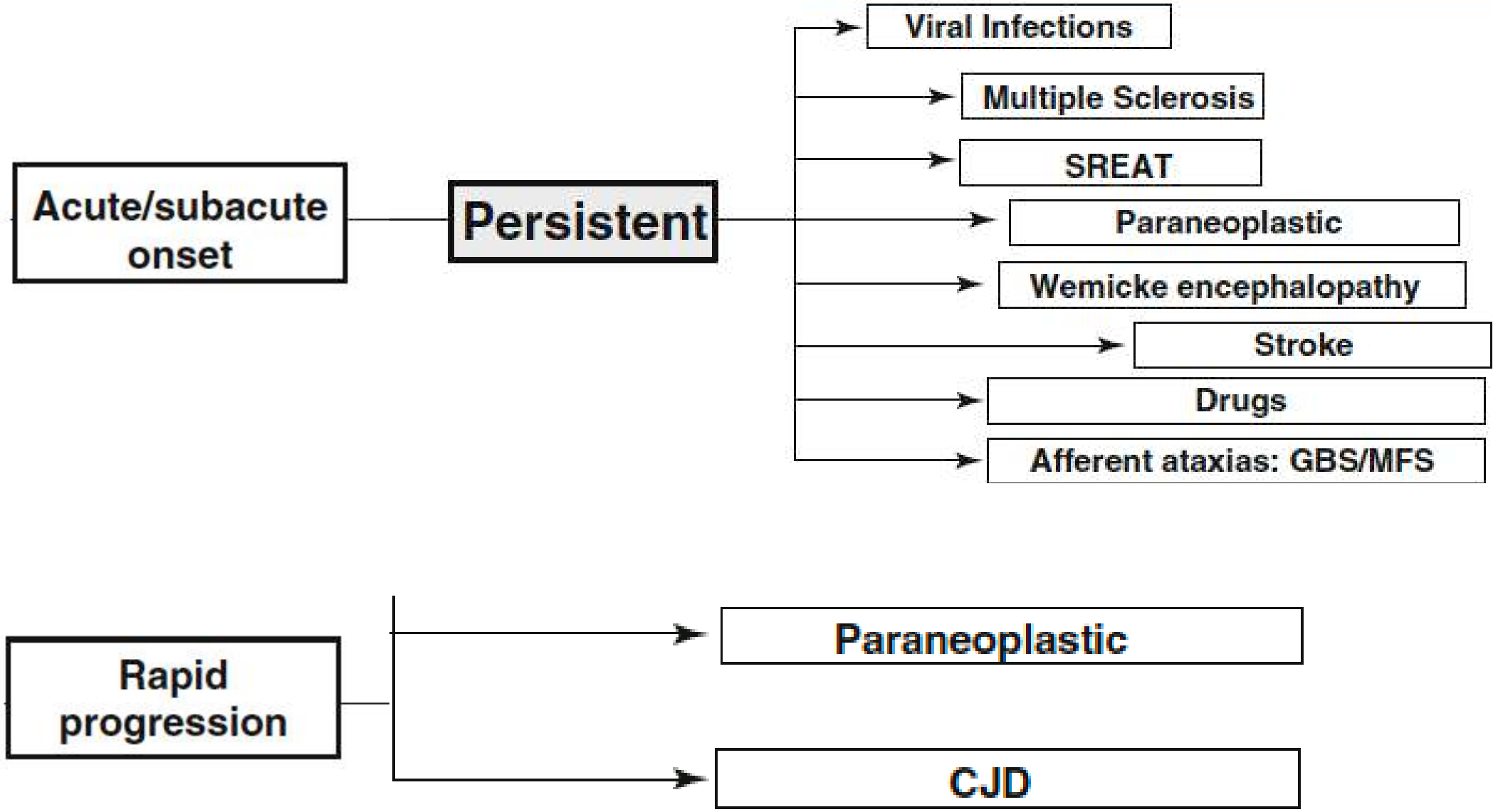
Ataxia Differential



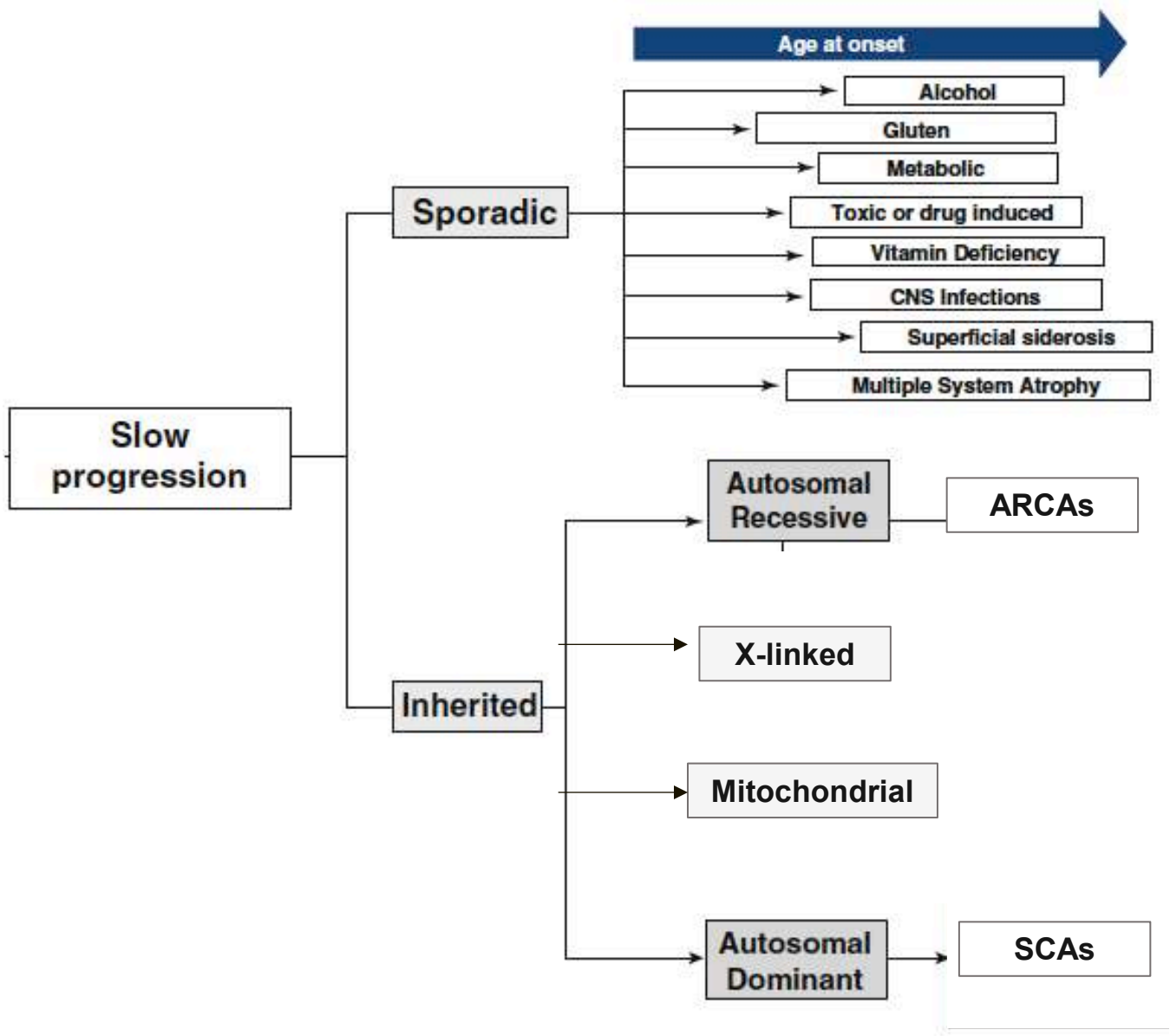




Ataxia Differential: Acute/Subacute Progression

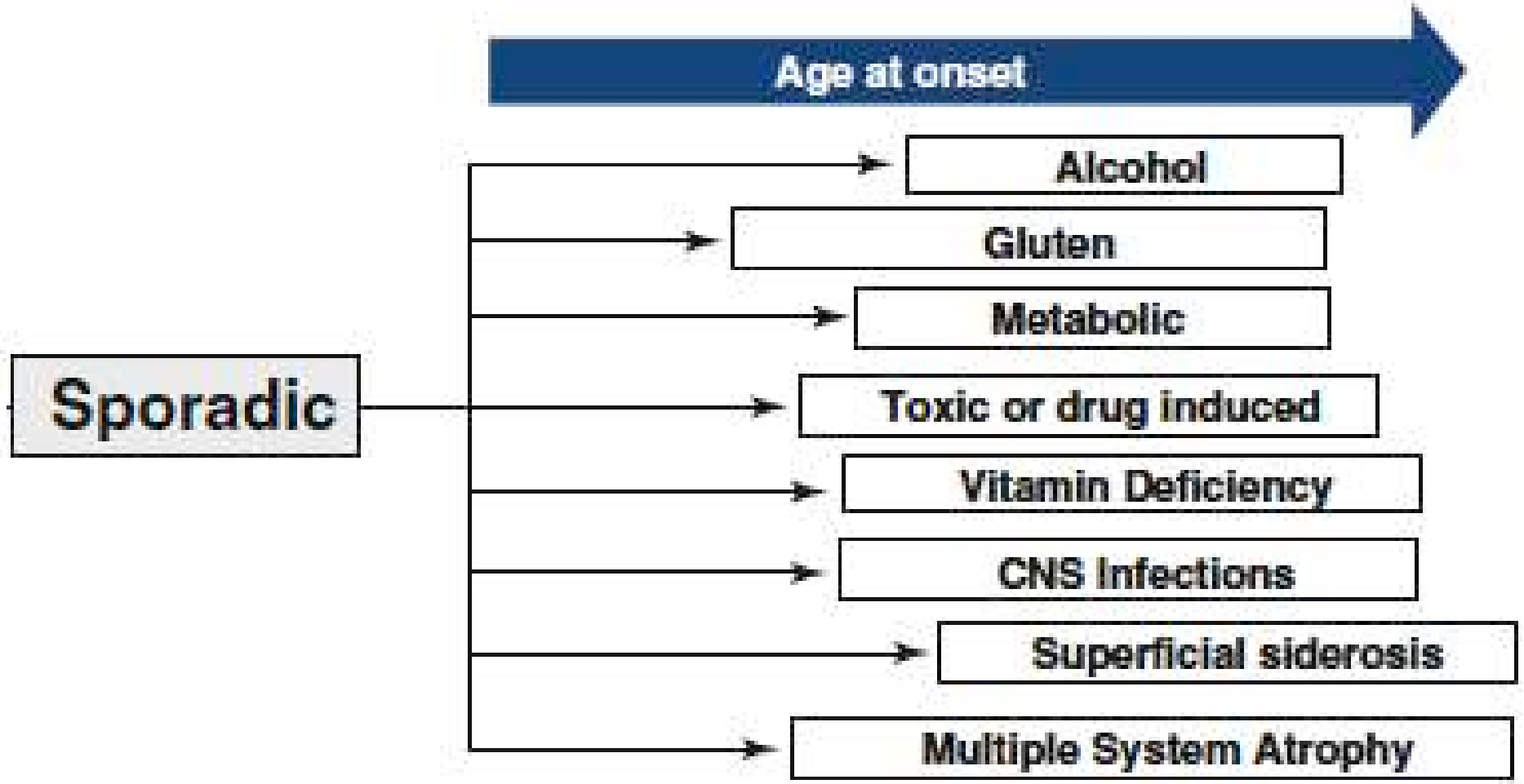


Ataxia Differential: Slow Progression



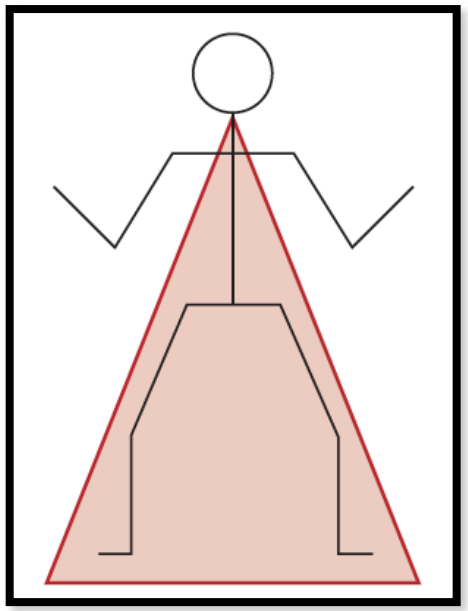
ACQUIRED ATAXIAS

Ataxia Differential: Slow Progression

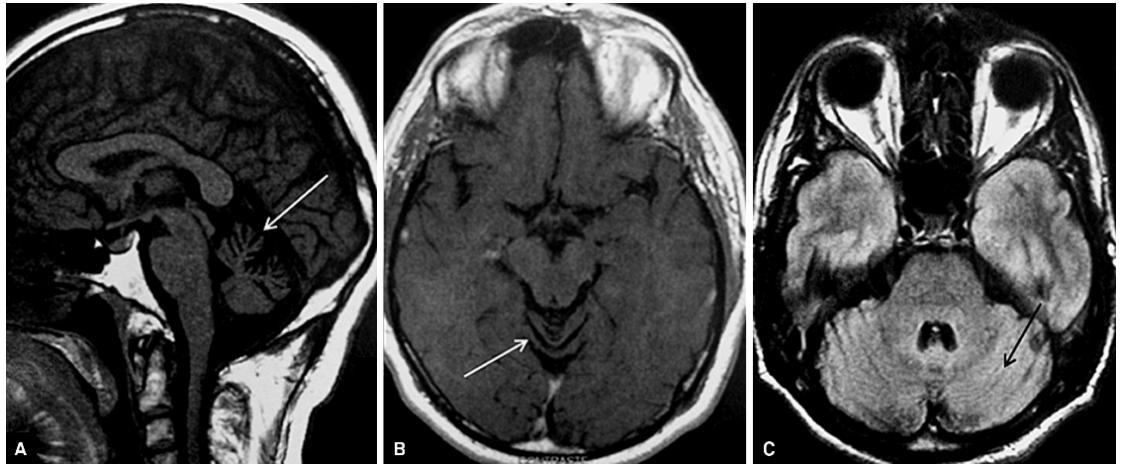


Consider other uncommon intoxications e.g., Lead, Toluene

Alcohol Induced Cerebellar Ataxia/Degeneration

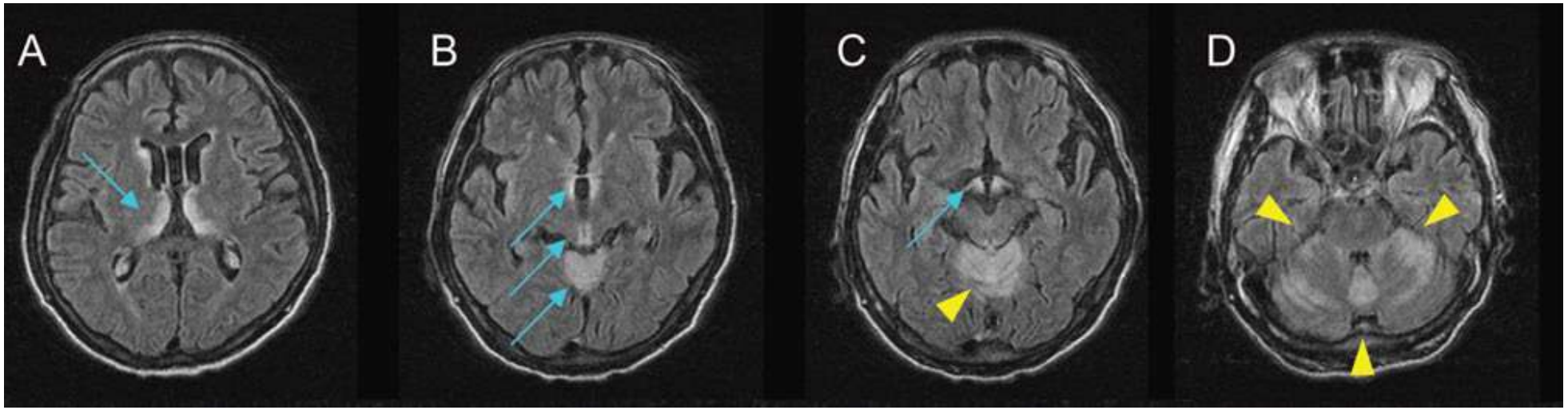


- Most common acquired toxic ataxia
- Onset middle-age; evolving weeks to months.
- “Lower body ataxia”, milder involvement UL, relatively preserve speech/ocular
- Imaging: cerebellar atrophy with predominance of the superior cerebellar vermis.
- Pathogenesis: toxicity to cerebellum and vitamin B1 def’y
- Treatment: alcohol abstinence +/- thiamine replacement; variable response.



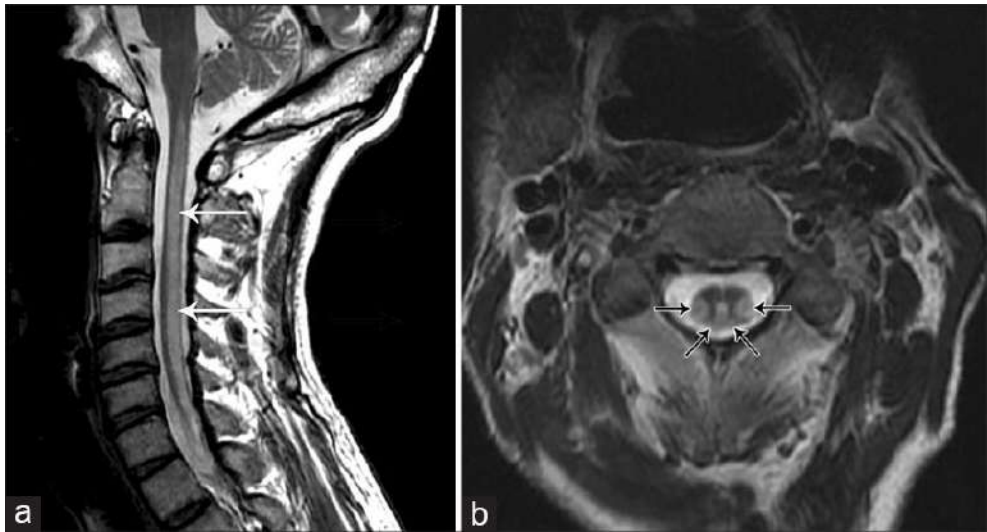
Vitamin Deficiencies: B1

- **Vitamin B1** (thiamine): Wernicke encephalopathy (ataxia, confusion and ophthalmoparesis)
- Most frequent alcohol use disorder; also anorexia, hyperemesis, parenteral nutrition without proper supplementation, bariatric surgery
- MRI: symmetric changes in thalami, MB, tectal plate, PAG
- IV Thiamine may improve symptoms and signs, residual ataxia common



Vitamin Deficiencies: B12

- **Cause**: atrophic gastritis, pernicious anemia, celiac disease, bariatric surgery etc.
- Features: **sensory ataxia**, peripheral neuropathy, pyramidal signs
- Serum B12 usually decreased, but high serum homocysteine and methylmalonic acid also useful
- TX: Intramuscular replacement of vitamin B12
- MRI: may show hyperintensity in posterior and lateral columns of cervical or thoracic spinal cord.



Drug-Induced Ataxia

- 57 drugs described in systematic review in 2014

- Most common drugs:

  Antiepileptics, Benzodiazepines, Antineoplastic

- Most are reversible, ***except***:

  Phenytoin, Lithium, Cytarabine

Gaalen et al. 2014 – systematic review drug-induced ataxia

- **NEW DRUGS- Immune Checkpoint Inhibitors:** rarely cause of ataxia, 46% improved with residual disability (treated) *Dentoni et al. 2024*

SARS-CoV-2 infection associated ataxia

- Ataxia/myoclonus common post-COVID movement disorders (63/81 cases)
- **Symptoms began ~**12.6 days post-infection
  - Persisted at 7.5 weeks (22%)
  - Risk factors (**HTN, cancer**)
- Imaging abnormalities (37%)
- Glutamate receptor delta autoantibodies reported
- COVID-19 cerebellitis improved with anti-virals/steroids/IVIG

J Neurol. 2023 May;270(5):2409-2415. doi: 10.1007/s00415-023-11661-x. Epub 2023 Mar 21.

COVID19-associated new-onset movement disorders: a follow-up study



Susanne A Schneider [1], Soaham Desai [2], Onanong Phokaewvarangkul [3], Elena Cecilia Rosca [4], Jirada Sringean [3], Pria Anand [5], Gary Álvarez Bravo [6], Francisco Cardoso [7], Anna M Cervantes-Arslanian [5], Harshad Chovatiya [2], David Crosiers [8 9], Femke Dijkstra [8 9], Conor Fearon [10], Francisco Grandas [11], Eric Guedj [12], Antonio Méndez-Guerrero [13], Muhammad Hassan [14], Joseph Jankovic [15], Anthony E Lang [10], Karim Makhoul [15], Lorenzo Muccioli [16], Sarah A O'Shea [17], Vahid Reza Ostovan [18], Javier Ricardo Perez-Sanchez [11], Ritesh Ramdhani [19], Victoria Ros-Castelló [20], Christina Schulte [21], Priyank Shah [22], Lars Wojtecki [21 23], Pramod Kumar Pal [24]

Case Reports › J Neurovirol. 2023 Dec;29(6):731-733. doi: 10.1007/s13365-023-01183-7. Epub 2023 Nov 6.

Acute cerebellitis following COVID-19 infection associated with autoantibodies to glutamate receptors: a case report



Takuya Watanabe [1], Yuki Kakinuma [1], Keiko Watanabe [1], Ryuta Kinno [2]

Affiliations + expand

PMID: 37930583 PMCID: PMC10794470 DOI: 10.1007/s13365-023-01183-7

› Heliyon. 2024 Jul 11;10(14):e34497. doi: 10.1016/j.heliyon.2024.e34497. eCollection 2024 Jul 30.

Cerebellitis following COVID-19 infection: A case-based systematic review and pooled analysis



Soroush Najdaghi [1], Delaram Narimani Davani [1], Mohammadreza Hashemian [2], Narges Ebrahimi [1 3]

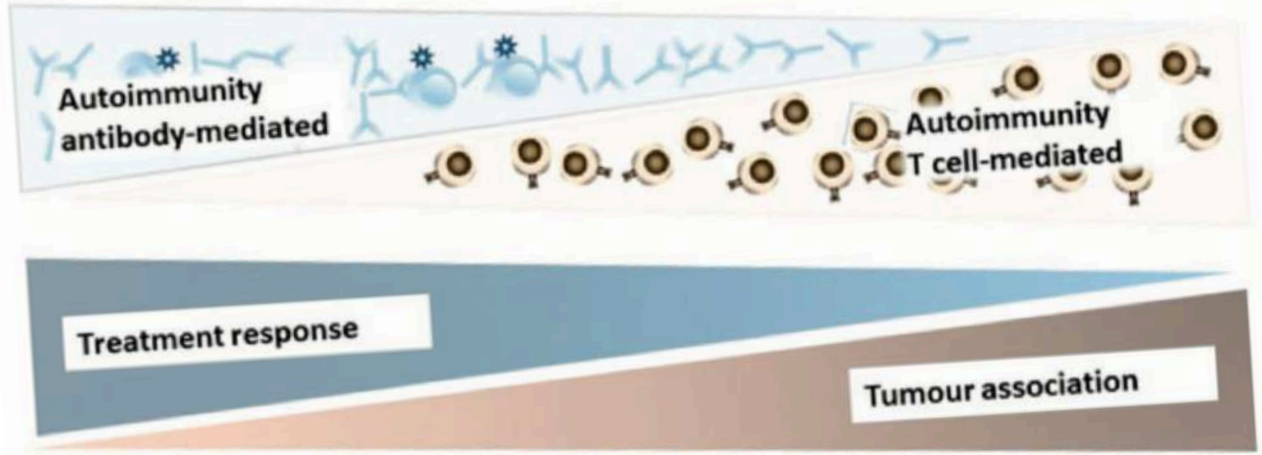
Affiliations + expand

PMID: 39113976 PMCID: PMC11305223 DOI: 10.1016/j.heliyon.2024.e34497

Paraneoplastic Cerebellar Degeneration

- Immune-mediated, affects cerebellar cortex
- Small cell lung CA, breast and ovarian, Hodgkin's lymphoma.
- Ataxia onset usually subacute, symptoms develop over weeks, rapid progression
- Brain imaging usually unremarkable, cerebellar atrophy may develop in late stages.
- CSF shows mild pleocytosis and / or elevated proteins.
- In general, no response to treatment of the underlying tumor. Exceptional cases improved after steroids/IVIG /PLEX

	Antibodies			
	Intracellular antigen	Cancer association	Cell-surface antigen	Cancer association
Ataxia	ANNA1 (Hu)	SCLC	CASPR2	Thymoma
	ANNA3 (DACH1)	Lung, GI	*Lgi1*	Lymphoma
	AGNA1 (SOX1)	SCLC	DPPX	SCLC
	VGCC	SCLC	$GABA_B$-R	Hodgkin lymphoma
	CRMP5 (CV2)	SCLC	PCA-Tr (DNER)	Lymphoma
	ANNA2 (Ri)	SCLC, thymoma	*IgLON5*	Endometrial (1 patient)
	PCA1 (Yo)	Breast, gynecologic	mGLuR1	Ovarian adenocarcinoma
	Ma2	Testicular germ cell, other	*Septin5*	(1 patient) (Small cell
	KLHL11	Seminoma	*AP3B2*	carcinoma, 1 patient)
	PCA2 (MAP1B)	SCLC	Neurochondrin	
	GAD65	Diverse (rare)	SEZ6L2	
	GFAP	Teratoma, other	mGluR2	
	NIF	SCLC, Neuroendocrine		
	RGS8	Lymphoma		
	Homer3	SCLC		
	TRIM9, 46, 67	SCLC, neuroendocrine, other		
	GRAF/ARHGAP26	SqCC H+N, lung		
	ITPR1	Breast, endometrial		



McKeon & Tracy 2024
Handbook Clin Neurol, vol 200

Treatable Causes of Ataxia: Autoimmune

ANTIBODIES	
GAD	PCA2
CASPR2	ANNA3
DPPX	Zic4
NMDAR	Sox1
IgLON5	DNER
VGCC	mGluR1
Yo/CDR2	$GABA_BR$
Hu/ANNA-1	GQ1b
Ri/ANNA-2	GFAP
RARE ANTIBODIES	
Ca/ARHGAP26	PKC-γ
Homer-3	GluR-δ2
ITPR1	Nb/AP3B2
CARP VIII	ATP1A3

Balint et al. Brain 2018

Kelch-like Protein 11

- Germ cell tumours mainly: testicular seminoma ♂, teratoma ♀

Non-paraneoplastic

- Septin- 5
- Neurochondrin
- SEZ6L2
- DAGLA
- Neurobeachin

Miske at al, JNNP 2024

Balint and Bhatia. Current Opinion Neurology 2021

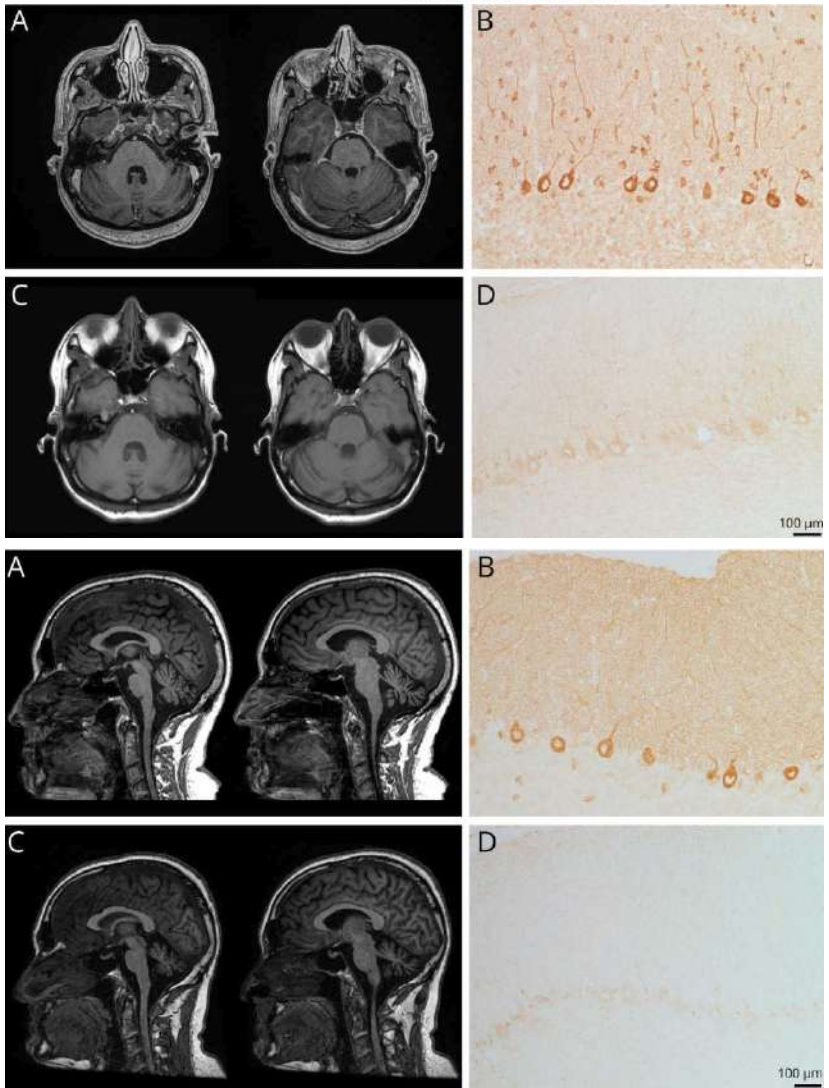
CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

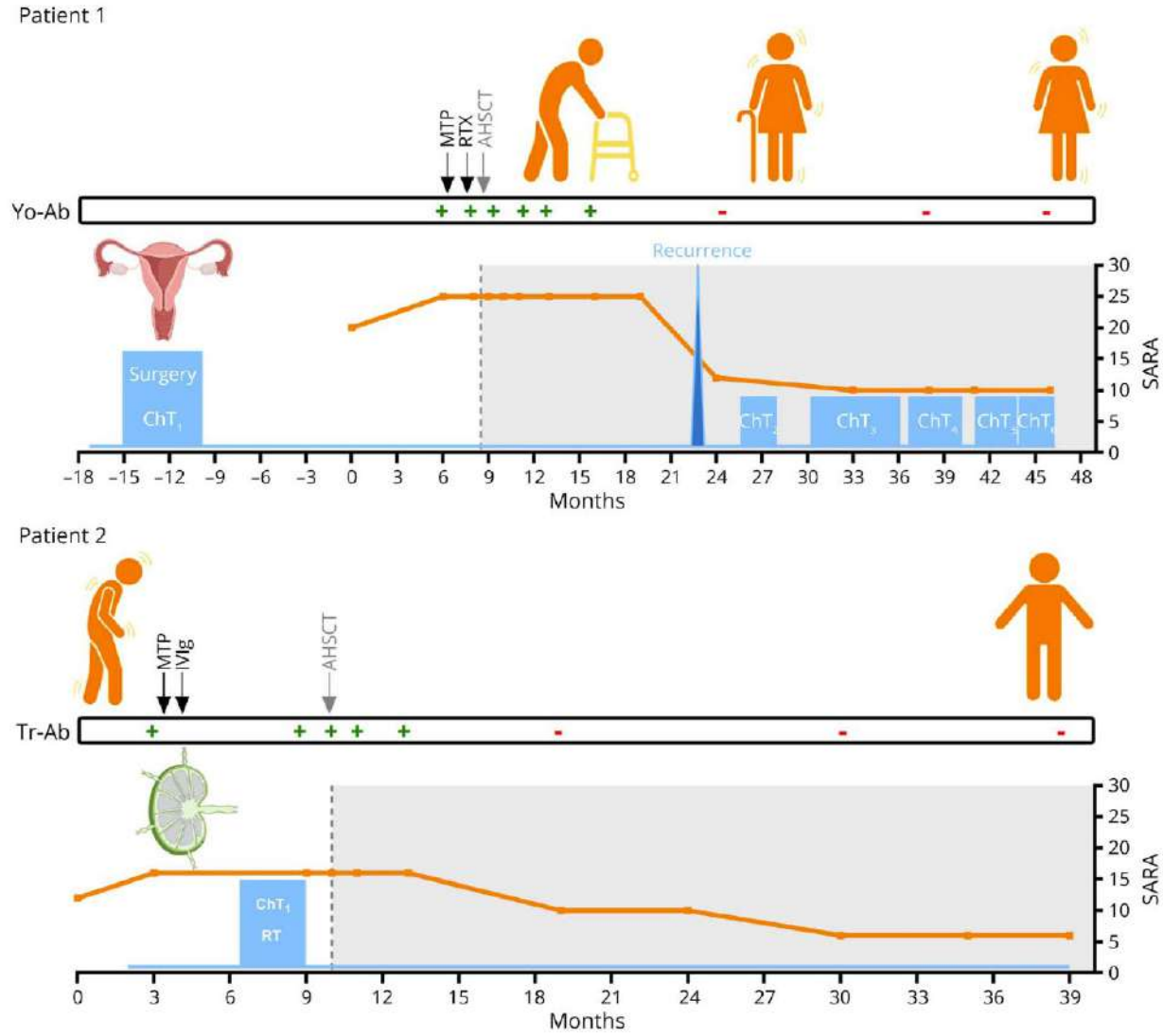
Neurol Neuroimmunol Neuroinflamm 2025

Autologous Hematopoietic Stem Cell Transplantation for Paraneoplastic Cerebellar Degeneration

Victor Guerra,[1,1]* Jose Maria Cabrera-Maqueda,[1,2]* Raquel Ruiz-Garcia,[2,3] Juan Francisco Luchoro,[3] Elianet Fonseca,[2] Mar Guasp,[1,2] Yolanda Blanco,[1] Maria Suarez-Lledo,[4] Francesc Fernandez-Aviles,[4] Carmen Martinez,[4] Montserrat Rovira,[4] Josep Dalmau,[2,5,6] Francesc Graus,[2,†] Albert Saiz,[1,2,†] and Eugenia Martinez-Hernandez[1,2,†]

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Dr. Martinez-Hernandez
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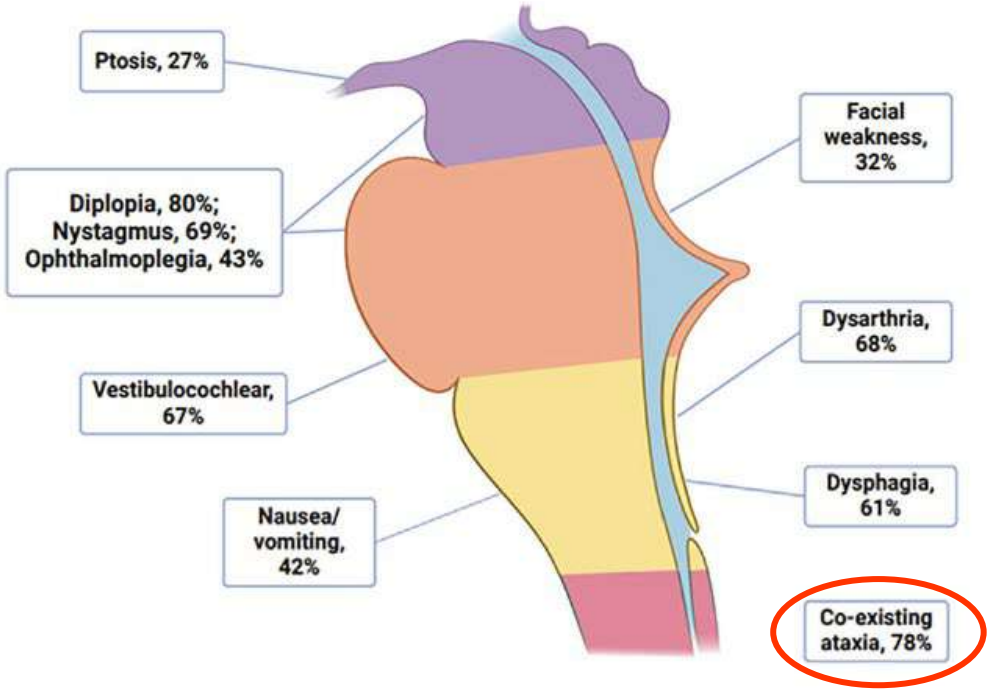


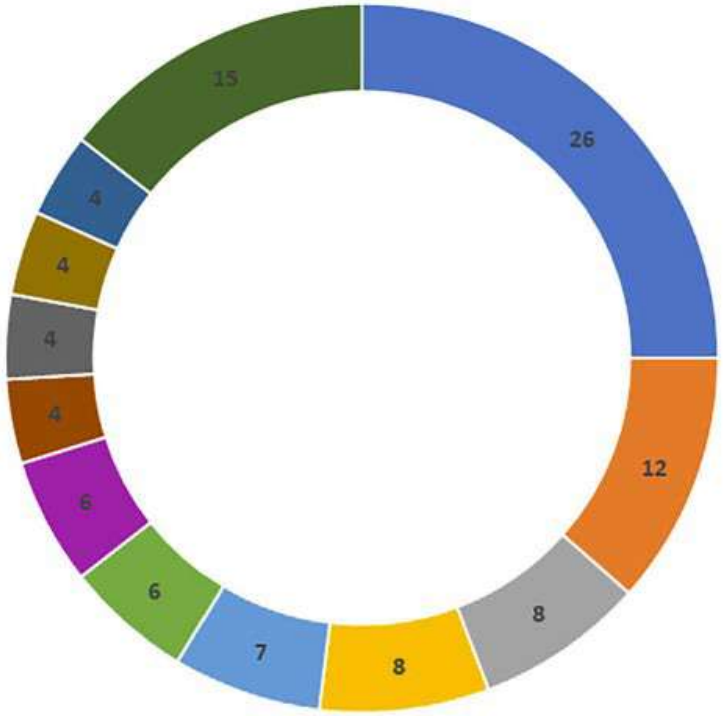


Annals of Clinical and Translational Neurology 2025; 12(1): 213–225

Autoimmune brainstem encephalitis: Clinical associations, outcomes, and proposed diagnostic criteria

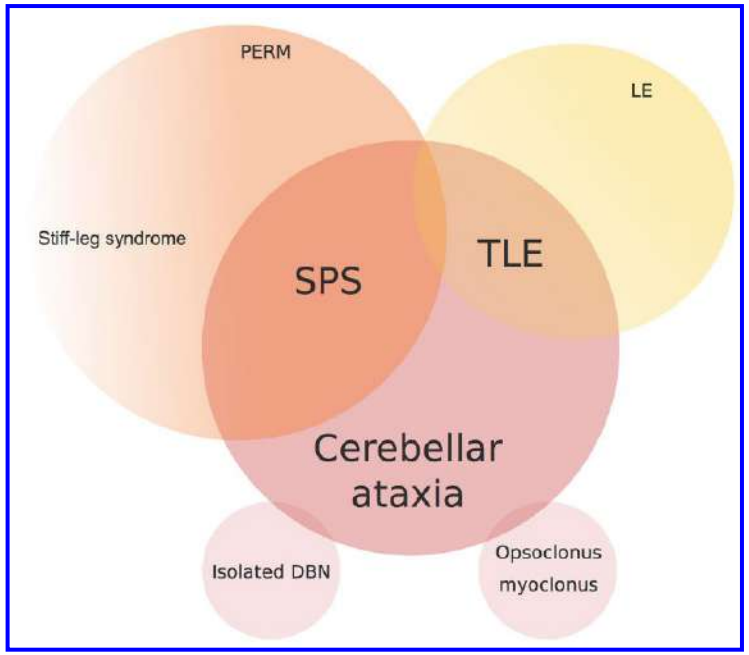
Michael Gilligan[1,2], Smathorn Thakolwiboon[3], Emma Orozco[1], Samantha Banks[3], Eoin P. Flanagan[1,3], Sebastian Lopez-Chiriboga[4], Jan-Mendelt Tillema[3], John R. Mills[1], Sean J. Pittock[1,3], Cristina Valencia Sanchez[5], Anastasia Zekeridou[1,3], Divyanshu Dubey[1,3] & Andrew McKeon[1,3]





* Each asterisk represents a single patient with multiple antibodies

Spectrum of Cerebellar Ataxia with GAD65 Antibodies

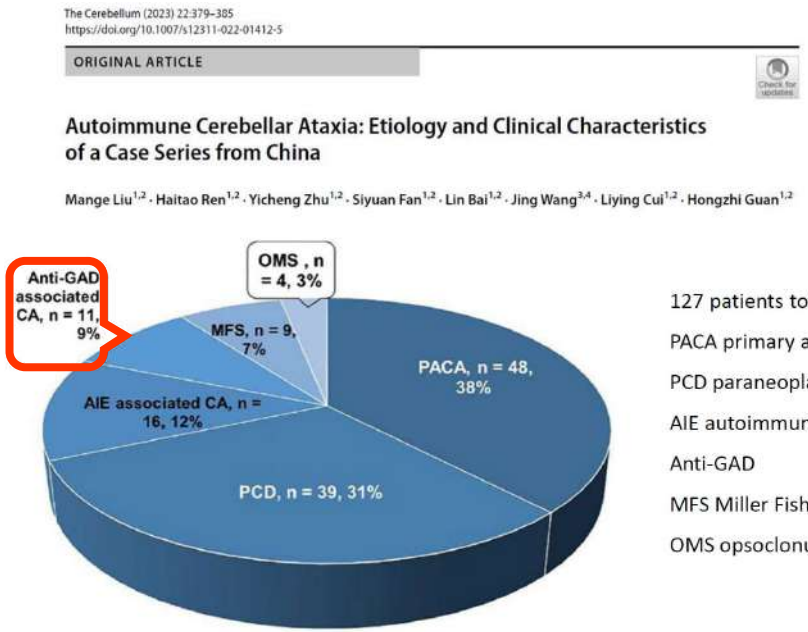


Muñiz-Castrillo et al, 2022

European Journal of Neurology. 2025; 32:e70166

Clinical Features and Outcomes of Glutamic Acid Decarboxylase-65 Antibody-Associated Pure Cerebellar Ataxia and Stiff Person Syndrome Spectrum Disorders: A Single-Center Cohort Study

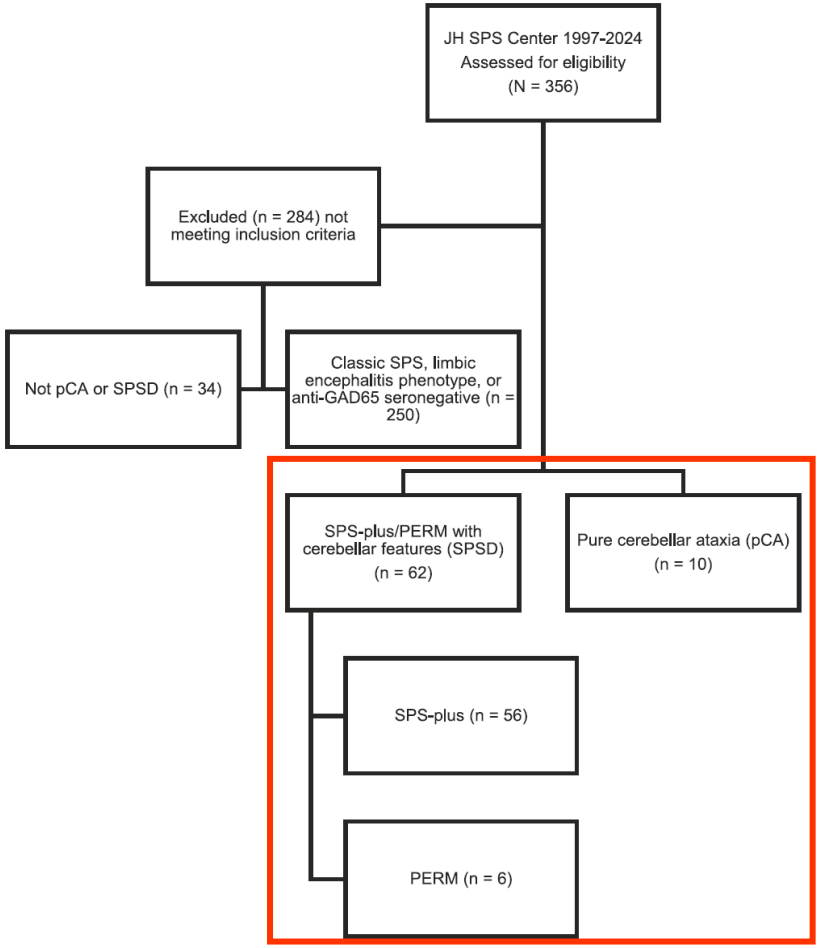
Jonathan D. Krett[1] | Yujie Wang[1,2] | Ashley Miles[1] | Herbert R. Chen[1] | Hanyeh Afshar[1] | Aisha Elfasi[1] | Doris D. Lin[3] | Scott D. Newsome[1]

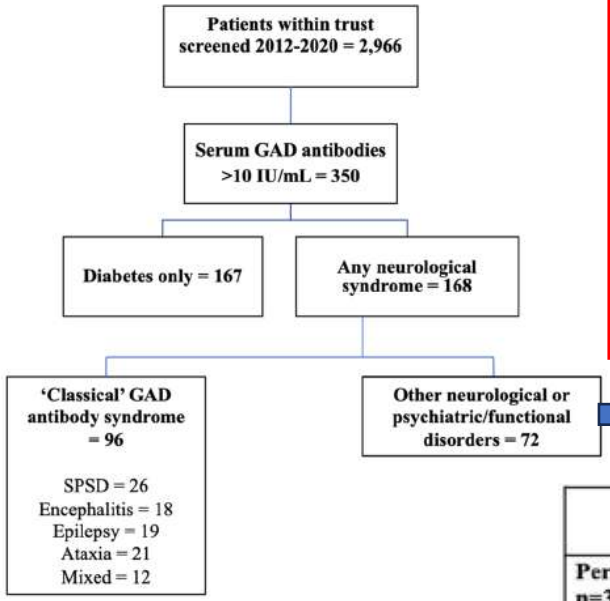

The Cerebellum (2023) 22:379–385
https://doi.org/10.1007/s12311-022-01412-5

ORIGINAL ARTICLE

Autoimmune Cerebellar Ataxia: Etiology and Clinical Characteristics of a Case Series from China

Mange Liu[1,2] · Haitao Ren[1,2] · Yicheng Zhu[1,2] · Siyuan Fan[1,2] · Lin Bai[1,2] · Jing Wang[3,4] · Liying Cui[1,2] · Hongzhi Guan[1,2]





Journal of Neurology (2025) 272:222

GAD antibodies in neurological disease: a critical evaluation of the utility and treatment implications of GAD antibodies in clinical practice

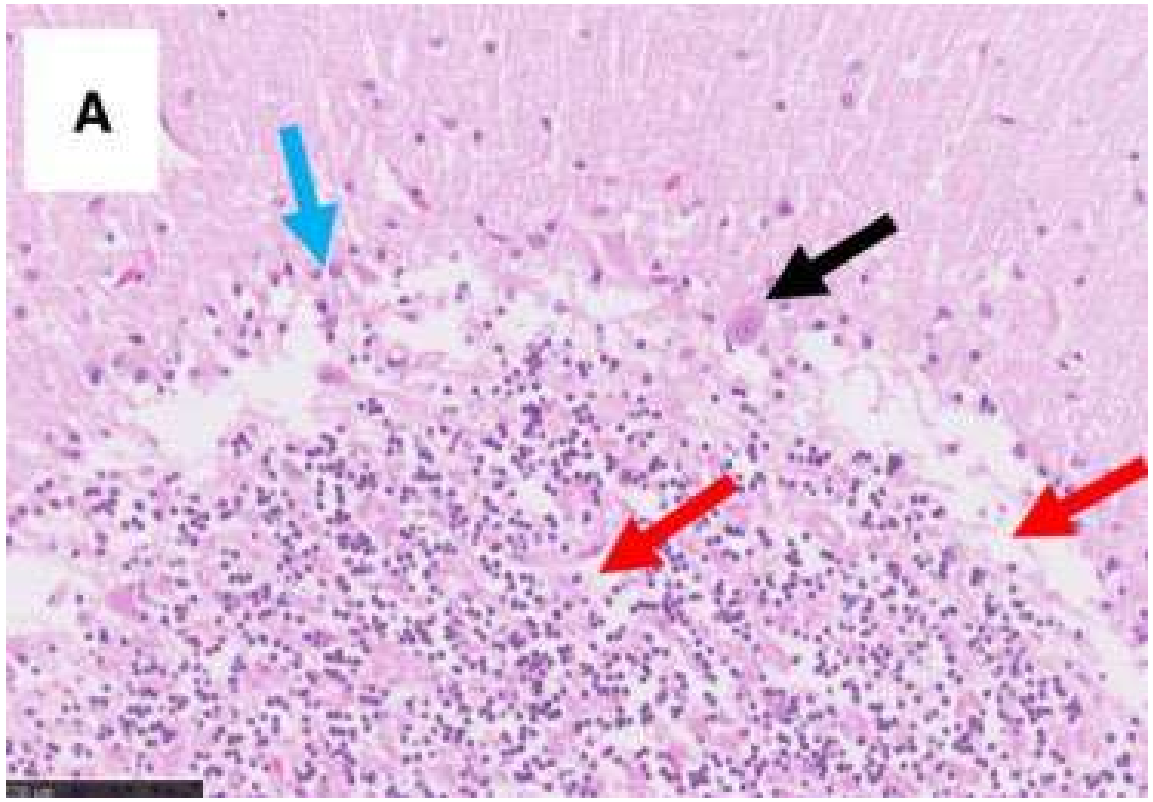
Rachel L. Brown[1,2,3] · Gilbert Thomas-Black[4] · Hector Garcia-Moreno[4] · Michael Chou[1,2] · Zofia Fleszar[4,5] · Michael S. Zandi[1,6] · Miles Chapman[1,2] · Andrew J. Church[1,6] · Melanie Hart[1,6] · Paola Giunti[4] · Angela Vincent[7] · Michael P. Lunn[1,2,8]

	Inflammatory, n=24	**Non-inflammatory, n=38**
Peripheral, n=33	Inflammatory neuropathy, n=10 (3 CIDP, 3 GBS, 1 MMN, 1 possible CANOMAD, 2 vasculitic neuropathies) Paraproteinaemic neuropathy, n=2 (1 anti-MAG, 1 AL amyloid) Myasthenia gravis, n=5 Autoimmune neuroretinopathy, n=1	Diabetic neuropathy, n=5 CMT, n=1 Other neuropathy, n=4 Confirmed or suspected MND, n=3 Unconfirmed neuromyotonia or cramp-fasciculation, n=2
Central, n=25	MOG disease, n=2 ADEM, n=1 PPMS, n=1, CIS, n=1 Primary CNS T cell lymphoma, n=1	Complex neurological/degenerative disorders, n=13 (1 dystonia, 1 NBIA, 1 Leigh's syndrome, 1 DLB, 2 DLB/AD overlap, 1 Parkinson's disease, 1 parkinsonism, 2 undifferentiated leukodystrophy, 1 negative myoclonus, 3 progressive spasticity with unclear cause) Stroke, n=3 Neurofibromatosis type 1, n = 1 Chronic cluster headache, n = 1
Mixed, n=4		Subacute combined degeneration of the cord or nutritional sensory/optic neuropathy related to B12 deficiency, n=4
Psychiatric /functional, n=10		Primary psychiatric, n=5 Functional neurological disorder, n=3 NEAD, n=2

Caution in overinterpreting GAD-Abs values

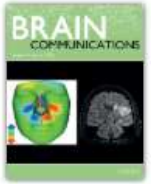
GLUTEN ATAXIA

- Chronic gluten ingestion (w/wo **enteropathy**)
- **Anti-TG6**
- Progressive gait/limb ataxia
- Pathology:
  - Purkinje cell loss
  - T-cell infiltrates (**CD20, CD8)**
  - Astrocytic gliosis and **microglial proliferation** (MHCII expression)



› Brain Commun. 2024 Mar 7;6(2):fcae078. doi: 10.1093/braincomms/fcae078. eCollection 2024.

Cerebellar degeneration in gluten ataxia is linked to microglial activation

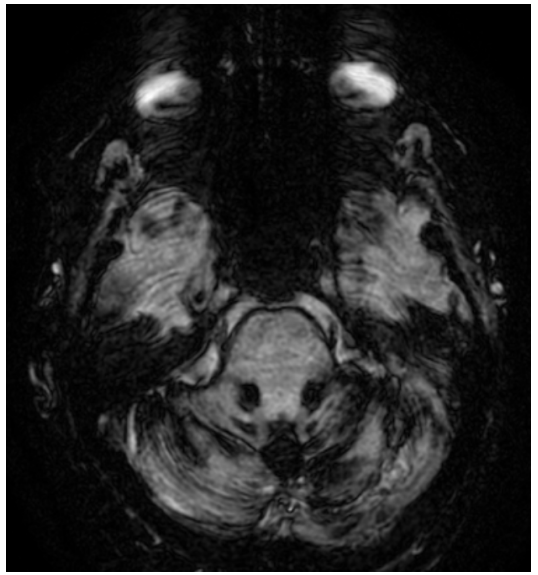


Mara-Luciana Floare [1], Stephen B Wharton [1], Julie E Simpson [1], Daniel Aeschlimann [2], Nigel Hoggard [3], Marios Hadjivassiliou [4]

Affiliations + expand

PMID: 38510211 PMCID: PMC10953628 DOI: 10.1093/braincomms/fcae078

SUPERFICIAL SIDEROSIS



CLINICAL FEATURES

- **Triad**: Progressive cerebellar **ataxia**, SN **hearing loss**, **pyramidal signs**
  - Ataxia- often a predominant and first symptom; most disabling
- Others: impaired cognition, seizures, visual loss, hyposmia

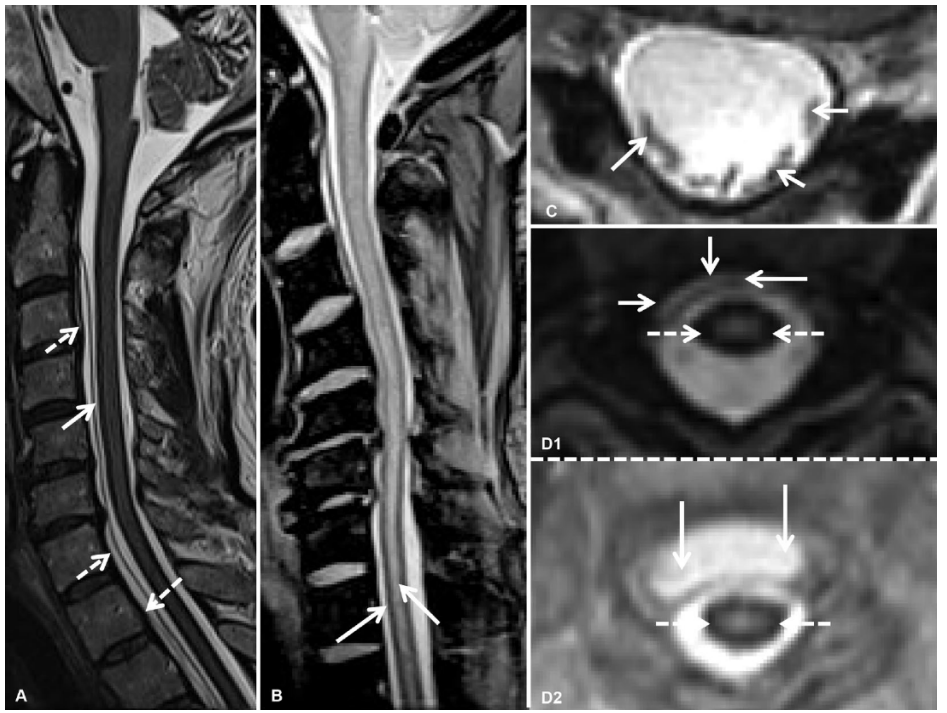
PATHOPHYSIOLOGY

- **Repeated subarachnoid bleeding** (commonest: dural tears – disk disease, trauma incl surgery)
  - → **deposition** of **iron** and **hemosiderin** along pia and subpia
  - → **damage** to cerebral & cerebellar cortex, cochlear nerves, spinal cord

ANN NEUROL 2021;89:1068–1079

Superficial Siderosis: A Clinical Review

Neeraj Kumar, MD

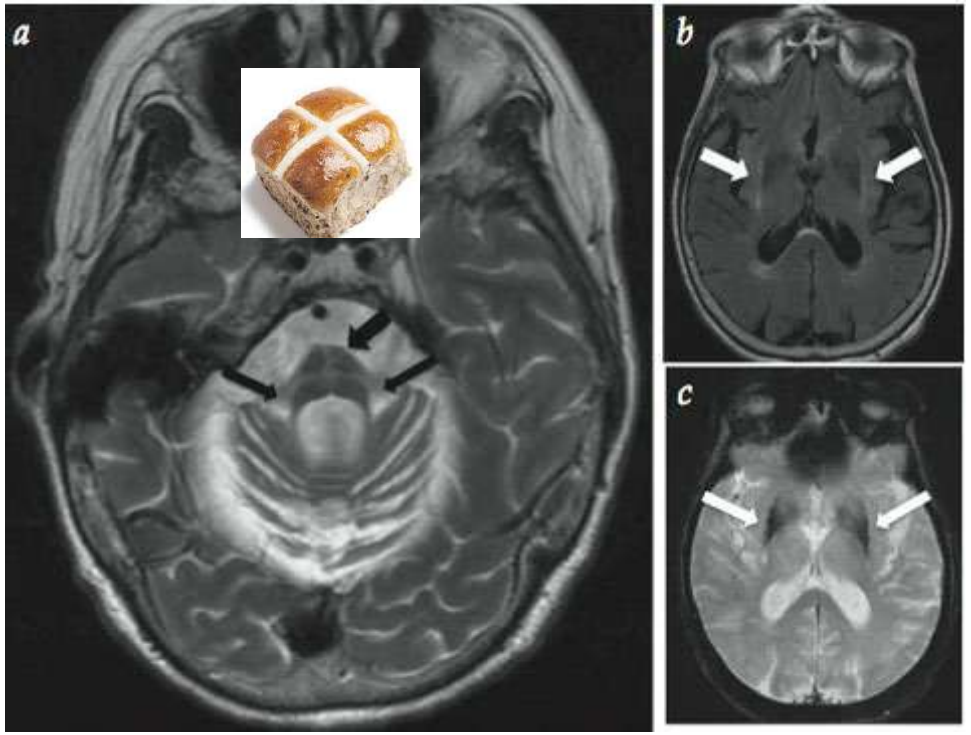


Ventral intraspinal fluid collection (dotted arrow in A) suggesting an associated dural tear.

Multiple System Atrophy
~ 20% present with MSA-C (more common in Asians)

Diagnostic clues

- Age of onset (mean ~ 60yr); More rapidly progressive than genetic ataxias
- Autonomic failure (more severe than other e.g. FXTAS)
- Hx of RBD – ***but*** occasionally seen in SCA3
- Additional parkinsonism (DAT scan may be very helpful – ***but*** SCA3, others)
- MRI features – ***but*** other CAs can have MCP and hot cross bun ***but*** not putamenal changes; HCB (cruciform) + MCP hyperintensities: highly specific for MSA
- Synucleinopathy – RT-QuIC SAA in CSF and skin; pSyn IHC in skin
- Beijer et al 2025: 18/148 "clinically probable" MSA-C had pathogenic or likely pathogenic variants (9 GAA-*FGF14*$_{>250}$ 3 RFC1; 6 SNVs); not confirmed in a S. Korean sample (Laß et al, 2025)



Intronic FGF14 GAA repeat expansions impact progression and survival in multiple system atrophy. Chelban et al, Brain 2025. (MSA-P = MSA-C)
Also found in PD: Akçimen et al, Brain 2026

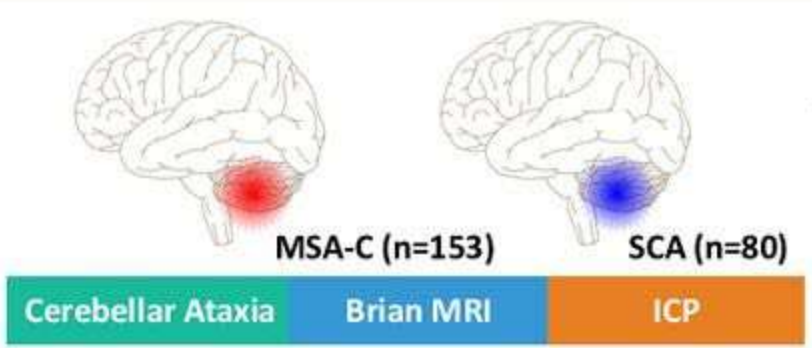
ICP Sign: New Imaging Marker for MSA-C vs SCA

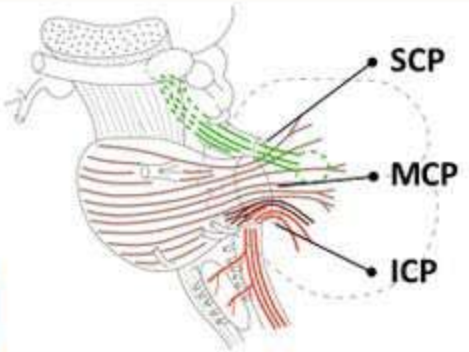
Chae Young Lim, Yujin Seo, Beomseok Sohn, Sungjun Hong, Jinyoung Youn, Eung Yeop Kim et al.

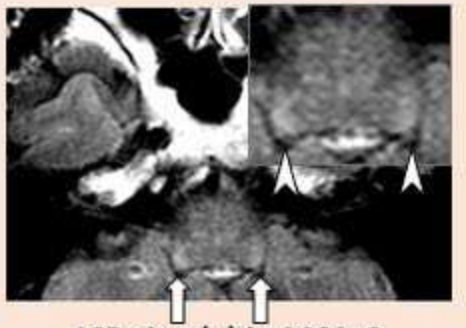
Main Teaching Points:

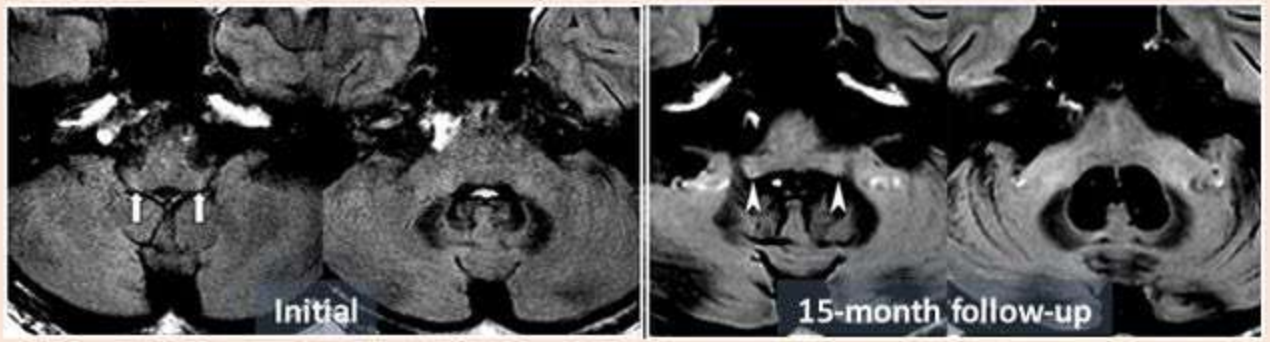
- The inferior cerebellar peduncle (ICP) is pathologically affected in multiple system atrophy - cerebellar type (MSA-C).
- T2-FLAIR hyperintensity of the ICP (ICP sign) shows high specificity (95%) and diagnostic performance (AUC 0.82) in differentiating MSA-C from spinocerebellar ataxia (SCA).
- Combining the ICP sign with clinical and imaging features further improves diagnostic accuracy to an AUC of 0.98.

Can ICP sign distinguish MSA-C from SCA in patients with cerebellar ataxia?

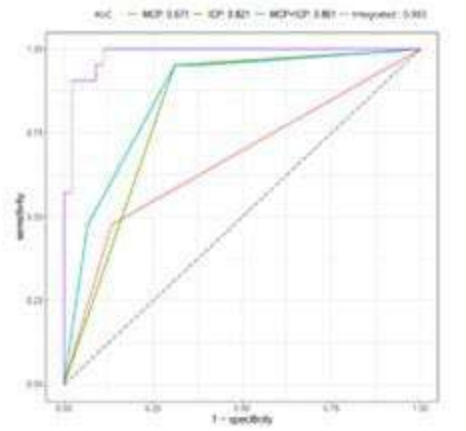








The ICP sign in a 53-year-old male with cerebellar ataxia on initial imaging (left). Follow-up imaging (right) reveals the MCP sign and cerebellar atrophy, confirming MSA-C.



Research | Original Research | Neurodegenerative Disorders

AJNR

AJNR Am J Neuroradiol 46:1223–30 Jun 2025

GENETIC ATAXIAS

GENETICS SERIES: REVIEW

CME

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

Mov Disord. 2017 May;32(5):724-725.

N= 25 Spinocerebellar ataxias (SCAs)
N= 4 complex phenotypes +/-ataxia

REVIEW

The Genetic Nomenclature of Recessive Cerebellar Ataxias

Mov Disord. 2018 May 14. [Epub ahead of print]

N= 62 ATX (Ataxia predominant)
N= 30 ATX/other MD
N= 89 complex phenotypes +/-ataxia



Review | Open Access

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

Mov Disord. 2022 Apr 28. [Epub ahead of print]

N= 11 new Autosomal Dominant
N= 18 new Autosomal Recessive
N= 10 new Other (mixed phenotypes with ataxia)

Molecular Testing Strategy in Ataxias

- **Stepwise Approach**
- **Targeted Gene Panels**
  - **First-line test** in clinically suspected recessive/dominant ataxias
  - Efficient, **cost-effective**, focused on known genes
  - Limitation: **cannot detect new/rare genes outside panel**
- **Whole Exome Sequencing (WES) / Whole Genome Sequencing (WGS)**
  - **Broader coverage when panels are negative**
  - Identifies novel or ultra-rare variants
  - WGS: better structural variant and non-coding region detection
- **Repeat Expansion Testing**
  - **Essential in hereditary ataxias** (e.g., SCA, FRDA, CANVAS)
  - Not reliably detected by WES/WGS → requires specific methods (PCR, RP-PCR)

The Impact of Next-Generation Sequencing on Recessive Ataxias Discovery

Why it matters

- **Before NGS**: many patients remained “idiopathic ataxia”
- **After NGS**: >100 genes linked to recessive ataxias in the past two decades

Key Impacts

- **Gene discovery** → identification of novel forms (e.g., ANO10, SYNE1, VPS13D, SPG7, POLG, etc.)
- **Repeat expansion detection** → *RFC1 AAGGG* → CANVAS, a common late-onset recessive ataxia
- **Reclassification of disorders** → overlap with SPGs, epileptic encephalopathies, neuropathies
- **Diagnostic yield**: up to **40–60%** in specialized ataxia cohorts
- **Precision medicine**: treatable ataxias recognized (e.g., AVED, CTX, CoQ10 deficiencies)

Clinical Relevance

- Reduces **time to diagnosis** (shortens “diagnostic odyssey”)
- Enables **carrier detection & counseling**
- Identifies **new therapeutic targets**

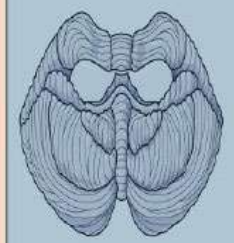
Diagnostic yield and limitations of whole-genome sequencing for hereditary cerebellar ataxia

Wai Yan Yau,[1,2] Roisin Sullivan,[1] Emer O'Connor,[1] David Pellerin,[1] Michael H. Parkinson,[3,4] Paola Giunti,[3,4] Marie-Josée Dicaire,[5] Matt C. Danzi,[6] Stephan Züchner,[6] Bernard Brais,[5,7] Nicholas W. Wood,[4,8] Henry Houlden[1,4] and Jana Vandrovcova[1]

BRAIN COMMUNICATIONS 2025: fcaf188

What is the yield of whole genome sequencing in ataxia?

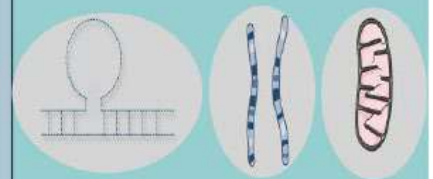
351 probands from United Kingdom Ataxia Centre
Underwent gene sequencing (100,000 Genomes Project)



46 distinct genetic diagnoses in 115 probands

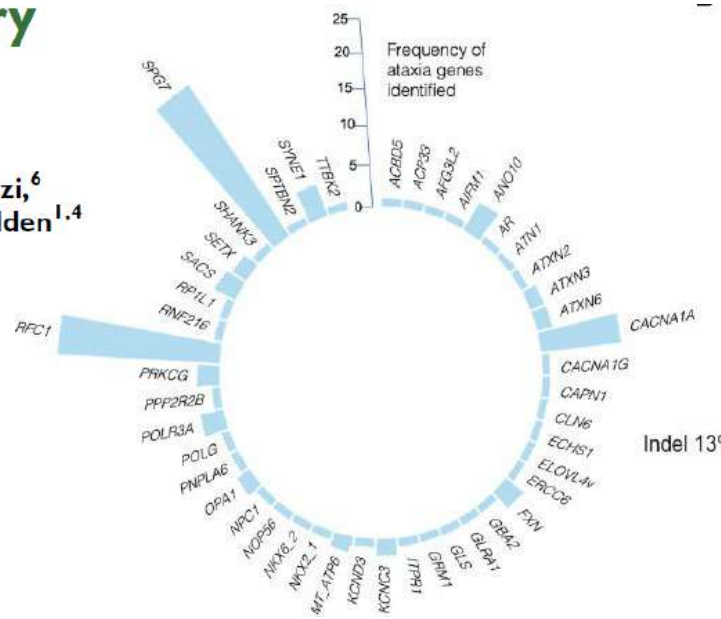
60 Single nucleotide variants

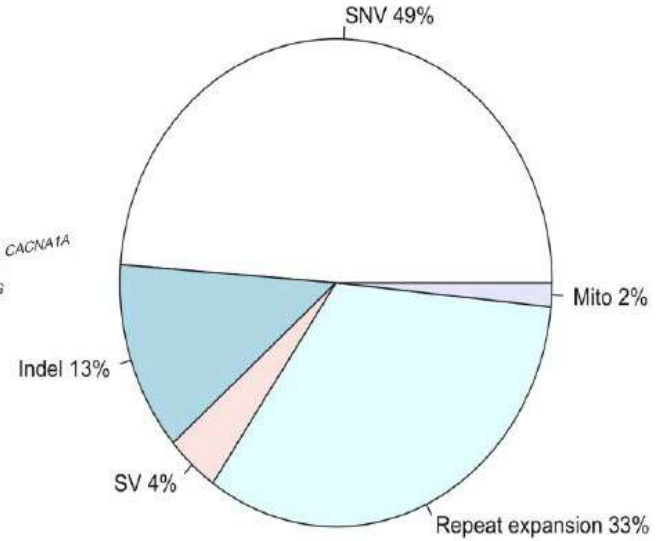
+

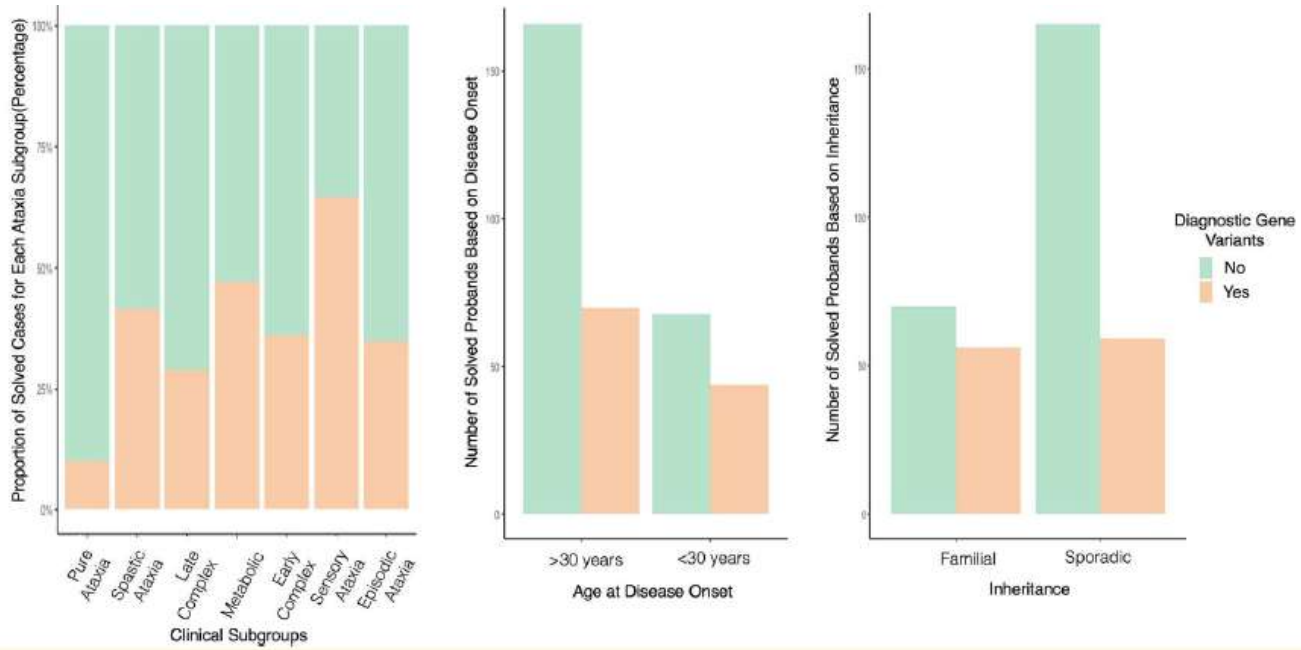


32 repeat expansions | 5 structural variants | 2 mito-chondrial variants

Whole genome sequencing achieved a diagnostic yield of 33% but is limited in identification of complex structural variants and specific repeat expansions (eg. *GAA-FGF14*)





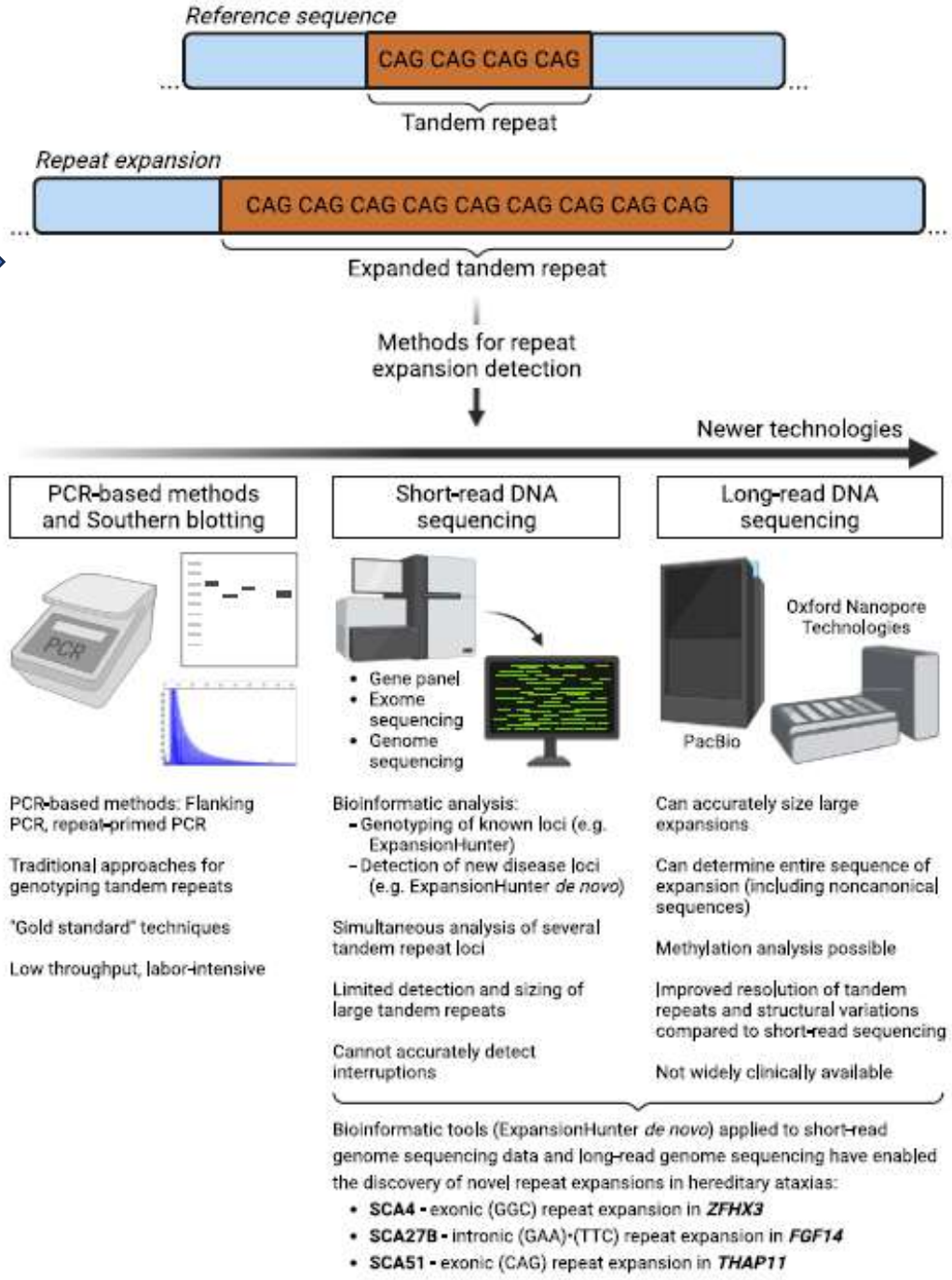


Current Neurology and Neuroscience Reports (2025) 25:16
https://doi.org/10.1007/s11910-024-01400-8

GENETICS (E.M. VALENTE, SECTION EDITOR)

Recent Advances in the Genetics of Ataxias: An Update on Novel Autosomal Dominant Repeat Expansions

David Pellerin[1,2,3] · Pablo Iruzubieta[3,4,5] · Isaac R. L. Xu[1] · Matt C. Danzi[1] · Andrea Cortese[2] · Matthis Synofzik[6,7] · Henry Houlden[2] · Stephan Zuchner[1] · Bernard Brais[3,8]



Genome Research Apr 2025

A prospective trial comparing programmable targeted long-read sequencing and short-read genome sequencing for genetic diagnosis of cerebellar ataxia

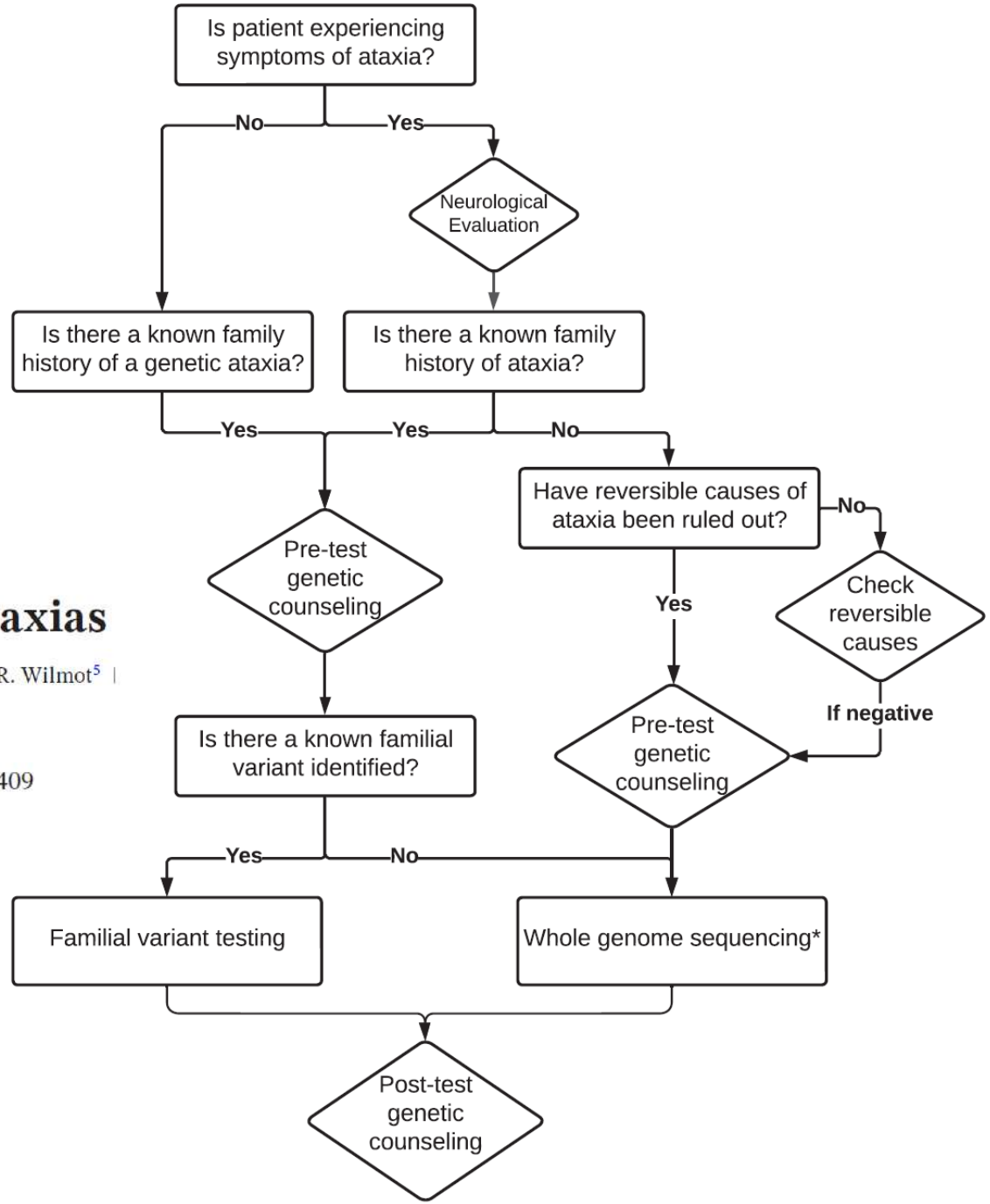
Haloom Rafehi,[1,2,43] Liam G. Fearnley,[1,2,43] Justin Read,[3,4,43] Penny Snell,[3] Kayli C. Davies,[3,5] Liam Scott,[1] Greta Gillies,[3] Genevieve C. Thompson,[3,5] Tess A. Field,[3] Aleena Eldo,[3] Simon Bodek,[6] Ernest Butler,[7] Luke Chen,[8] John Drago,[9,10] Himanshu Goel,[11] Anna Hackett,[11,12] G. Michael Halmagyi,[13,14] Andrew Hannaford,[15,16,17] Katya Kotschet,[18] Kishore R. Kumar,[19,20,21,22] Smitha Kumble,[23,24] Matthew Lee-Archer,[25] Abhishek Malhotra,[26] Mark Paine,[27] Michael Poon,[28] Kate Pope,[3] Katrina Reardon,[9,29] Steven Ring,[30] Anne Ronan,[12,31] Matthew Silsby,[15,16,17] Renee Smyth,[32] Chloe Stutterd,[23] Mathew Wallis,[33,34] John Waterston,[4] Thomas Wellings,[35] Kirsty West,[36] Christine Wools,[37,38] Kathy H.C. Wu,[32,39,40] David J. Szmulewicz,[41,42] Martin B. Delatycki,[3,5,23] Melanie Bahlo,[1,2,44] and Paul J. Lockhart[3,5,44]

RESEARCH ARTICLE OPEN ACCESS

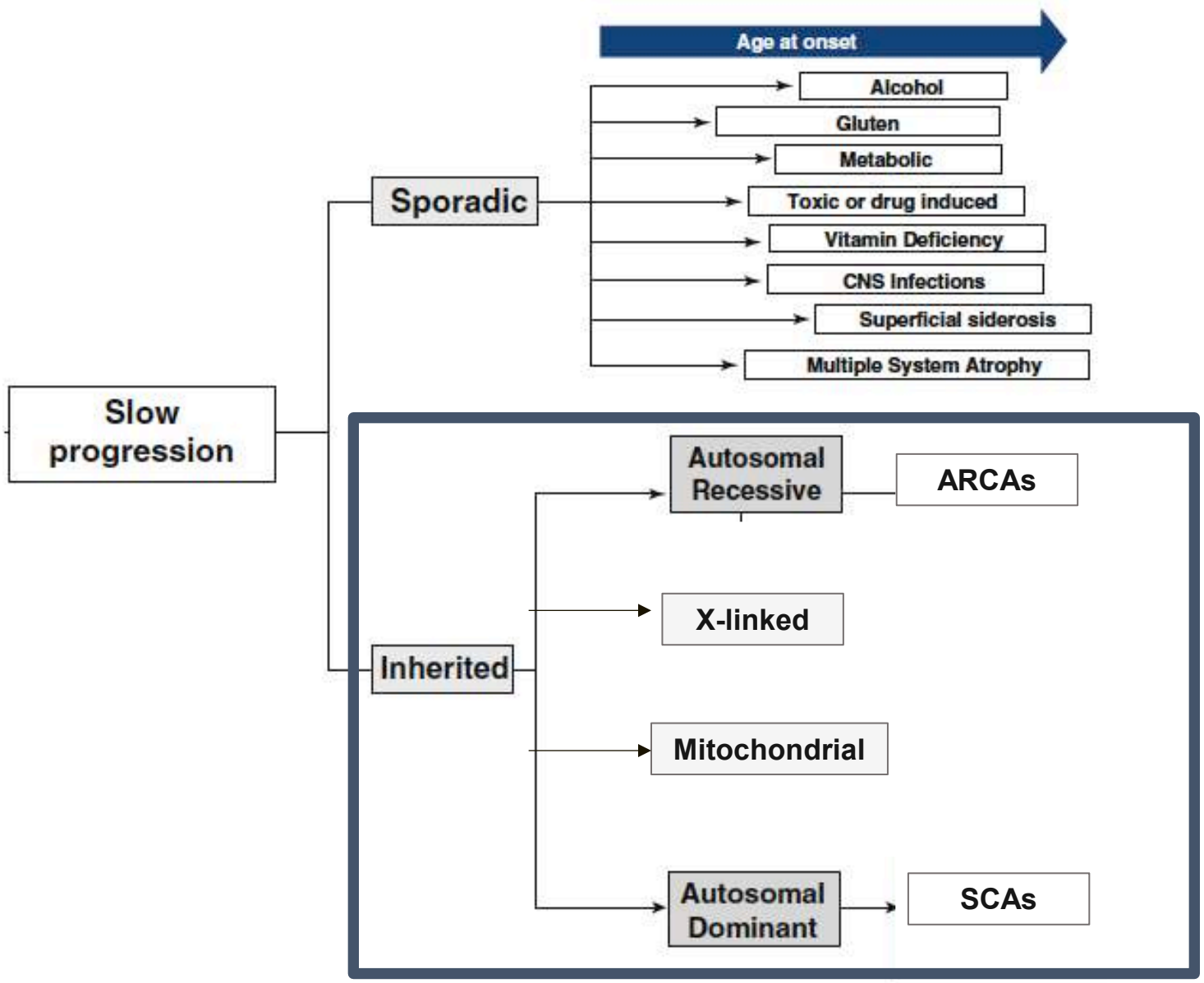
Practice Recommendations for Genetic Testing of Ataxias

Sharan R. Srinivasan[1] | Amy D. Mook[1] | Michelle Rochman[2] | Jin Yun Helen Chen[3] | Weiyi Mu[4] | George R. Wilmot[5] | Liana S. Rosenthal[4] | Wendy R. Uhlmann[6,7]

Annals of Clinical and Translational Neurology, 2025; 12:2398–2409



Ataxia Differential: Slow Progression



Diagnosis of Hereditary Ataxia

- Insidious onset, progressive course, relatively symmetrical
- Age at onset
  - Early (< 25 years): autosomal recessive, mitochondrial
  - Late (> 25 years): autosomal dominant, X-linked
- Family history:

  - Direct questioning of patient and relatives.
  - Consanguinity
  - Always recheck on follow up
  - Negative family history does not exclude the diagnosis:

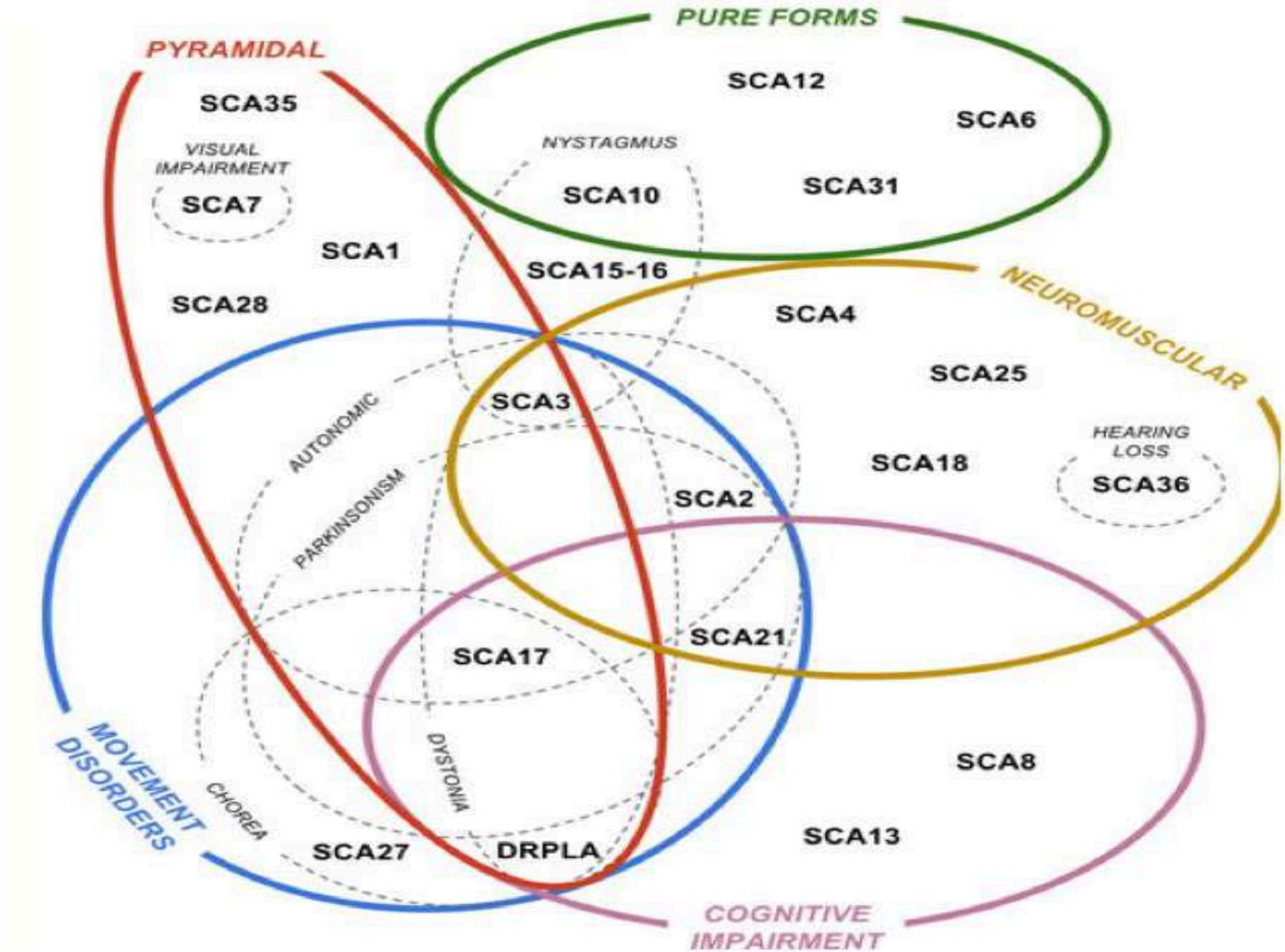
    ➢ Adoption
    ➢ Genetic non paternity
    ➢ Anticipation/repeat instability
    ➢ De novo mutation
    ➢ Small family size
    ➢ In X-linked inheritance only males
    ➢ In mitochondrial disorders matrilineal inheritance

Autosomal Recessive vs. Dominant Ataxias

	Recessive Ataxias	**Dominant Ataxias**
Inheritance pattern	Usually siblings affected, sporadic	Vertical transmission
Age at onset	Often **childhood/adolescence**	Usually **adult** onset
Neuropathy	**Common**, sometimes severe	**Uncommon**, usually mild or absent
Oculomotor apraxia	Frequent (AOA1, AOA2, ATM)	Rare (characteristic of SCA50 only)
Non-neurological involvement	Often (cardiac, endocrine, immunologic)	Usually absent
Progression	Variable; can be rapid or slow	Often **slow** and insidious
Genetic diversity	Many rare genes, frequent new discoveries	Fewer genes, repeat expansions dominate (SCA1, SCA2, *etc.*)

Autosomal dominant ataxias - SCAs

- Heterogeneous disorders with onset after the 2nd decade
- 51 different loci (SCA1 to SCA51); CAG SCA1, 2, 3, 6, 7, 8, 17
- Range: pure to complex phenotypes:
  - Retinopathy, optic atrophy
  - Extra pyramidal or pyramidal signs
  - Peripheral neuropathy
  - Cognitive impairment
  - Epilepsy
- Most common SCA3, SCA2 (depends on ethnic region) SCA27B?



Rossi et al., European Journal of Neurology 2014

Movement Disorders 2025; 12(6): 784–795.
RESEARCH ARTICLE
CLINICAL PRACTICE

Movement Disorders in Hereditary Cerebellar Ataxia

Joana Damásio, MD, PhD,[1,2,3,*] Sara Costa, MD,[1] João Moura, MD,[1] Mariana Santos, PhD,[2] Carolina Lemos, PhD,[3] Alexandre Mendes, MD, PhD,[1,3] Jorge Oliveira, PhD,[2] José Barros, MD, PhD,[1,3] and Jorge Sequeiros, MD, PhD[2,3]

	With MD	Without MD
Number of patients	105 (54.4%)	88 (45.6%)
Male gender	47 (54.0%)	40 (46.%)
Age at onset	19.0y [1.0–33.0]	21.0y [8.0–40.0]
Onset symptoms/signs		
Cerebellar	58 (56.9%)	44 (43.1%)
Non-cerebellar	47 (51.6%)	44 (48.4%)
Mode of inheritance		
Autosomal dominant*	52 (70.3%)	22 (29.7%)
Autosomal recessive	50 (45.0%)	61 (55.0%)
Mitochondrial	3 (37.5%)	5 (62.5%)
Type of genetic defect		
Oligonucleotide repeat expansion	42 (51.2%)	40 (48.8%)
Conventional disease-causing variants	63 (56.8%)	48 (43.2%)

	With MD	Without MD
Most frequent genes		
ATXN2 **	6 (66.7%)	3 (33.3%)
ATXN3	21 (77.8%)	6 (22.2%)
FXN	9 (60.0%)	6 (40.0%)
CACNA1A	2 (18.2%)	9 (81.8%)
SACS	4 (44.6%)	5 (55.6%)
SETX	0 (0.0%)	6 (100%)
SYNE1	4 (50.0%)	4 (50.0%)
PNKP	3 (50.0%)	3 (50.0%)
RFC1	5 (17.2%)	24 (82.8%)
Type of movement disorder		
Dystonia	105 (54.4%)	NA
Tremor	21 (10.9%)	NA
Parkinsonism	8 (4.1%)	NA
Chorea	7 (3.6%)	NA
Myoclonus	5 (2.6%)	NA
Tics	1 (0.5%)	NA

* p = 0.002

** p < 0.001

Clues to the SCAs

Clinical Features	Genetic Forms
Age at onset	Young adult (±35): SCA 1, 2, 3, 10 Older adult (>40): SCA 6 Early onset (<30): SCA 7, 13, DRPLA
Upper motor neuron signs	SCA 1, 3, 7 Mild in SCA 6, 8, 10 Rare in SCA 2
Slow saccades	Early, prominent: SCA **2**, 7, 12 Late: SCA 1, 3 Rare: SCA 6
Extra-pyramidal signs	Early chorea: DRPLA Akinetic-rigid parkinsonism: SCA 2, 3, 21 Dystonia: SCA 3
Generalized areflexia	SCA 2, 4, 21 Late: SCA 3 Rare: SCA 1
Visual loss	SCA 7
Dementia	Prominent: SCA 17, DRPLA Early: SCA 2, 7
Myoclonus	SCA 2, 14
Tremor	SCA 12, 16, 19
Seizures	SCA 10

SCA27B

- Newly identified case of adult-onset ataxia (2022-2023)
- Found in up to 61% of undiagnosed and up to 50% sporadic cases
- Genetic instability; contracts with **paternal transmission**
- Key features
  - **Late onset** (~60 years)
  - High rates of:
    - Ataxia (96%) (often lateral veering with corrective sidesteps)
    - Postural tremor (27%)
    - Loss of independent walking (58%)
    - Episodic and ocular symptoms (46-50%)
    - Vestibulopathy (10-75%); (rare cause of bilateral vestibulopathy)
    - Cognitive dysfunction
    - Other less common – myokymia, myoclonus, dystonia, parkinsonism

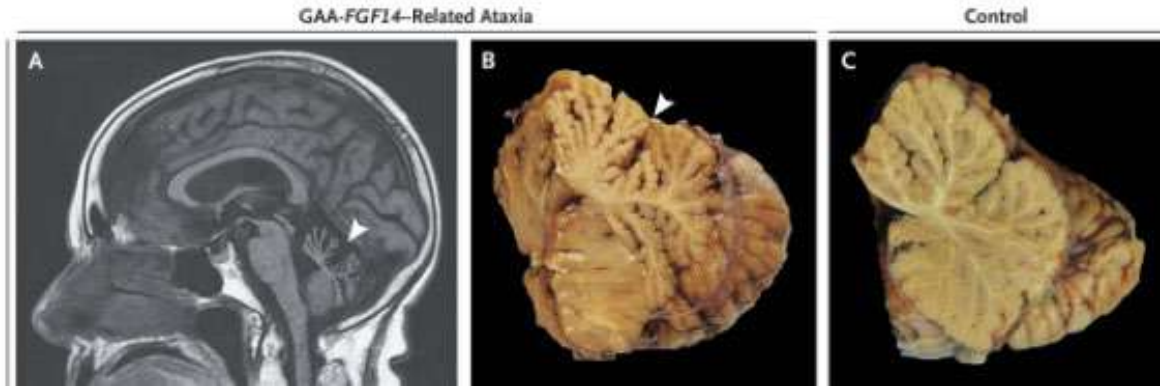
ORIGINAL ARTICLE

Deep Intronic FGF14 GAA Repeat Expansion in Late-Onset Cerebellar Ataxia

Authors: David Pellerin, M.D., Matt C. Danzi, Ph.D., Carlo Wilke, M.D., Mathilde Renaud, M.D., Ph.D., Sarah Fazal, Ph.D., Marie-Josée Dicaire, B.Sc., Carolin K. Scriba, B.Sc., +44, and Bernard Brais, M.D., C.M., Ph.D. Author Info & Affiliations

Published December 14, 2022 | N Engl J Med 2023;388:128-141 | DOI: 10.1056/NEJMoa2207406

> 250 GAA repeats



The Cerebellum (2026) 25:99
https://doi.org/10.1007/s12311-026-02043-w

RESEARCH

Clinical and Genetic Characteristics of SCA27B: A Global Systematic Review and Meta-Analysis

Farsana Mustafa[1] · Ayush Agarwal[1] · Ajay Garg[2] · Mohammed Faruq[3,4] · Achal Kumar Srivastava[1] · Divyani Garg[1]

- **Cerebellar atrophy** seen in 60-97%

SCA27A – rare LoF *FGF14* variants – childhood tremor and later progressive cerebellar ataxia

https://doi.org/10.1093/brain/awae312 BRAIN 2025: 148; 1258–1270 | 1258

BRAIN
ORIGINAL ARTICLE

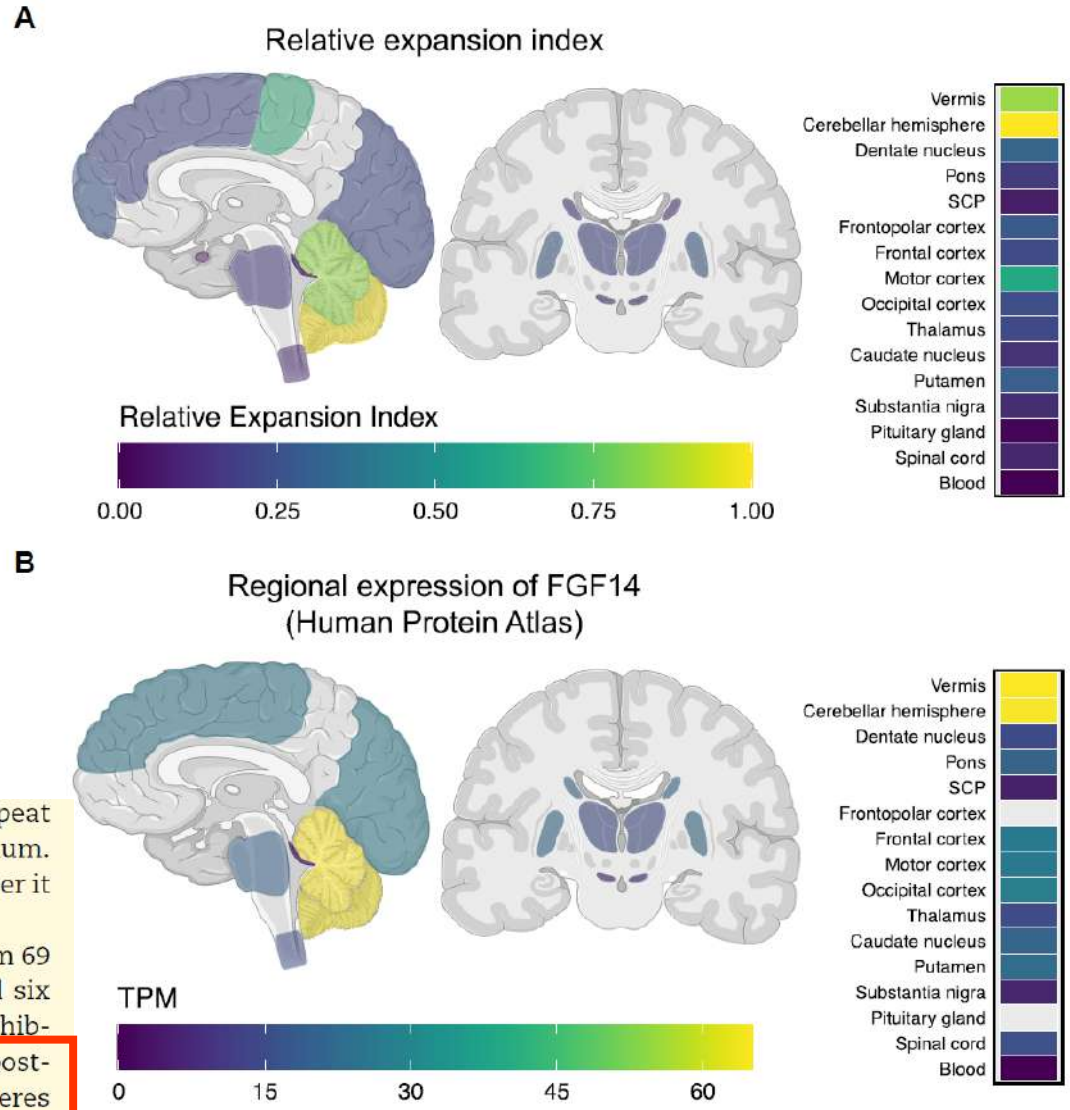
Somatic instability of the FGF14-SCA27B GAA•TTC repeat reveals a marked expansion bias in the cerebellum

David Pellerin,[1,2,3,†] Jean-Loup Méreaux,[4,†] Susana Boluda,[4] Matt C. Danzi,[1] Marie-Josée Dicaire,[2] Claire-Sophie Davoine,[4] David Genis,[5] Guinevere Spurdens,[1] Catherine Ashton,[2,6] Jillian M. Hammond,[7,8] Brandon J. Gerhart,[9] Viorica Chelban,[3,10] Phuong U. Le,[2] Maryam Safisamghabadi,[2] Christopher Yanick,[11] Hamin Lee,[3] Sathiji K. Nageshwaran,[12,13,14,15] Gabriel Matos-Rodrigues,[16] Zane Jaunmuktane,[17,18,19] Kevin Petrecca,[2] Schahram Akbarian,[12,13,14] André Nussenzweig,[16] Karen Usdin,[20] Mathilde Renaud,[21,22,23] Céline Bonnet,[21,24] Gianina Ravenscroft,[25] Mario A. Saporta,[11] Jill S. Napierala,[9] Henry Houlden,[3] Ira W. Deveson,[7,8,26] Marek Napierala,[9] Alexis Brice,[4] Laura Molina Porcel,[27,28] Danielle Seilhean,[4] Stephan Zuchner,[1] Alexandra Durr[4,‡] and Bernard Brais[2,29,‡]

Spinocerebellar ataxia 27B (SCA27B) is a common autosomal dominant ataxia caused by an intronic GAA•TTC repeat expansion in *FGF14*. Neuropathological studies have shown that neuronal loss is largely restricted to the cerebellum. Although the repeat locus is highly unstable during intergenerational transmission, it remains unknown whether it exhibits cerebral mosaicism and progressive instability throughout life.

We conducted an analysis of the *FGF14* GAA•TTC repeat somatic instability across 156 serial blood samples from 69 individuals, fibroblasts, induced pluripotent stem cells and post-mortem brain tissues from six controls and six patients with SCA27B, alongside methylation profiling using targeted long-read sequencing. Peripheral tissues exhibited minimal somatic instability, which did not significantly change over periods of more than 20 years. In post-mortem brains, the GAA•TTC repeat was remarkably stable across all regions, except in the cerebellar hemispheres and vermis. The levels of somatic expansion in the cerebellar hemispheres and vermis were, on average, 3.15 and 2.72 times greater relative to other examined brain regions, respectively. Additionally, levels of somatic expansion in the brain increased with repeat length and tissue expression of *FGF14*. We found no significant difference in methylation of wild-type and expanded *FGF14* alleles in post-mortem cerebellar hemispheres between patients and controls.

In conclusion, our study revealed that the *FGF14* GAA•TTC repeat exhibits a cerebellar-specific expansion bias, which may explain the pure cerebellar involvement in SCA27B.



Manifestations of SCA27B

Feature	Frequency (range)	Comment
Gait ataxia	95–100%	
Upper limb ataxia	44–71%	
Episodic symptoms	13–80%	May be triggered by alcohol intake, physical activity, or caffeine
Cerebellar dysarthria	12–74%	Rarely severe
Cerebellar oculomotor signs	80–96%	Includes saccadic pursuit, dysmetric saccades, rebound nystagmus, gaze-evoked nystagmus, downbeat nystagmus, impaired visual fixation suppression of the vestibulo-ocular reflex
Downbeat nystagmus	10–67%	May be episodic and/or occur in isolation with other cerebellar oculomotor signs at disease onset
Diplopia, oscillopsia, visual blurring	40–68%	
Vertigo and/or dizziness	21–67%	
Postural tremor of upper limbs	10–27%	
Bilateral vestibulopathy	10–75%	Vestibular function remains mildly impaired
Cerebellar atrophy on brain MRI	60–97%	Cerebellar vermis > hemisphere; remains mild to moderate despite prolonged disease duration

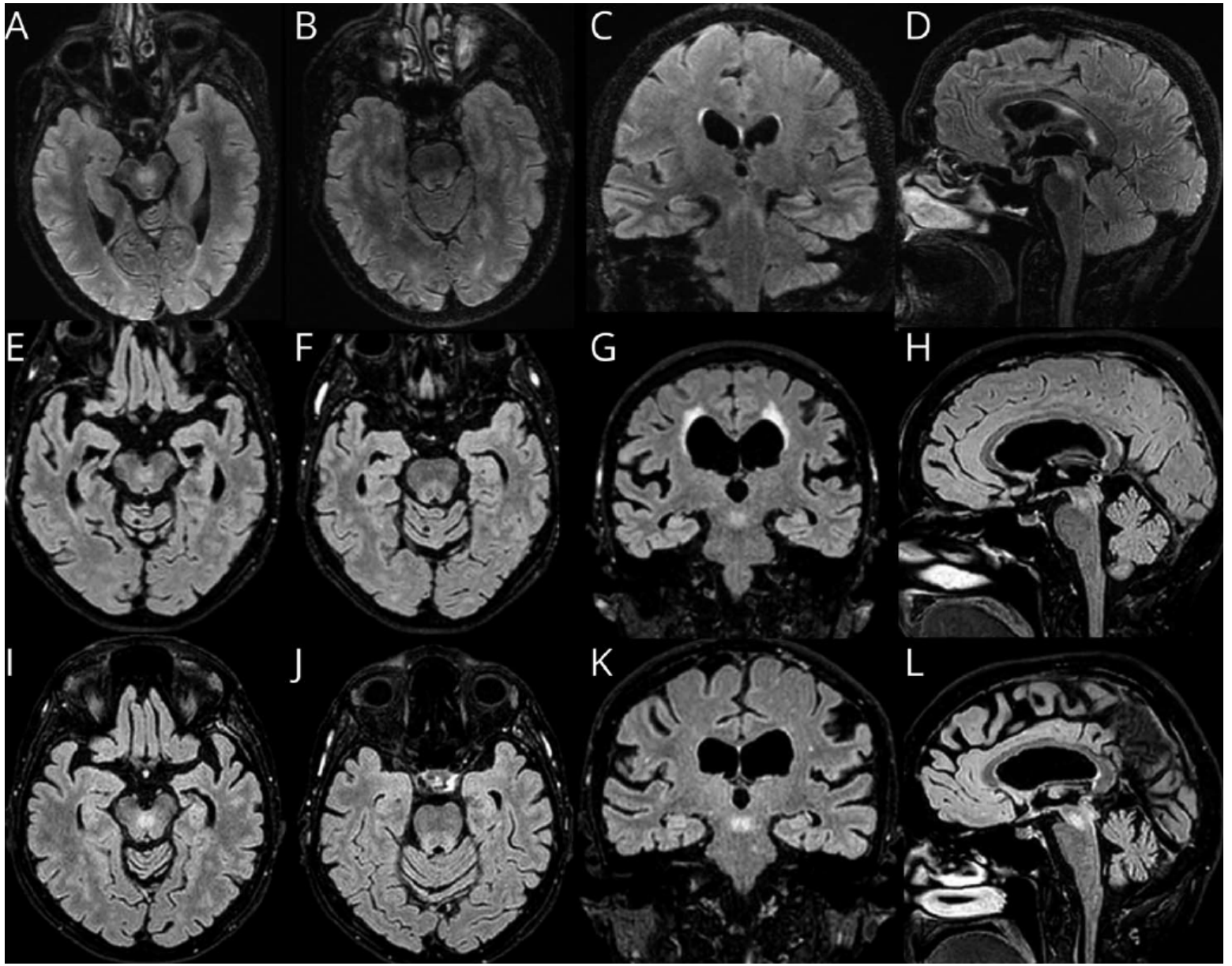
Pellerin et al, 2024

Involvement of the Superior Cerebellar Peduncles in GAA-*FGF14* Ataxia

Shihan Chen,[1] Catherine Ashton,[1,2] Rawan Sakalla,[1] Guillemette Clement,[3] Sophie Planel,[3] Céline Bonnet,[3] Phillipa J. Lamont,[2] Karthik Kulanthaivelu,[4] Atchayaram Nalini,[5] Henry Houlden,[6] Antoine Duquette,[7] Marie-Josée Dicaire,[1] Pablo Iruzubieta Agudo,[8] Javier Ruiz-Martinez,[8] Enrique Marco De Lucas,[9] Rodrigo Sutil Berjon,[9] Jon Infante Ceberio,[10] Elisabetta Indelicato,[11] Sylvia M. Boesch,[11] Matthis Synofzik,[12,13] Benjamin Bender,[14] Matt C. Danzi,[15] Stephan Zuchner,[15] David Pellerin,[1,6] Bernard Brais,[1,16] Mathilde Renaud,[3] and Roberta La Piana[1,16,17]

Neurol Genet 2025;11:e200253. doi:10.1212/NXG.0000000000200253

Abnormally high T2 signal in SCP in ~60% of cases (52/87)



MANAGEMENT

- Supportive therapies: PMR/PT/OT/Speech
- Medications:
  - **Acetazolamide**:
    - Mild benefit reported
  - **4-aminopyridine**:
    - Moderate benefit in 7/8 patients
    - 86% improvement

N Engl J Med. 2023 Jan 12;388(2):128-141. doi: 10.1056/NEJMoa2207406. Epub 2022 Dec 14.

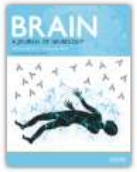
Deep Intronic *FGF14* GAA Repeat Expansion in Late-Onset Cerebellar Ataxia



David Pellerin [1], Matt C Danzi [1], Carlo Wilke [1], Mathilde Renaud [1], Sarah Fazal [1], Marie-Josée Dicaire [1], Carolin K Scriba [1], Catherine Ashton [1], Christopher Yanick [1],

Brain. 2023 Oct 3;146(10):4144-4157. doi: 10.1093/brain/awad157.

GAA-FGF14 ataxia (SCA27B): phenotypic profile, natural history progression and 4-aminopyridine treatment response



Carlo Wilke [1 2], David Pellerin [3], David Mengel [1 2], Andreas Traschütz [1 2], Matt C Danzi [4], Marie-Josée Dicaire [3], Manuela Neumann [2 5], Holger Lerche [6], Benjamin Bender [7], Henry Houlden [8]; RFC1 study group; Stephan Züchner [4], Ludger Schöls [2 9], Bernard Brais [3], Matthis Synofzik [1 2]

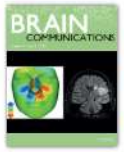
MOVEMENT DISORDERS CLINICAL PRACTICE 2026

ON/OFF Phenomenon in 4-Aminopyridine Therapy in Spinocerebellar Ataxia 27B: Therapeutic and Diagnostic Insights

Chiara Caneda, MD,[†] Eleonora Bertoncello, MD,[†] Alessia Peghin, MD,[1] Sara Satolli, MD,[2] Filippo Maria Santorelli, MD,[3] Michele Tinazzi, MD, PhD,[†] and Ilaria Antonella Di Vico, MD, PhD[†,]*

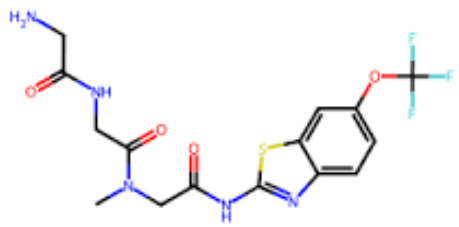
Brain Commun. 2023 Sep 10;5(5):fcad239. doi: 10.1093/braincomms/fcad239. eCollection 2023.

Spinocerebellar ataxia 27B: episodic symptoms and acetazolamide response in 34 patients



Catherine Ashton [1 2], Elisabetta Indelicato [3], David Pellerin [1 4], Guillemette Clément [5 6 7], Matt C Danzi [8], Marie-Josée Dicaire [1], Céline Bonnet [5 9], Henry Houlden [4], Stephan Züchner [8], Matthis Synofzik [10 11], Phillipa J Lamont [11], Mathilde Renaud [5 6 7], Sylvia Boesch [3], Bernard Brais [1 12 13]

TRORILUZOLE



- Third generation tripeptide prodrug riluzole offers:
  - Improved absorption and **liver safety**
  - More **consistent** drug levels
  - Once **daily** dosing
  - Better bioavailability and pharmacokinetics

- Initial negative phase 3 clinical trial (SCA-1, SCA-2, SCA-3, SCA-6, SCA-7, SCA-8, SCA-10); SCA-3 subgroup met primary endpoint
- Follow-up: Comparison of treated patients vs. Untreated natural history patients positive (at 3 years 50-70% slower decline in f-SARA)

Neurol Ther. 2024 Aug;13(4):1287-1301. doi: 10.1007/s40120-024-00625-6. Epub 2024 May 30.

Video-Based Kinematic Analysis of Movement Quality in a Phase 3 Clinical Trial of Troriluzole in Adults with Spinocerebellar Ataxia: A Post Hoc Analysis



Gilbert J L'Italien [1], Evangelos K Oikonomou [2], Rohan Khera [2], Michele H Potashman [3], Melissa W Beiner [1], Grant D H Maclaine [4], Jeremy D Schmahmann [5], Susan Perlman [6], Vladimir Coric [1]

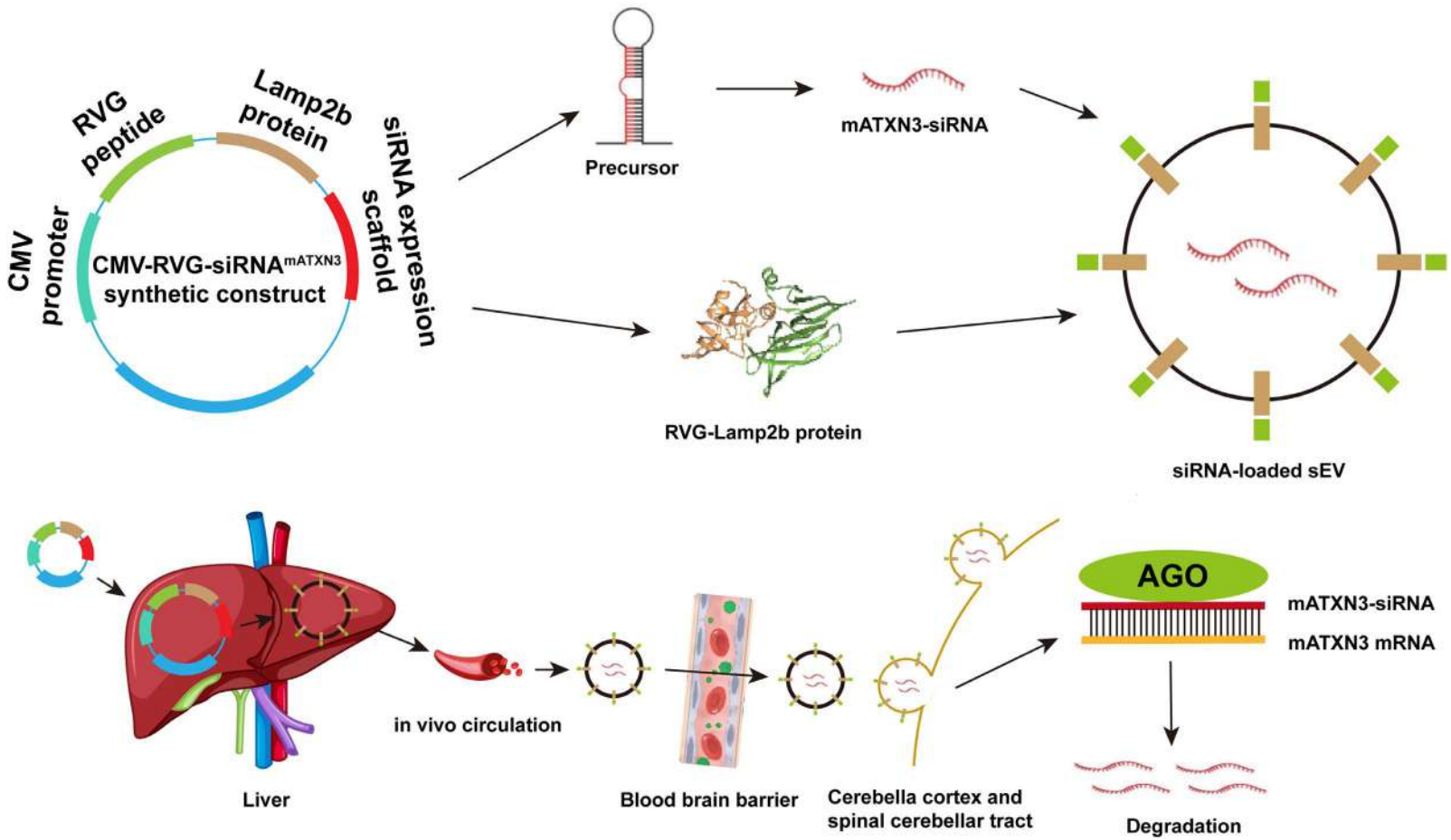
From 218 randomized participants, 67 and 56 participants had interpretable videos of a tandem and natural walk attempt, respectively. At Week 48, individuals assigned to troriluzole exhibited significant ($p = 0.010$) improvement in tandem walk Pose Dispersion Index versus placebo {adjusted interaction coefficient: 0.584 [95% confidence interval (CI) 0.137 to 1.031]}. A similar, nonsignificant trend was observed in the natural walk assessment

https://doi.org/10.1093/brain/awae304 BRAIN 2025: 148; 817–832 | 817

BRAIN
ORIGINAL ARTICLE

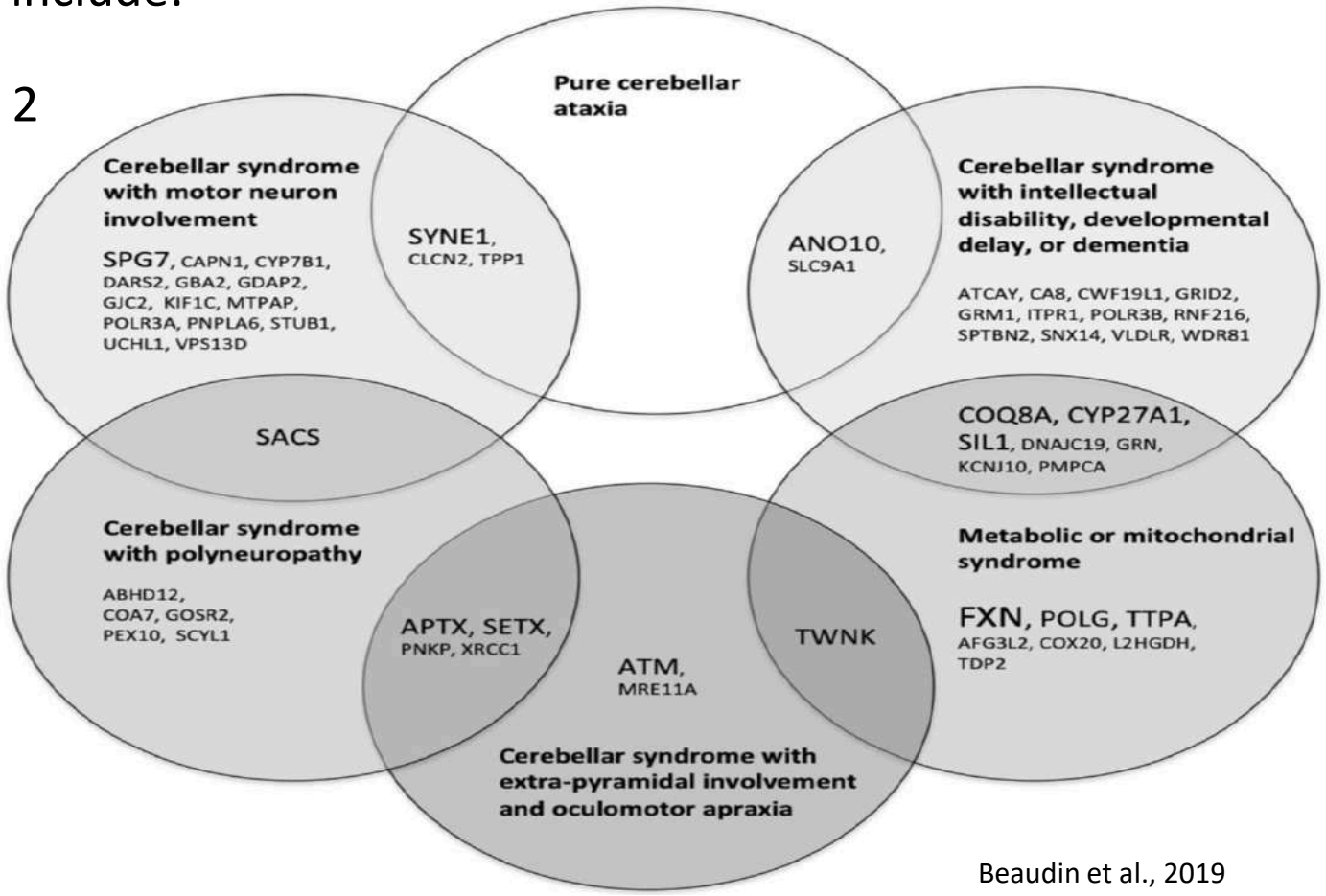
Treatment of neurological pathology and inflammation in Machado–Joseph disease through *in vivo* self-assembled siRNA

Zhizong Li,[1,2,†] Xinghu Du,[1,†] Yixuan Yang,[1] Li Zhang,[3] Penglu Chen,[1] Yansheng Kan,[1] Jinmeng Pan,[1] Lishan Lin,[2] Ding Liu,[1] Xiaohong Jiang,[1] Chen-Yu Zhang,[1,4] Zhong Pei[2] and Xi Chen[1,4,5]



Autosomal Recessive Cerebellar Ataxias - ARCAs

- Currently 45 types plus 20 formally called “complex disorders with ataxia”
- Commonest Friedreich's ataxia (FA), CANVAS?
- The other most common recessive ataxias include:
  - Ataxia telangiectasia
  - *Ataxia with ocular motor apraxia 1 & 2
  - *Ataxia with vitamin E deficiency *
  - ARSACS
- Among the “other” (all treatable):
  - *Abetalipoproteinemia *
  - *Nieman-Pick type C *
  - *Refsum disease *
  - *Ataxia with CoQ10 deficiency *



Beaudin et al., 2019

* Treatable ataxia*

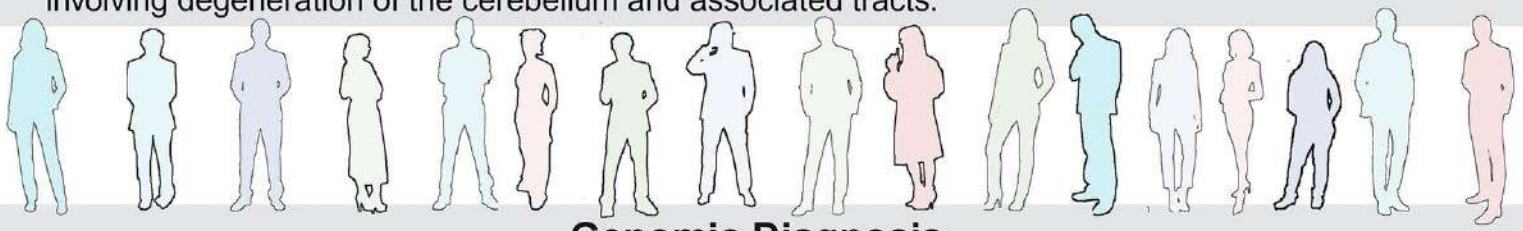
ANN NEUROL 2025;00:1–23

Autosomal Recessive Cerebellar Ataxias: Translating Genes to Therapies

Brent L. Fogel, MD, PhD,[1] Thomas Klopstock,[2,3,4] David R. Lynch,[5] Francesca Maltecca,[6] Mayank Verma,[7] Berge A. Minassian,[7] Frances M. Platt,[8] Débora Farina Gonçalves,[9] Hélène Puccio,[9] Andreas Roos,[10,11,12] and Matthis Synofzik, MD[13,14]

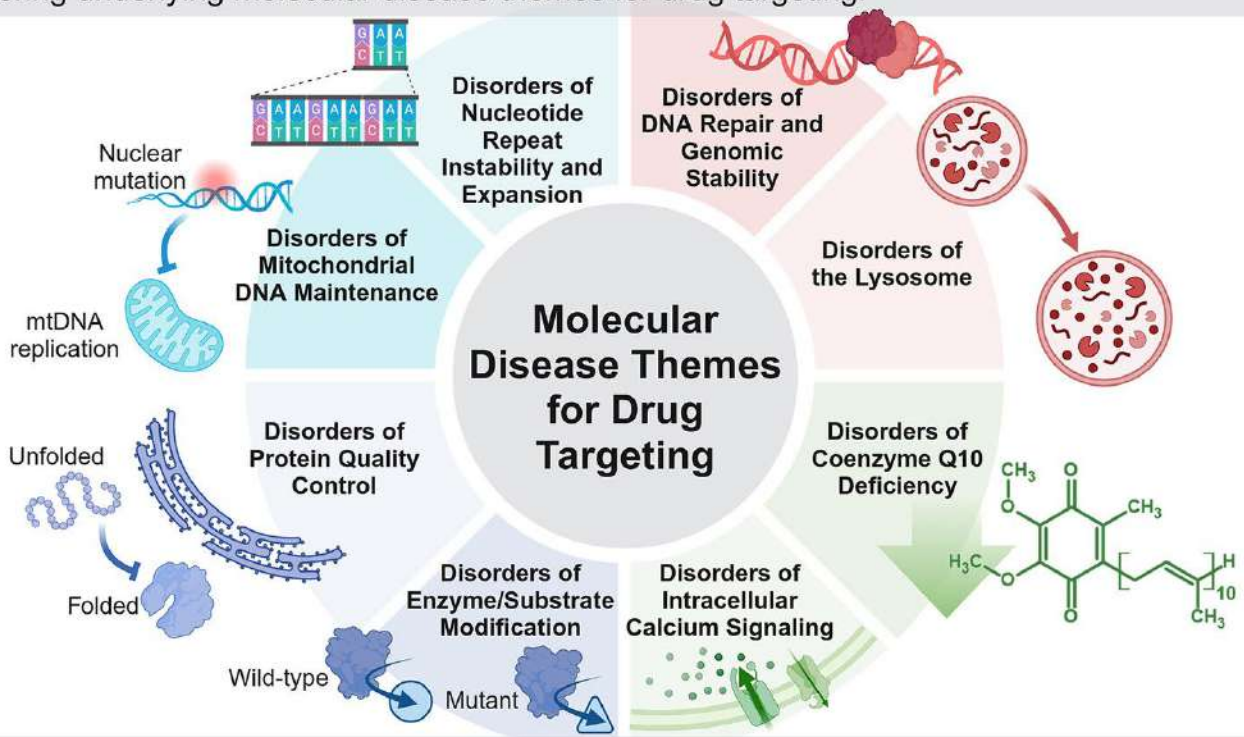
Autosomal recessive cerebellar ataxias: Translating genes to therapies

- Autosomal recessive cerebellar ataxias represent over 200 clinically heterogenous genetic conditions involving degeneration of the cerebellum and associated tracts.



Genomic Diagnosis

- Genomic testing advances have facilitated rapid identification of most known recessive disorders, uncovering underlying molecular disease themes for drug targeting.



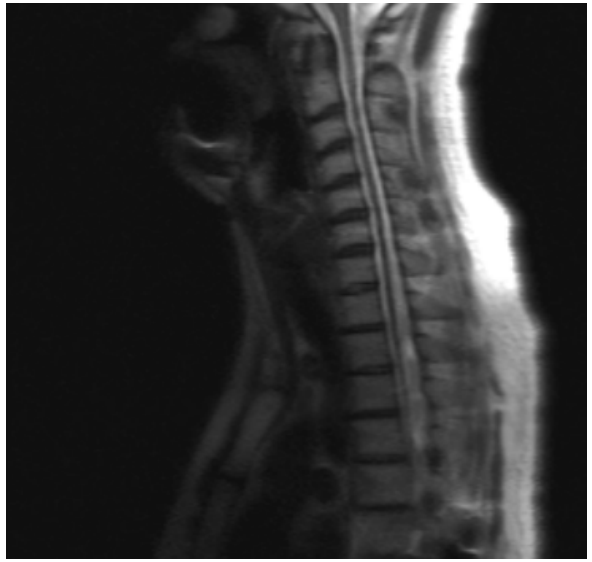
Clinical Trial Readiness

- Focus is now shifting to research on the development of targeted mechanistic treatments poised for clinical trials.

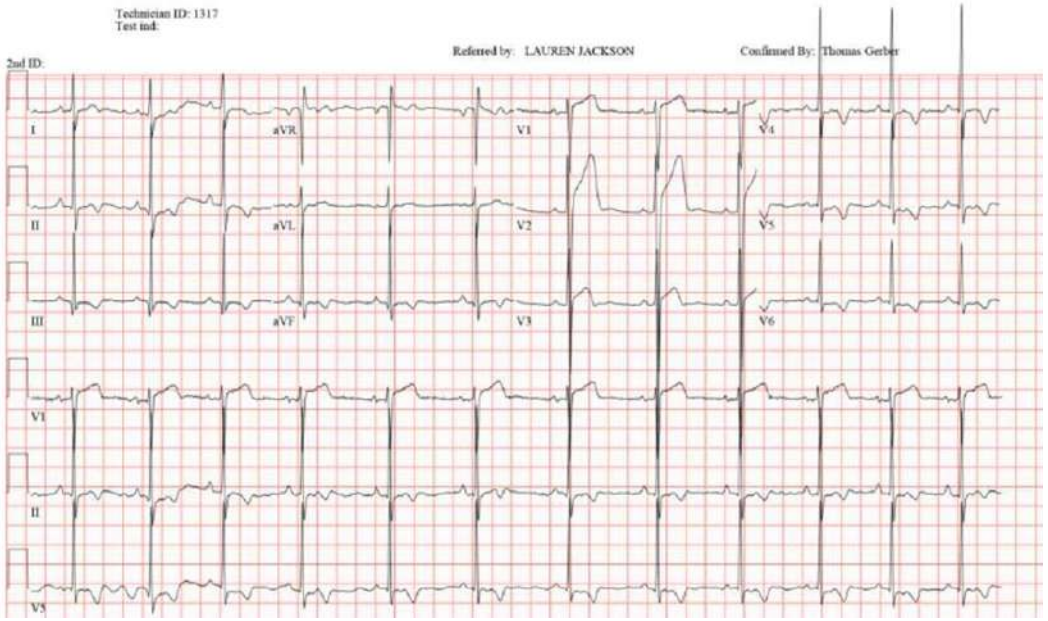
Friedreich Ataxia

- GAA expansion in gene encoding Frataxin (mitochondrial protein, iron transport).
  - Normal repeats: 6-34 GAA
  - FRDA chromosomes: 90% homozygous with 67-1700 GAA; 10% have an expanded and a point mutation allele
- Mean onset: 10 – 15 yr
- Loss of ambulation: 15 ± 7 years after disease onset
- Age of death of 37 ± 14 years (range 21-69), often cardiomyopathy.

Friedreich Ataxia



- Cardinal features:
  - Progressive ataxia
  - Absent lower limb reflexes
  - Extensor plantar responses
  - Decreased vibration sense and proprioception
- Non-essential common features:
  - Cardiomyopathy
  - Scoliosis
  - Foot deformity
  - Diabetes
  - Pyramidal weakness of the lower limbs



Friedreich Ataxia

https://doi.org/10.1093/braincomms/fcag143 BRAIN COMMUNICATIONS 2026:
BRAIN COMMUNICATIONS
REVIEW ARTICLE

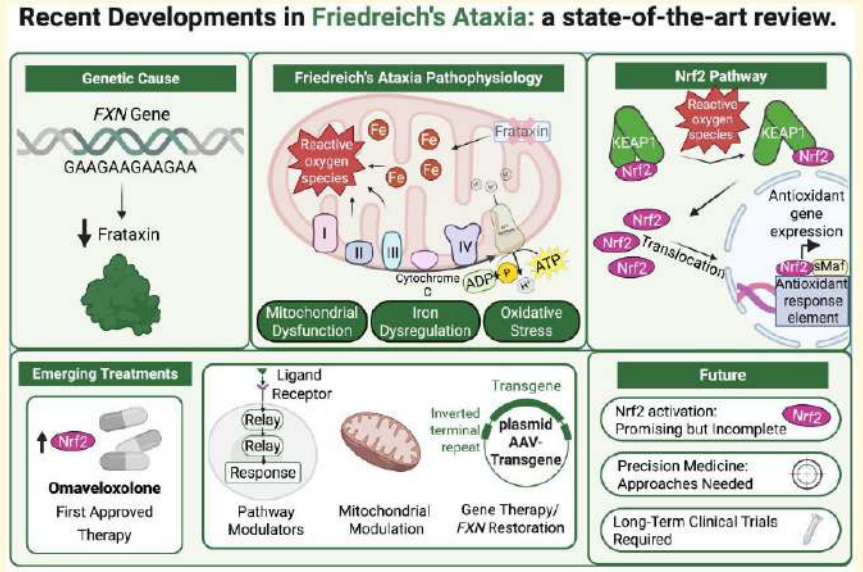
Recent developments in Friedreich's ataxia: a state-of-the-art review

Laura R. Chapman,[1,2] Heather Mortiboys[1*] and Pamela J. Shaw[1,3*]

GAA expansion in gene encoding Frataxin (mitochondrial protein, iron transport). FRDA chromosomes: 90% homozygous 67-1700 GAA repeats (N 6-34); 10% expanded and a point mutation allele

Classical

- Cardinal features:
  - Progressive ataxia (onset 10-15 yo; loss of ambulation 15+/- yr later)
  - Absent lower limb reflexes
  - Extensor plantar responses
  - Decreased vibration sense and proprioception
- Non-essential common features:
  - Cardiomyopathy (often cause of death)
  - Scoliosis
  - Foot deformity
  - Diabetes
  - Pyramidal weakness of the lower limbs



Late Onest

- If later, LOFA (25-39) or VLOFA ≥40 years), both have:
  - Retained DTR
  - Milder impairment and slower progression
  - Fewer 2ry complications
  - Shorter GAA expansions in one **or** compound heterozygosity

Friedreich Ataxia

- If later, LOFA (25-39) or VLOFA ≥40 years), both have:
  - Retained DTR
  - Milder impairment and slower progression
  - Fewer 2ry complications
  - Shorter GAA expansions in one **or** compound heterozygosity

Friedreich Ataxia: Omaveloxelone

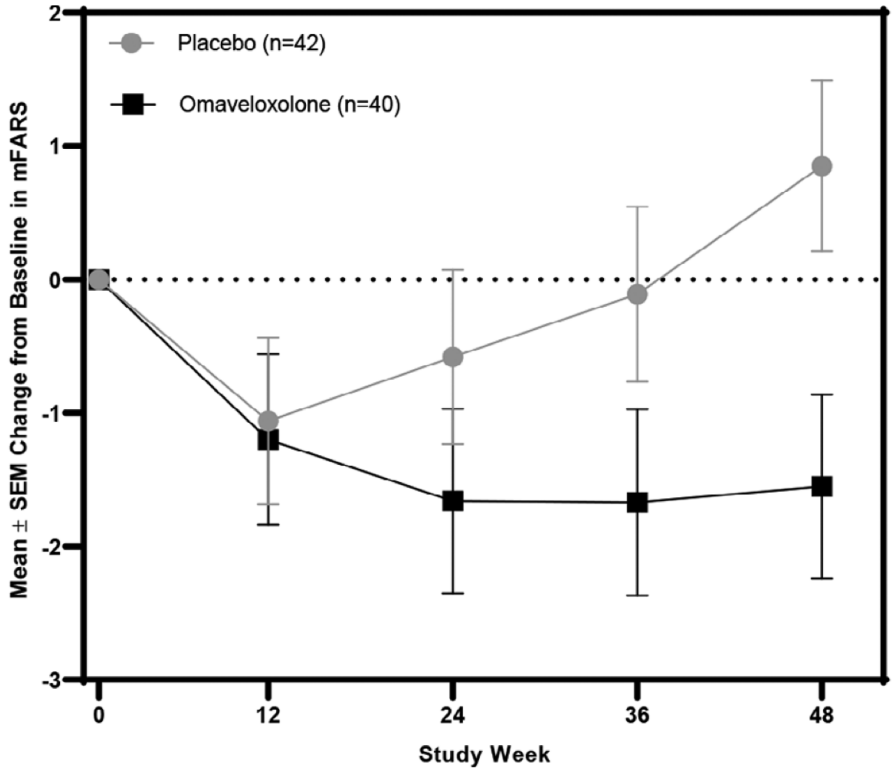
- Omaveloxelone is an Nrf2 activator targeting oxidative stress and mitochondrial dysfunction
- MOXIe: International, randomized, placebo-controlled trial, parallel group

- Primary endpoint: △ in mFARS at 48wk
- +ve outcome: mFARS difference of 2.4 points at 48wk
- FDA Approval: Feb. 2023
- Buchinger et al, 2026: shift to more atherosclerotic lipid profile → routine lipid monitoring

Slowing the curve: a single-arm meta-analysis of mFARS outcomes following omaveloxolone treatment in Friedreich ataxia

BMJ Neurol Open 2026

Aasim Ali ,[1] Waqar Ahmed Cheema ,[2] Fiza Nisar,[1] Ufaq Reyaz,[2] Muhammad Saad,[1] Muhammad Talha,[2] Sameen Sarfraz,[1] Ahmad Butt,[2] Muhammad Shamoon,[1] Armaghana Abdullah,[2] Muhammad Asad Shabbir,[2] Muhammad Talha,[2] Hammad Azam,[2] Muhammad Abdullah,[2] Aimen Anwaar[2]



Ataxia with Vit. E Deficiency *vs.* FA

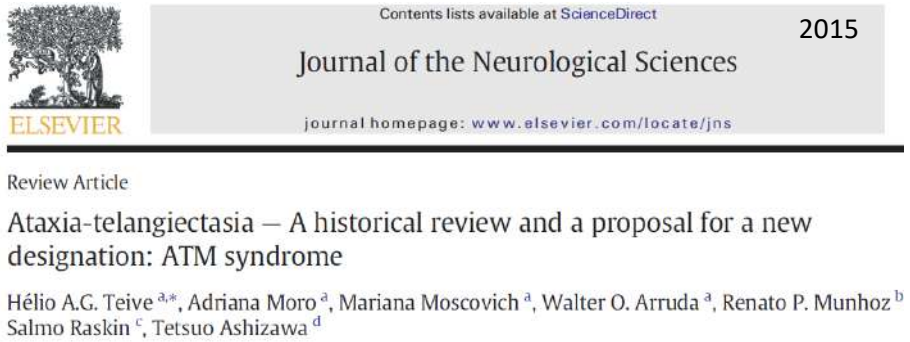
	AVED	FA
Onset	Late childhood early teens (7-15y)	Late childhood early teens (10-15y)
Progression	Better for AVED if detected and treated early	
Similar signs	Ataxia, absent lower limb reflexes, extensor plantars, loss of vibration sense and proprioception, cardiomyopathy	
Divergent signs	Head titubation, macular atrophy, retinitis pigmentosa	Deformities, diabetes
Gene/inheritance	*TTPA* / AR	*X25* / AR
Time to loss of ambulation	6 (untreated) to 35 years	7 to 22 years
Other findings	**Very** low α-tocopherol	Blood work typically normal

Ataxia Telangiectasia – ATM syndrome

- 1:100.000, loss of function of the *ATM* gene: DNA Repair
- Very early onset (<5y)
- Classic neurological features:
  - Progressive ataxia (early, wheelchair-bound by age 10y)
  - Oculomotor apraxia
  - Choreoathetosis
  - Pyramidal weakness lower limbs (DTRs decreased, extensor plantars)

Ataxia Telangiectasia

- Systemic features:
  - Oculocutaneous telangiectasia (2 to 3 years after ataxia)
  - Sinopulmonary infections
  - Susceptibility to cancer (most often leukemia/lymphoma)
  - Hypersensitivity to ionizing radiation
  - Deformities
  - Cardiomyopathy
  - Diabetes
- After genotyping for the gene became more available:
  - Several phenotypic variants were added to the spectrum
    - Cases with neither ataxia or telangiectasia!


Contents lists available at ScienceDirect
Journal of the Neurological Sciences
journal homepage: www.elsevier.com/locate/jns
2015

Review Article

Ataxia-telangiectasia — A historical review and a proposal for a new designation: ATM syndrome

Hélio A.G. Teive [a,*], Adriana Moro [a], Mariana Moscovich [a], Walter O. Arruda [a], Renato P. Munhoz [b], Salmo Raskin [c], Tetsuo Ashizawa [d]


REVIEW
Movement Disorders, Vol. 33, No. 8, 2018

CME Ataxia-Telangiectasia: A Review of Movement Disorders, Clinical Features, and Genotype Correlations

online video

Ariel Levy, MD, FRCPC[1,2,3] and Anthony E. Lang, MD, FRCPC[1,2*]

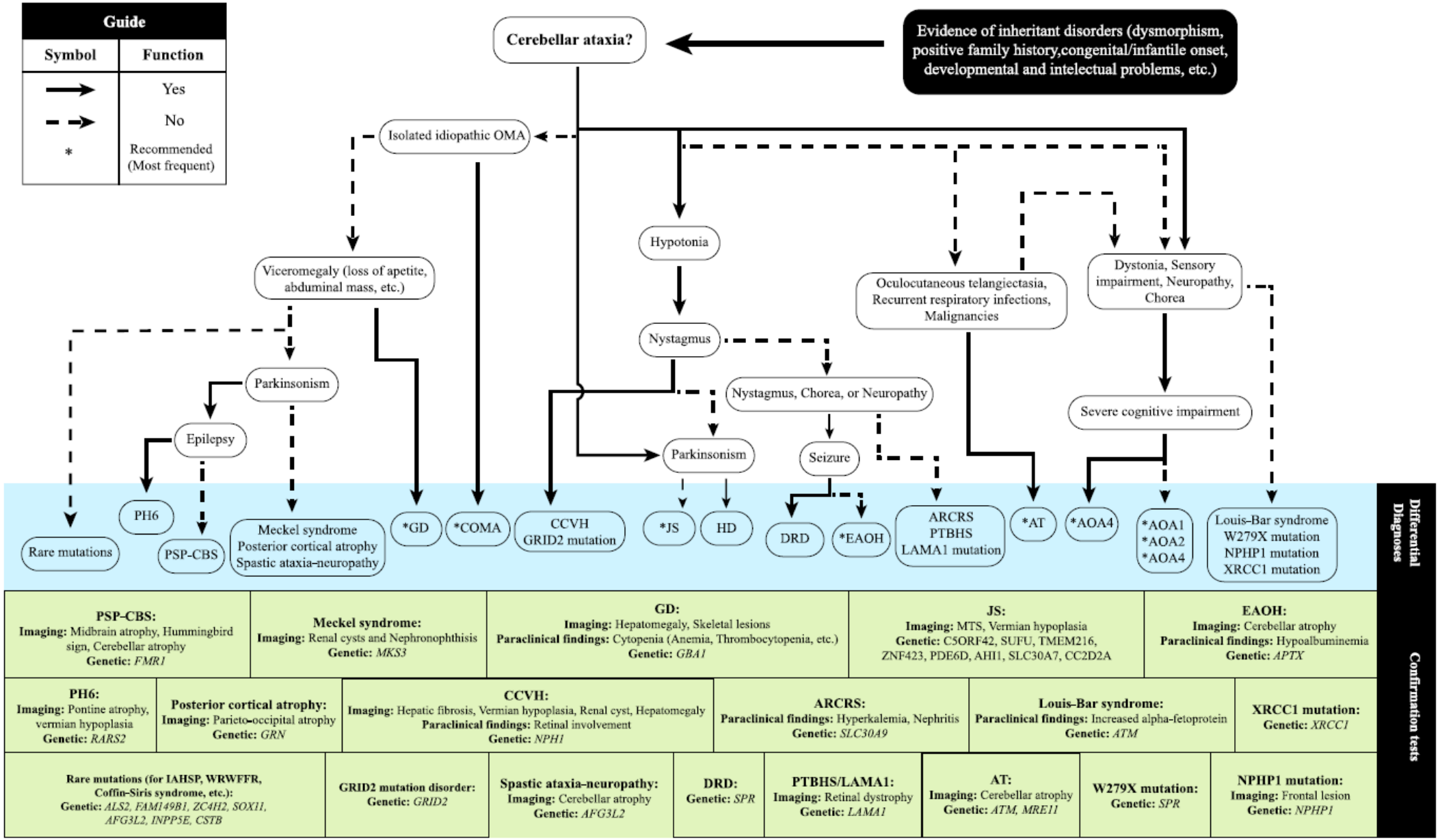
Ataxia Oculomotor Apraxia

- Core features:
  - Ataxia
  - Oculomotor apraxia
  - Neuropathy (atrophy, areflexia, weakness)
- Four disorders: AOA 1 – 4; AOA1 and AOA2 best studied
- OA: Inability to volitionally initiate horizontal saccades away from primary gaze, compensated by making a head thrust.

Ataxia Oculomotor Apraxia

	AOA Type 1	AOA Type 2	AOA Type 4
Gene mutation	APTX	SETX	PNKP
Onset age	~4 years (childhood)	10–25 years (later childhood/adolescence)	~4 years (childhood)
Main clinical signs	Ataxia, OA, neuropathy, chorea, myoclonus (early, fades), distal muscle wasting	Ataxia, OA, axonal S/M neuropathy, dystonia, chorea, early menopause	Ataxia, OA, dystonia (can be 1st sign, fades), distal muscle wasting, neuropathy
Blood findings	⇩ albumin, ⇧ cholesterol	⇧ **α**-FP	⇩ albumin, ⇧ cholesterol, ⇧ **α**-FP; can be normal
Prevalence/location	Portugal, Japan; rare	Worldwide; rarer than FA	Portugal; rare
Progression	**Faster**; wheelchair 10–15 years after onset	**Slowly progressive**	Slowly progressive

Approach to Oculomotor Apraxia

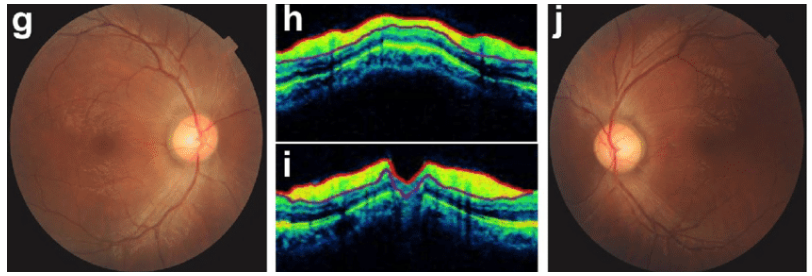


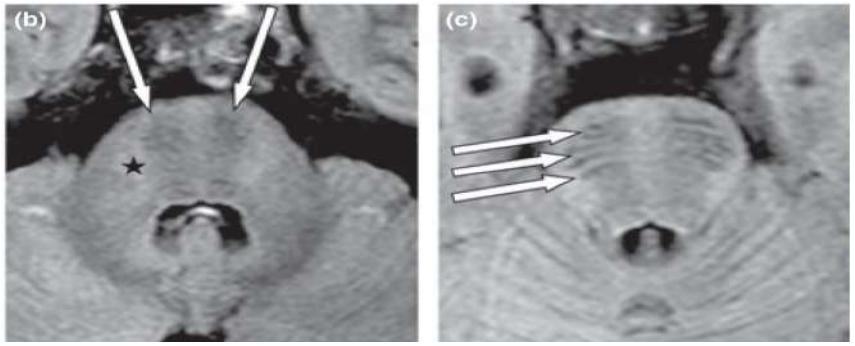
Salari et al, 2025

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay

ARSACS

- Gene *SACS* encoding protein sacsin
- Core features:
  - Ataxia
  - Early spasticity (age 1-2, up to 12yr)
  - Neuropathy (atrophy, areflexia- in 20s, weakness).
- Other:
  - Retinal myelinated fibres
  - MRI: atrophy superior cerebellar vermis, pons with T2-hypointense stripes
- ARSACS found worldwide





Spastic Ataxias

Autosomal dominant spastic ataxias
- Spinocerebellar ataxia type 1 (SCA1)
- Spinocerebellar ataxia type 3 (SCA3)
- Other spinocerebellar ataxias (SCAs)
- Autosomal dominant hereditary spastic paraplegias with cerebellar signs
- Spastic paraplegia, ataxia and mental retardation (SPAR)
- Spastic ataxia associated with optic atrophy type 1
- Presenile dementia with spastic ataxia
- Adult-onset Alexander's disease

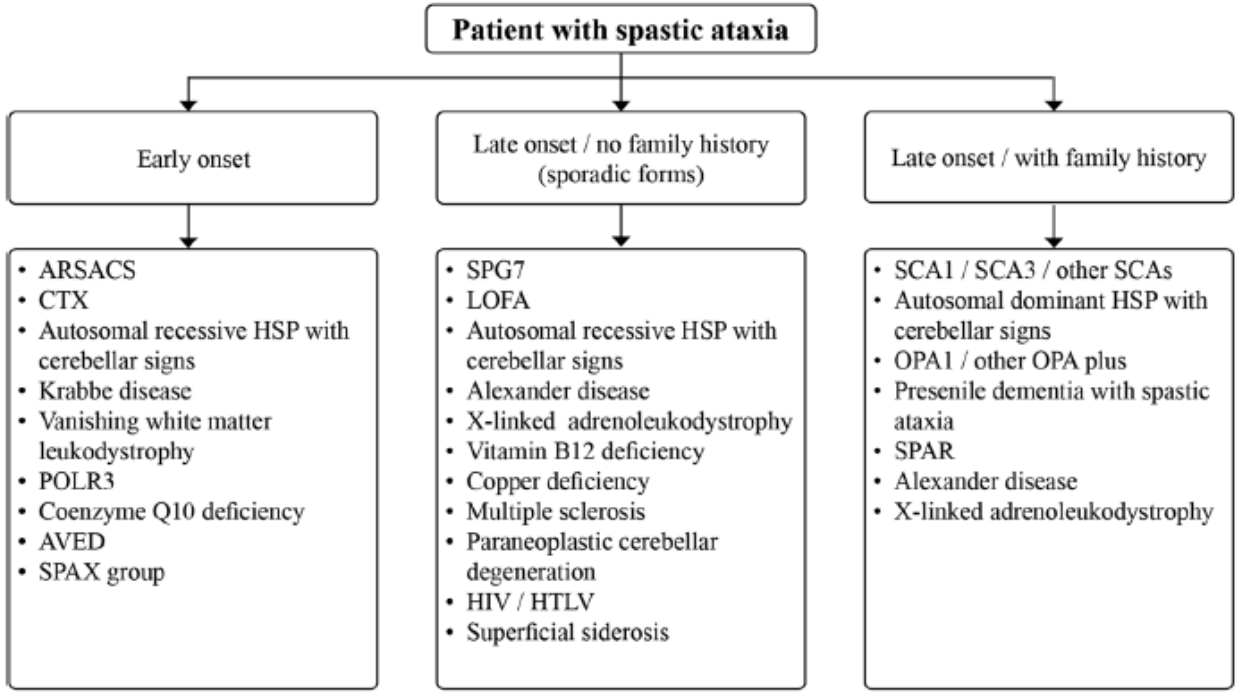
Autosomal recessive spastic ataxias
- Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)
- Hereditary spastic paraplegia type 7 (SPG7)
- Late onset and very-late onset Friedreich ataxia (LOFA and VLOFA)
- Cerebrotendinous xanthomatosis (CTX)
- Autosomal recessive hereditary spastic paraplegias with cerebellar signs
- Leucodystrophies
- Genetic metabolic causes
- SYNE-1 mutation

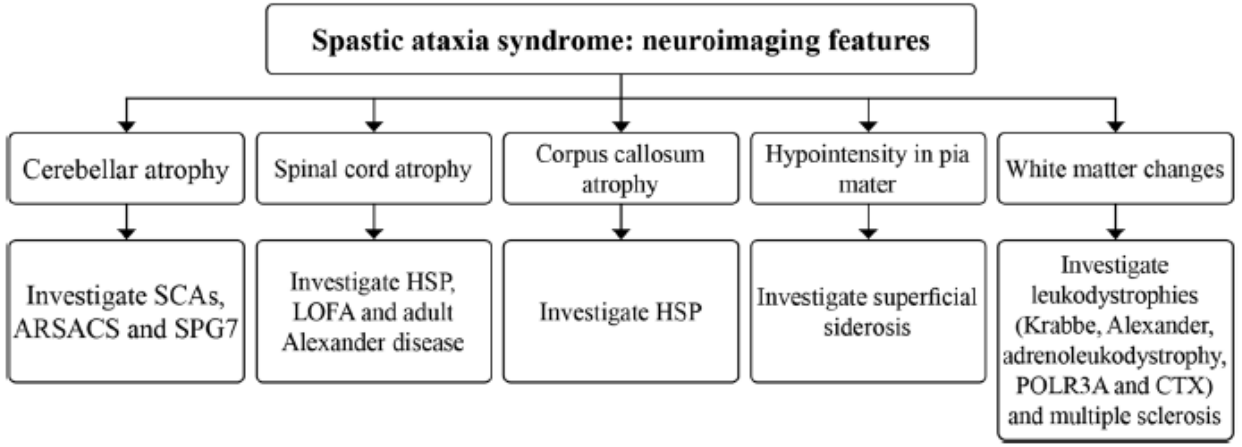
X-linked spastic ataxias
- Pelizaeus-Merzbacher syndrome
- Adrenomyeloneuropathy

Loss-of-function variants in the CAPN1 activator CD99L2: Nat Comm 2026

Other rare genetic causes of spastic ataxias
- SPAX 1 to SPAX 9 (Table 2)

Sporadic (non-genetic) and acquired spastic ataxias
- Metabolic and nutritional causes (vitamin B12, vitamin E and copper deficiency)
- Immune-mediated spastic ataxias (multiple sclerosis, paraneoplastic cerebellar degeneration)
- Infectious causes of spastic ataxias (HTLV-1 and HIV)
- Superficial siderosis and other structural causes (trauma, arteriovenous malformations, aneurysms and tumors)





Pedroso et al, 2022

Table 2 Clinical and genetic features of SPAX (spastic ataxia) group

SPAX subtype	Clinical features	Inheritance	Genetics
SPAX1	Onset between the ages of 10 and 20 years, lower-limb spasticity and global ataxia, dysarthria, impaired ocular movements	AD	*VAMP1* gene
SPAX2	Early onset, spasticity, ataxia, amyotrophy, microcephaly, chorea, atrophy of the cerebellum, corpus callosum, or brainstem (SPG58)	AR	*KIF1C* gene
SPAX3	Age at onset from 2 to 59 years, ataxia, spasticity, scoliosis, dystonia, hearing and cognitive impairment, white matter changes	AR	*MARS2* gene
SPAX4	Amish origin, early childhood onset, ataxia, spasticity, optic atrophy and nystagmus	AR	*MTPAP* gene
SPAX5	Early onset, spasticity, ataxia, myoclonic epilepsy, amyotrophy, ptosis, oculomotor apraxia, dystonia, neuropathy	AR	*AFG3L2* gene
SPAX6	Similar do ARSACS	AR	*SACS* gene
SPAX7	Late onset, ataxia, spasticity, chorea, ptosis slow pupillary reaction, myopia, optic disc pallor, color blindness, retinal atrophy	AD	Unknown
SPAX8	Early onset, ataxia, spasticity, nystagmus, hypometric saccades, dystonia, cerebellar atrophy and hypomyelinating leukodystrophy	AR	*NKX6–2* gene
SPAX9	Early onset, ataxia, spasticity, amyotrophy, *pes cavus*, slow saccades, motor neuropathy, growth retardation, cognitive changes and ovarian failure	AR	*CHP1* gene

*SPAX6 is the same as autosomal recessive spastic ataxia of Charlevoix-Saguenay (*ARSACS*), described in another topic. *AR* autosomal recessive, *AD* autosomal dominant, *SPG* Spastic paraplegia

Pedroso et al, 2022

Annals of Clinical and Translational Neurology, 2025; 12:832–841

Targeted Long-Read Sequencing as a Single Assay Improves the Diagnosis of Spastic-Ataxia Disorders

Laura Ivete Rudaks[1,2,3,4] | Igor Stevanovski[3,5] | Dennis Yeow[1,2,3,6,7] | Andre L. M. Reis[3,5,8] | Sanjog R. Chintalaphani[3] | Pak Leng Cheong[1,2] | Hasindu Gamaarachchi[3,5,9] | Lisa Worgan[2,10] | Kate Ahmad[11] | Michael Hayes[1] | Andrew Hannaford[1] | Samuel Kim[12] | Victor S. C. Fung[2,12] | Gabor M. Halmagyi[13] | Andrew Martin[12] | David Manser[14] | Michel Tchan[2,14] | Karl Ng[2,11] | Marina L. Kennerson[1,2,15] | Ira W. Deveson[3,8,16] | Kishore Raj Kumar[1,2,3,16]

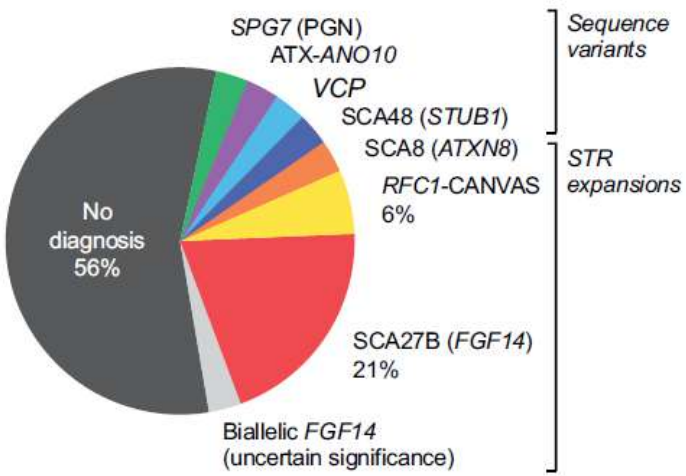
ABSTRACT

Objective: The hereditary spastic-ataxia spectrum disorders are a group of disabling neurological diseases. The traditional genetic testing pathway is complex, multistep and leaves many cases unsolved. We aim to streamline and improve this process using long-read sequencing.

Methods: We developed a targeted long-read sequencing strategy with the capacity to characterise the genetic variation of all types and sizes within 469 disease-associated genes, in a single assay. We applied this to a cohort of 34 individuals with unsolved spastic-ataxia. An additional five individuals with a known genetic diagnosis were included as positive controls.

Results: We identified causative pathogenic variants that would be sufficient for genetic diagnosis in 14/34 (41%) unsolved participants. The success rate was 5/11 (45%) in those who were naïve to genetic testing and 9/23 (39%) in those who were undiagnosed after prior genetic testing, completed on a clinical basis. Short tandem repeat expansions in *FGF14* were the most common (7/34, 21%). Two individuals (2/34, 6%) had biallelic pathogenic expansions in *RFC1* and one individual had a monoallelic pathogenic expansion in *ATXN8OS/ATXN8*. Causative pathogenic sequence variants other than short tandem repeat expansions were found in four individuals, including in *VCP*, *STUB1*, *ANO10* and *SPG7*. Furthermore, all five positive controls were identified.

Interpretation: Our results demonstrate the utility of targeted long-read sequencing in the genetic evaluation of patients with spastic-ataxia spectrum disorders, highlighting both the capacity to increase overall diagnostic yield and to streamline the testing pathway by capturing all known genetic causes in a single assay.



RFC1/CANVAS Spectrum

- **CANVAS: C**erebellar **A**taxia, **N**europathy, **V**estibular **A**reflexia **S**yndrome
- Mutation: Biallelic expansion of intronic pentanucleotide repeat AAGGG in *RFC1* (pathogenic= 400 to >2000)
- *RFC1: Replication factor C Subunit 1*: largest subunit in DNA replication/repair complex
- Allele frequency up to 4% of population, prevalence up to 1:625
- Mean age of onset >50
- Progressive unsteadiness most common

Biallelic expansion of an intronic repeat in *RFC1* is a common cause of late-onset ataxia

Andrea Cortese[1,*], Roberto Simone[2], Roisin Sullivan[1,11], Jana Vandrovcova[1,11], Huma Tariq[1], Wai Yan Yau[1], Jack Humphrey[1], Zane Jaunmuktane[2], Prasanth Sivakumar[1], James Polke[3], Muhammad Ilyas[4], Eloise Tribollet[1], Pedro J. Tomaselli[5], Grazia Devigili[6], Ilaria Callegari[7], Maurizio Versino[7,8], Vincenzo Salpietro[1], Stephanie Efthymiou[1], Diego Kaski[1], Nick W. Wood[1], Nadja S. Andrade[9], Elena Buglo[10], Adriana Rebelo[10], Alexander M. Rossor[1], Adolfo Bronstein[2], Pietro Fratta[1], Wilson J. Marques[5], Stephan Züchner[10], Mary M. Reilly[1,12], Henry Houlden[1,3,12,*]

RFC1/CANVAS Spectrum

1. **Peripheral nerve:**
- distal sensory symptoms
- NCS: abnormal sensory in 100%
- Severe loss of myelinated fibers on BX

2. **Cerebellar:**
- Eye movement abnormalities
- Dysarthria/dysphagia
- MRI: cerebellar atrophy 63%

3. **Vestibular System:**
- Abnormal bedside head impulse test 87%
- Bilalateral reduced/absent VOR- confirmed by testing in 91%

Chronic Cough:
- 64% patients
- Up to 3 decades before onset

8% of patients with Refractory Chronic Cough

(Hirons et al 2025)

Dysautonomia:
- 32% patients
- Mild and late

Slowly progressive:
- ~50% cane in 10 years
- 25% wheelchair in 15 years

Other: UMN (18%); LMN (11%); parkinsonism (8%); cognitive (executive) (31%); biallelic AAGGG expansions found in 2.3% of patients with idiopathic peripheral neuropathy

REVIEW OPEN ACCESS

Motor, Extrapyramidal, and Cognitive Involvement in RFC1 Disease

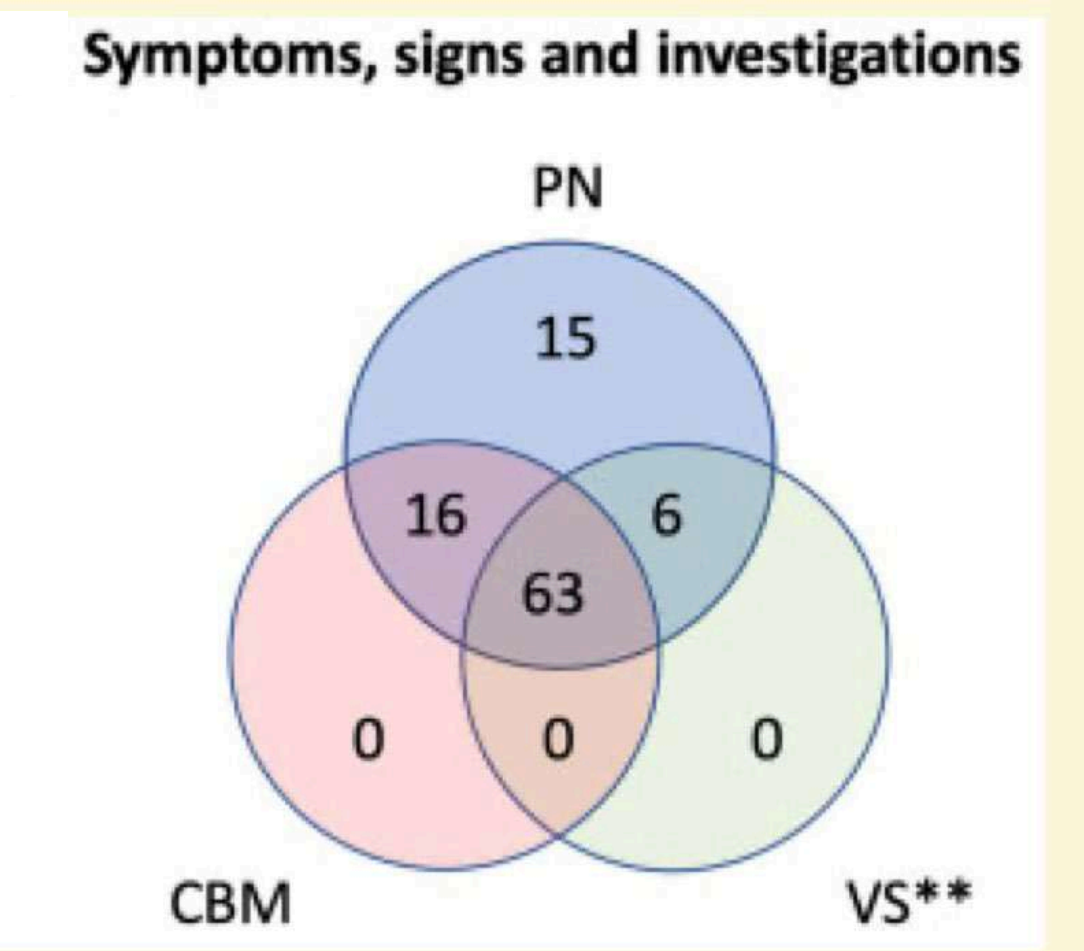
A Systematic Review and Meta-Analysis

Sara Massucco,[1,*] Mehrnaz Hamedani,[1,*] Marta Ponzano,[2] Riccardo Manca,[3] Edoardo Roveta,[1] Anna Pichiecchio,[4,5] Carlo Asteggiano,[4] Federico Zaottini,[6] Maria João Malaquias,[7] Riccardo Currò,[8] Matteo Pardini,[1,6] Angelo Schenone,[1,6] Federico Massa,[1,6] Andrea Cortese,[8,9] and Marina Grandis[1,6]

Correspondence
Dr. Massucco
massucco.sara@gmail.com

Neurol Genet 2026;12:e200393. doi:10.1212/NXG.0000000000200393

RFC1/CANVAS Spectrum



1. Peripheral nerve:

- distal sensory symptoms
- NCS: abnormal sensory in 100%
- Severe loss of myelinated fibers on BX

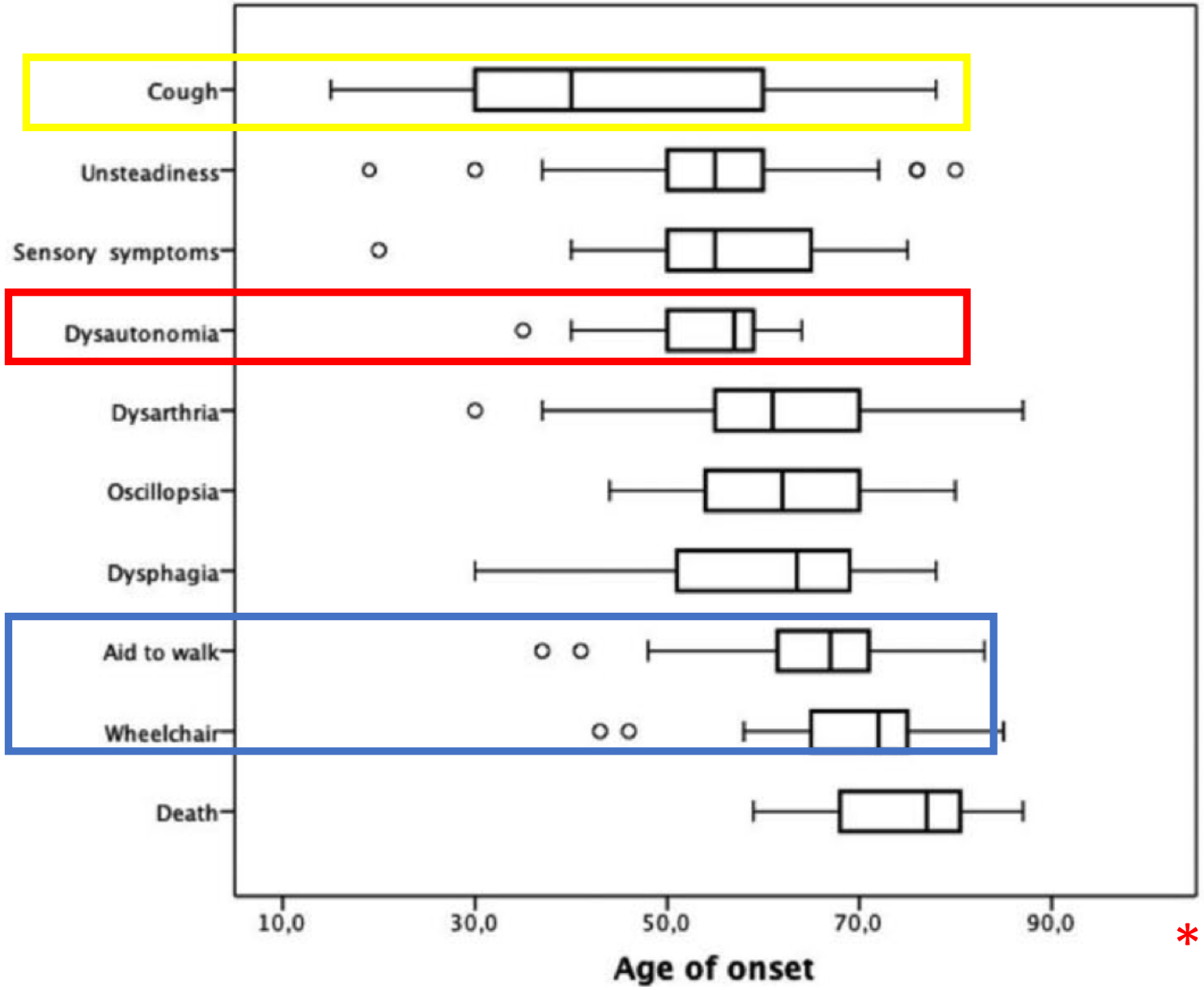
2. Cerebellar:

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- MRI: cerebellar atrophy 63%

3. Vestibular System:

- Abnormal bedside head impulse test 87%
- Bilalateral reduced/absent VOR- confirmed by testing in 91%

RFC1/CANVAS Spectrum



1. **Chronic Cough***:
   - 64% patients
   - Up to 3 decades before onset

2. **Dysautonomia:**
   - 32% patients
   - Mild and late

3. **Slowly progressive:**
   - ~50% cane in 10 years
   - 25% wheelchair in 15 years

* 8% of patients with Refractory Chronic Cough

(Hirons et al 2025)

Journal of Neurology (2025) 272:235
https://doi.org/10.1007/s00415-025-12964-x

ORIGINAL COMMUNICATION

Late-onset vestibulocerebellar ataxia: clinical and genetic studies in a long follow-up series of 50 patients

David Genís[1,2] · Berta Alemany[1,2] · David Pellerin[4,5] · Bernard Brais[4] · Marie-Josée Dicaire[4] · Víctor Volpini[6] · Berta Campos[6] · Jordi Corral[6] · Josep Gardenyes[6] · Laura de Jorge[6] · Héctor San Nicolás[6] · Maria Buxó[7] · Joan Martínez Sancho[7] · Maria Obon[8] · Carles Roig[8,9] · Laia Rodriguez-Revenga[10,11] · María Isabel Alvarez-Mora[10,11] · Matt C. Danzi[12] · Henry Houlden[5] · Stephan Zuchner[12] · Fabián Márquez[13] · Lluís Ramió i Torrentà[2,3,13]

Abstract

Background To describe the epidemiology, clinical features, degree of disability and genetic characteristics of a cohort of patients with a vestibulo-cerebellar ataxia of very late onset (LOVCA).

Methods We analysed the clinical, radiological, and genetic characteristics of a cohort of 50 patients with LOVCA. Where possible, patients were followed over the full course of the disease, including clinical, and molecular genetic analysis of genes known to cause episodic ataxia.

Results Ten patients are familial and 40 sporadic. Forty-three patients had an episodic onset, with episodes of gait ataxia characterized especially by sudden instability with downbeat nystagmus, visual symptoms, dizziness, and falls. Progression began on average 1.5 years after the onset of episodes. Of the patients followed over the full course of the disease, 87% became disabled. Women seem more prone to disability than men. An *FGF14* intronic GAA repeat expansion was found in 61% of patients with available DNA. The prevalence of LOVCA is $5.03/10^5$ inhabitants. Treatment with 4-aminopyridine reduced the number and severity of episodes.

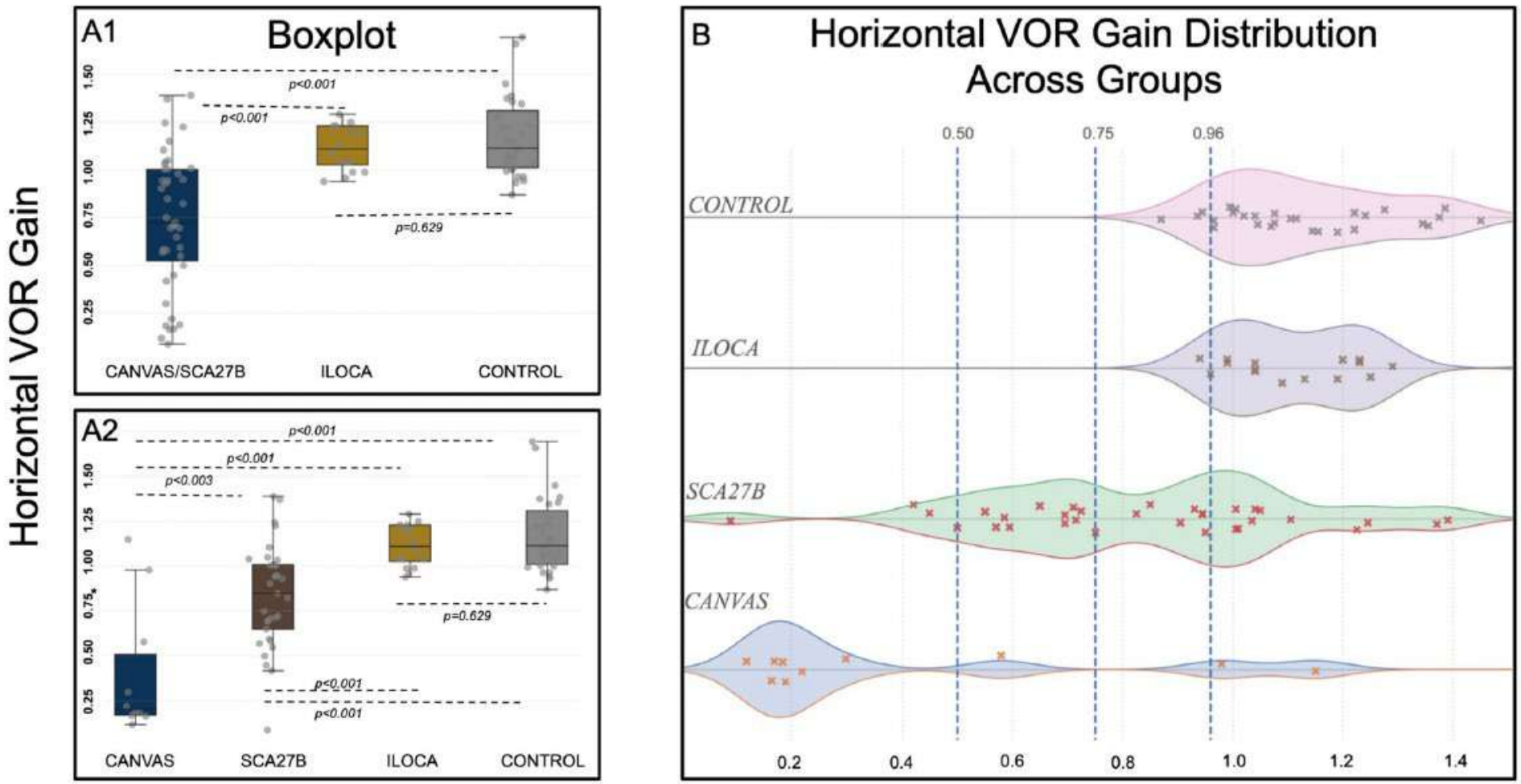
Conclusion LOVCA appears after the age of 50 and commonly leads to an inability to stand up and walk. The disease caused mild atrophy only in half of the patients and few changes were observed by MRI. The most common genetic cause was a heterozygous GAA expansion in *FGF14* (SCA27B). One third of our patients have no aetiological diagnosis. Disability seems to be a result of the complete loss of the vestibulocerebellar function, which is presumably a result of degeneration of this system.

Journal of Neurology (2025) 272:679
https://doi.org/10.1007/s00415-025-13433-1

ORIGINAL COMMUNICATION

Video head impulse test differentiates *RFC1*-CANVAS, *FGF14*-SCA27B, and idiopathic late-onset cerebellar ataxias

Leonardo E. Ariello[1,2] · Daniel R. Gold[3] · Jennifer L. Millar[4] · Michael C. Schubert[4,5] · Weiyi Mu[1,6] · Liana Rosenthal[1] · David P. W. Rastall[1]



Newly Recognized Recessive Ataxias

	Gene	Key Clinical Features	Phenotypic Spectrum	Onset & Progression	Diagnostic Advances
CANVAS	*RFC1*	Cerebellar ataxia, vestibular areflexia, sensory neuropathy, chronic cough.	Initially isolated neuropathy, vestibular symptoms, or cough before full syndrome.	**Late onset**, slow progression.	**Repeat-primed PCR**. Conventional exome sequencing misses intronic expansion.
POLG-related Ataxia-neuropathy spectrum	*POLG*	Cerebellar ataxia, peripheral neuropathy, epilepsy, ophthalmoplegia, myopathy, liver dysfunction.	Ataxia-neuropathy, epilepsy syndromes, mitochondrial encephalopathy.	**Late onset**. Course can be multisystemic, variable severity.	POLG sequencing. MtDNA deletions and depletion are secondary.
SYNE1 Ataxia	*SYNE1*	Typically cerebellar ataxia ± mild pyramidal signs, possible MND.	**Pure** adult-onset ataxia. **Complex forms**: MND, spasticity, cognition.	**Early adult onset**, slow progression.	Exome/genome sequencing identifies truncating variants.

Newly Recognized Autosomal Recessive Ataxias

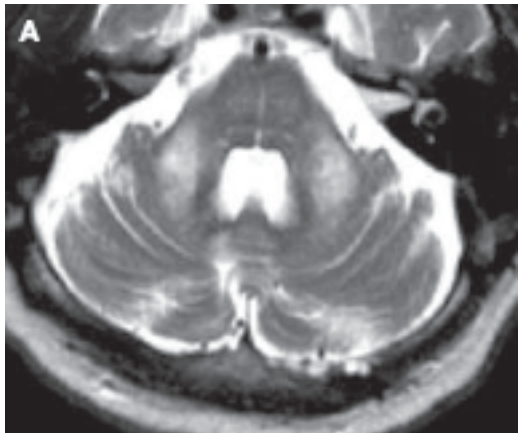
SPG7 vs. ARAs

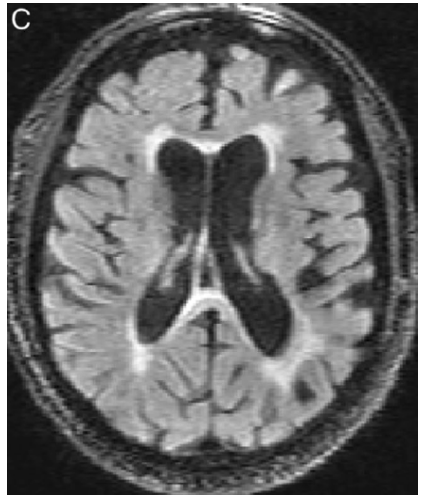
- **SPG7 gene** encodes paraplegin, originally an HSP, but phenotypic spectrum is broad.
- **Overlap with recessive ataxias:**
  - **Prominent features:** Cerebellar ataxia, spasticity, mild neuropathy, and sometimes cognitive symptoms.
  - **SPG7 ataxia phenotype:** may present primarily cerebellar rather than spastic-dominant; **indistinguishable from classic and new ARAs**
  - **Shared features:**
    - Gait disturbance (ataxia + spasticity)
    - Dysarthria, ocular movement abnormalities (saccadic/pursuit slowing)
    - Mild peripheral neuropathy
- **Ataxia in other HSPs**: SPG15, SPG76, SPG5a, SPG46

Fragile X Tremor Ataxia Syndrome



- $(CGG)_n$ expansion in the FMR1 gene:
  - $(CGG)_n$ < 50 seen in normal population
  - $(CGG)_n$ > 200 cause fragile X syndrome
  - $(CGG)_n$ premutation range (50-200) cause FXTAS
    - Mean age of onset 61yo (>50)
    - Clinical signs:
      - Cerebellar ataxia (93%)
      - Tremor similar to ET (70%)
      - Peripheral neuropathy (60%)
      - Parkinsonism (40%)
      - Dysautonomia (33%)
      - Cognitive decline (25%)





Progressive Ataxia Palatal Tremor (PAPT)

Sporadic

- Degenerative
  - Idiopathic PAPT – tauopathy (one recent case with Lewy pathology (Costa et al, 2026)
  - PSP-C
- Acquired – static lesion
  - “Oculo-palatal tremor and tardive ataxia”

Hereditary

- Alexander’s disease (*GFAP* mutations)
- SCA 20 (chr 11; gene unknown)
- *Polymerase gamma (POLG)* mutations
- HSP7
- GM2-Gangliosidosis
- Cerebrotendinous xanthomatosis
- Neuroferritinopathy/Aceruloplasminemia
- *ADCK3*-related ataxia (SCAR9)

Episodic / Paroxysmal Ataxias

- Characterized by episodes lasting minutes to hours:
  - Ataxia
  - Dysarthria
  - Tremor
  - Nystagmus.
- Episodic ataxias are subdivided into eight disorders: EA1 – 8
- “Classic” forms are EA1 and EA2, both respond to acetazolamide*

→ **TREATABLE**

- Some patients may experience progressive interictal features
- Also “symptomatic” forms – e.g., CASPR-2 Autoimmunity, SCA27B

* Shimazaki 2025 – addition of levetiracetam may improve response rate

Episodic Ataxia 1 vs. 2

	EA1	EA2
Onset	Childhood and adolescence	Childhood and adolescence
Precipitant factors	Emotion and stress	Emotion, stress, caffeine, alcohol, heat, phenytoin
Duration	Seconds to minutes	Hours to days
Associated signs	Myokymia, contractures	Migraine, hemiplegia
Gene/inheritance	*KCNA1* / AD	*CACNA1A* / AD
Interictal findings	Epilepsy, delayed motor and cognitive development	Nystagmus, ataxia
TREATMENT	Acetazolamide, Anti-epileptic drugs	Acetazolamide, **4-aminopyridine**

Recent postmortem study de Vries 2026

Clin Neuropathol

. 2026 Jun 15. doi: 10.5414/NP301727. Online ahead of print.

Postmortem cerebellar and brainstem alterations in episodic ataxia type 1 and 2: Expanding the clinicopathological spectrum

Jeroen J de Vries, Maria João da Costa Caiado, Wilfred F A den Dunnen

PMID: 42290287 DOI: 10.5414/NP301727

Abstract

Background: Episodic ataxias (EAs) are rare autosomal-dominant channelopathies presenting with recurrent attacks of ataxia and variable neurological features. While MRI studies suggest mild cerebellar atrophy in some patients, detailed neuropathological descriptions are lacking.

Materials and methods: We examined postmortem brains and spinal cords from two genetically confirmed patients: EA1 (KCNA1 Val174Phe mutation) and EA2 (CACNA1A A253Y mutation). Routine histology and immunohistochemistry were performed.

Results: In EA1, the cerebellar vermis and hemispheres showed narrowing of the folia, segmental Purkinje cell loss, Bergmann gliosis, and scattered torpedoes. The dentate nucleus contained focal lipofuscin-laden macrophages and Rosenthal fibers. Concurrently, α-synuclein pathology (Braak stage 3) was also present, along with sparse age-related tau tangles and minimal vascular amyloid. In EA2, only focal Purkinje cell loss was detected, but novel p62-positive axonal and dendritic inclusions were observed in the cerebellar cortex and inferior olive. No additional α-synuclein, tau, or amyloid pathology was found. A concurrent glioblastoma was identified as the immediate cause of death.

Conclusion: These are the first detailed autopsy reports of EA1 and EA2. Both revealed cerebellar pathology, with EA1 showing more pronounced Purkinje cell degeneration, while EA2 demonstrated previously undescribed p62-positive inclusions. These findings expand the clinicopathological spectrum of EAs and highlight the value of postmortem studies in elucidating underlying disease mechanisms.

Genetic causes of episodic ataxia.

	GENE	PROTEIN	INHERITANCE	OMIM	EA PHENOTYPE	ONSET AGE	ATTACK DURATION	MYOKYMIA	NYSTAGMUS	TINNITUS	EPILEPSY	CHRONIC ATAXIA	OTHER FEATURES	ACETAZOLAMIDE RESPONSE
Primary EAs														
EA1	KCNA1	Kv1.1	AD	160120 176260	Brief attacks, interictal myokymia	Child (<age 20)	Secs-Mins	Yes	No	+/−	+/−	+/−	+/−cramps, stiffness, deafness	Variable
EA2	CACNA1A	Cav2.1	AD	108500 601011	Long attacks, interictal nystagmus	Child, adult	Mins-hours (days)	No	Yes	No	+/−	+/−	Migraine (50%)	Yes
EA3	Locus 1q42	Unknown	AD	606554	Like EA1 plus tinnitus	Child, adult	Mins	Yes	+/−	Yes	+/−	No		Yes
EA4	Linkage excluded EA1 & 2	Unknown	AD	606552	Like EA2, no nystagmus	Adult	Hours	No	No	No	+/−	No		
EA5	CACNB4	Cav2.1	AD	613855 601949	Like EA2	Adult	Hours	No	Yes	No	Yes	No		Yes
EA6	SLC1A3	EAAT1	AD	612656 600111	Like EA2	Child, adult	Hours	No	Yes	No	+/−	+/−	+/−migraine, alternating hemiplegia	Yes
EA7	Maps 19q13	Unknown	AD	611907	Like EA2, no nystagmus		Hours	No	No	No	No	No		
EA8	UBR4	Unknown	AD	616055 609890	Overlap with EA1 and EA2	Age 2	Mins-hours	+/−	+/−	No	No	No	Intention tremor	No
EA9?	FGF14	Fibroblast growth factor 14	AD	601515 609307	Like EA2 with tremor, may be brief	Child, adult	Secs-days	No	Yes	No	No	Yes	Vertigo, tremor	Yes
EA9?	SCN2A	Nav1.2	AD	182390 607743		Infant, child	Mins-hours	No	No	No	Yes	No	Neonatal seizures	Variable
EA10?	CACNA1G	VGCC	AD	604065		Adult	Up to months	No	No	No	No	Yes	Facial numbness, movement-induced vertigo, bilateral vestibulopathy	No

Hasssan 2023

J Vet Intern Med. 2025;39:e17268.
https://doi.org/10.1111/jvim.17268

Clinical characterization of a novel episodic ataxia in young working Cocker Spaniels

Clara Sarró[1] | Catherine Stalin[1,2] | Rodrigo Gutierrez-Quintana[1] | Ana Cloquell[1]

Diseases Affecting the Dentate Nuclei

Cerebrotendinous xanthomatosis: **3**
Neurofibromatosis: **1**
L-2 hydroxy glutaric aciduria
Krabbe's disease: **1**
Infantile neuroaxonal dystrophy
Alexander's disease: **3, 6**
Canavan's disease: **3**
Mucopolysaccharidosis: **7**

Brain calcifications*: **1, 2, 4**
Neuroferritinopathy: **2, 4**
Glutaric aciduria: **3**
Wilson's disease: **1, 3**
Aceruloplasminemia: **2, 4**
NBIA's: **2, 4**

Cognitive Decline

Movement Disorder

MRI pattern

1. **T1 hyperintensity**
2. **T2 hypointensity**
3. **T2/FLAIR hyperintensity**
4. **T2 shortening on GRE**
5. **Diffusion restriction**
6. **Post-contrast enhancement**
7. **FLAIR hypointensity**

Metronidazole toxicity: **3, 5**
Monohalothane toxicity

Cerebellar Ataxia

Peripheral Neuropathy

Encephalopathy

Pyramidal Dysfunction

Maple syrup urine disease: **5**
Wernicke's encephalopathy: **5**
Leigh's disease: **5**

Spinocerebellar ataxia 20*: **1, 2, 4**
SCA 28; SPG7: **3**
Erdheimer-Chester disease: **1, 6**
Multiple sclerosis: **1**

Revised from Khadilkar et al, 2016

*** CT: Ca^{2+} in DN (isolated in SCA20)**

Movement Disorders, Vol. 40, No. 5, 2025

Alessandro et al

Artificial Intelligence-Based Virtual Assistant for the Diagnostic Approach of Chronic Ataxias

CME

TABLE 1 . *Diagnostic performance between groups*

	Correct diagnoses			
	Neurologists n/total (%)	GPT-4 n/total (%)	Virtual assistant n/total (%)	*P*-value
Pediatrics	40/265 (15.1)	47/265 (17.7)	242/265 (91.3)	<0.001[a,b]
Adults	43/188 (22.9)	41/188 (21.8)	170/188 (90.4)	<0.001[a,b]
Frequent ataxias	46/120 (38.3)	49/120 (40.8)	109/120 (90.8)	<0.001[a,b]
Infrequent ataxias	37/333 (11.1)	39/333 (11.7)	303/333 (91.0)	<0.001[a,b]
Pure phenotype	2/20 (10)	6/20 (30)	20/20 (100)	<0.001[a,b]
Combined phenotype	81/433 (18.7)	82/433 (18.9)	392/433 (90.5)	<0.001[a,b]
Treatable ataxias	18/84 (21.4)	24/84 (28.6)	77/84 (91.7)	<0.001[a,b]
Non-treatable ataxias	65/369 (17.6)	64/369 (17.3)	335/369 (90.8)	<0.001[a,b]
Autosomal dominant inherited ataxias	27/135 (20)	25/135 (18.5)	125/135 (92.6)	<0.001[a,b]
Autosomal recessive inherited ataxias	40/276 (14.5)	45/276 (16.3)	251/276 (90.9)	<0.001[a,b]
X-linked inherited ataxias	5/15 (33.3)	5/15 (33.3)	14/15 (93.3)	<0.001[a,b]
Mitochondrial inherited ataxias	5/12 (41.7%)	6/12 (50%)	12/12 (100%)	<0.001[a,b]
Sporadic ataxias	2/9 (22.2)	3/9 (33.3)	5/9 (55.6)	0.3
Ataxias diagnosed by repeat expansion tests	21/57 (36.8)	24/57 (42.1)	55/57 (96.5)	<0.001[a,b]
Ataxias diagnosed by next-generation sequencing	60/387 (15.5)	61/387 (15.8)	352/387 (90.9)	<0.001[a,b]

Nature Reviews Neurology | Volume 21 | December 2025 | 687–705

nature reviews neurology

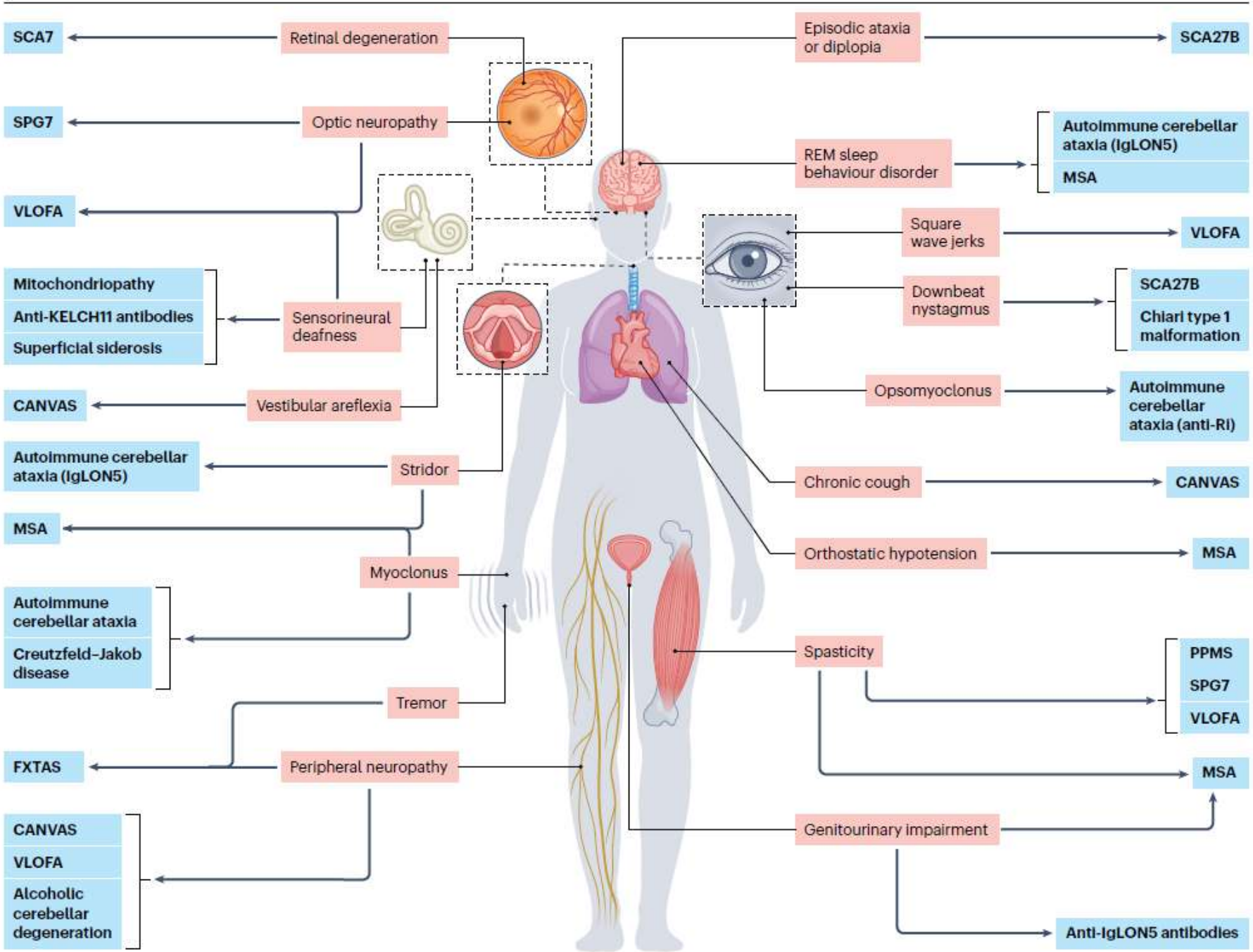
https://doi.org/10.1038/s41582-025-01136-0

Review article

Check for updates

Progress and challenges in sporadic late-onset cerebellar ataxias

Thomas Wirth[1,2,3], Jennifer Faber[4,5], Christel Depienne[6], Emmanuel Roze[7], Jérôme Honnorat[8,9], Wassilios G. Meissner[10,11,12,13], Paola Giunti[14,15], Christine Tranchant[1,2,3], Thomas Klockgether[4,5] & Mathieu Anheim[1,2,3]



Wirth et al, 2025

Treatment of Cerebellar Ataxias

- No symptomatic treatment is very effective for ataxia
- Always consider inborn errors of metabolism – specific treatments

Top 12 Of Treatable Inborn Errors Of Metabolism With Movement Disorders

#12	**Pyruvate dehydrogenase deficiency**	(*PDHA1*;(*PDHA2, PDHX or DLAT*))	*High dose thiamine; Ketogenic diet*
#11	**Primary Coenzyme Q10 deficiency**	(*ADCK3*)	*CoQ10 (200 mg tid)*
#10	**Niemann-Pick type C disease**	*(NPC1 or NPC2)*	*Miglustat*
#9.	**Dystonia with hypermanganesemia**	*(SLC30A10 or SLC39A14)*	*EDTA, Fe supplementation*
#8.	**Cerebrotendinous xanthomatosis**	*(CYP27A1)*	*Chenodeoxycholic acid*
#7.	**Glutaric aciduria type 1**	*(GCDH)*	*Low lysine diet, carnitine suppl, intercurrent illnes care*
#6.	**Cerebral folate deficiency**	(*FOLR1)*	*Folinic acid*
#5.	**Biotin-thiamine-responsive BGD**	*(SLC19A3)*	*Biotin (5-10 mg /kg/d) + thiamine (300-900mg/d)*
#4.	**Ataxia with vitamin E deficiency**	*(TTPA)*	*Vitamin E (800-1500 mg/d)*
#3.	**GLUT1-deficiency syndrome**	*(SLC2A1)*	*Ketogenic diet; (? Triheptanoin)*
#2.	**Wilson's disease**	*(ATP7B)*	*Chelation; Zn; Liver transplantation*
#1.	**Dopa-responsive dystonia**	*(GCH1; others)*	*Levodopa (other depending on genetic defect)*

Revised Courtesy Darius Ebrahimi-Fakhari

Disease-Specific Interventions in Ataxias

- **Ataxia with Vitamin E Deficiency (TTPA)**
  - High-dose **Vitamin E** (lifelong, prevents progression)
- **Abetalipoproteinemia (MTTP)**
  - Low-fat diet + **Vitamins A, D, E, K**
- **Cerebrotendinous Xanthomatosis (CYP27A1)**
  - **Chenodeoxycholic acid (CDCA)** ± statins: slow decline
- **Refsum Disease (PHYH, PEX7)**
  - **Phytanic acid–restricted diet**, plasmapheresis if severe
- **CoQ10 Deficiency (COQ8A and others)**
  - **High-dose CoQ10 supplementation**

Treatment of Cerebellar Ataxias

- No symptomatic treatment is very effective for ataxia
- Symptomatic treatment for tremors – eg Propranolol in SCA12 (RCT), FXTAS
- Always consider inborn errors of metabolism – specific treatments
- Friedreich Ataxia - Omaveloxelone
- Symptomatic treatment for “episodic symptoms” – EAs, SCA27B
  - Acetazolamide; 4-aminopyridine
- ? Toriluzole
- ? Others – Ganglioside GM1; N-Acetyl-leucine (NAL) for CACNA1A ataxia
- ? rTMS / tDCS; cerebello-spinal DCS with gait training
- ? DBS – Thalamic (incl. PSA) for associated tremor (SCA12, FXTAS); ? Dentate / Interposed nuclei – experimental (DN-DBS: ↓43% SARA, Zhao et al, 2026)
- Rehabilitation
  - Home high-intensity aerobic training – Barbuto et al, 2025

Table 2

Comparative efficacy of pharmacological interventions in primary adult-onset neurodegenerative cerebellar ataxias (PANCA), based on quantitative scales and clinical outcomes.

Drug	Disease	Results
Omaveloxolone	Friedreich's ataxia	−2.40 (mFARS, 48wks); 55 % slower progression vs natural history
Riluzole	Hereditary ataxias (SCA, FA)	68 % ICARS ≥5 pts (8wks); 50 % SARA ≥1 pt (12 m)
Troriluzole	SCA1, SCA2, SCA3, SCA7, SCA10	Improved PDI; −0.71 fSARA (SCA3 subgroup)
4-Aminopyridine	Episodic ataxia type 2 (EA2)	Attack frequency ↓ from 6.5 to 1.65
GM1	SCA3	−3.80 (high dose) vs +0.34/ +0.73 (12wks)
Valproic acid	SCA3	−2.05 (1200 mg) vs −0.75 placebo ($p = 0.021$)
Varenicline	SCA3	Improved axial signs (stance, gait); no appendicular effect
Lithium	SCA2/SCA3	No improvement; some worsening in SCA3
Vatiquinone	Friedreich's ataxia	−3.7 mFARS (144wks vs natural history)
Acetyl-DL-Leucine	Mixed ataxias	No significant difference in SARA (6 wks)
Miglustat	Niemann-Pick type C	Slower neurological progression (NNSS +1.8 vs + 6.0 placebo, 12 m)

Ariello et al, 2026

Movement Disorders, Vol. 41, No. 2, 2026

BRIEF REPORT

Dentate Nucleus Deep Brain Stimulation for Spinocerebellar Ataxia: Results of a 6-Month Follow-Up

Liang Zhao, Chang Qiu, Wenwen Dong, Bei Luo, Jian Sun, Jiuqi Yan, Xiang Wei, Guanghan Lu, Jingxuan Liu, and Wenbin Zhang*

ABSTRACT: **Background:** Spinocerebellar ataxia (SCA) is a genetically heterogeneous neurodegenerative disorder with no effective treatments. Although noninvasive cerebellar neuromodulation has shown positive outcomes, invasive approaches such as deep brain stimulation (DBS) remain inadequately evaluated in SCA.
Objectives: This study assessed the treatment outcomes of DBS targeting the cerebellar dentate nucleus (DN) in SCA patients over a 6-month follow-up.
Methods: Six patients with heterogeneous SCA underwent bilateral DN-DBS. The stimulation parameters were programmed iteratively, and ataxia symptoms were evaluated at predefined intervals using the Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS).
Results: Individualized appropriate stimulation parameters (current, frequency, and pulse width) were established. At the 6-month follow-up, the SARA scores decreased by 43% ($P = 0.014$) and the ICARS scores by 51% ($P = 0.013$) compared with baseline.
Conclusions: These findings provide evidence for the potential therapeutic efficacy of DN-DBS in SCA and offer preliminary insights for stimulation parameter programming. © 2025 International Parkinson and Movement Disorder Society.

Key Words: spinocerebellar ataxia; deep brain stimulation; dentate nucleus; neuromodulation parameters

JAMA Neurology | Original Investigation *JAMA Neurol.* 2025;82(11):1162-1170.

Home Training for Cerebellar Ataxias
A Randomized Clinical Trial

Scott Barbuto, MD, PhD; Seonjoo Lee, PhD; Joel Stein, MD; Sheng-Han Kuo, MD; Lori Quinn, PT, EdD; Michael Spinner, MS; Yaakov Stern, PhD

IMPORTANCE Clinical practice guidelines advise balance training for cerebellar ataxia, but little is known regarding high-intensity aerobic exercise.

OBJECTIVE To compare home high-intensity aerobic training to home balance training on improvements of ataxia symptoms using the Scale for the Assessment and Rating of Ataxia (SARA).

DESIGN, SETTING, AND PARTICIPANTS This assessor-masked randomized clinical trial was conducted between January 1, 2021, and September 1, 2024, through home training, with in-person assessments at a single ataxia care center in a large urban US city. Individuals with various cerebellar ataxia types were eligible for inclusion. Data analysis was performed from November 2024 to February 2025.

INTERVENTIONS Individuals in the aerobic group trained for 30 minutes/session, 5 times/week, at up to 85% predicted maximum heart rate. Individuals in the balance group performed 30 minutes of balance exercises of varying difficulty 5 times/week. Participants were given study support of biweekly phone calls for only the first 6 months of this 12-month study.

MAIN OUTCOMES AND MEASURES The primary outcome was SARA score to measure ataxia symptoms (range, 0-40 points, with higher scores indicating more ataxia). Secondary outcomes included number of adverse events, training adherence, balance measures, gait speed, quality of life, fatigue, and fitness levels (assessed via $\dot{V}O_2$max). Assessments were conducted at baseline and at 6, 9, and 12 months.

RESULTS A total of 114 individuals with various cerebellar ataxia types were approached: 52 individuals declined participation or did not meet inclusion criteria, while 62 individuals were enrolled. The 62 participants included 29 women (46.8%), with a mean (SD) age of 54.4 (12.9) years and mean (SD) SARA score of 12.1 (4.1) points. Linear mixed-effects model analysis revealed that the home aerobic group had significantly larger improvement in outcomes than the balance group, particularly for SARA score (β, −1.53; 95% CI, −2.44 to −0.61; $P = .001$), fatigue (β, −9.38; 95% CI, −15.1 to −3.7; $P = .001$), and $\dot{V}O_2$max (β, 4.26; 95% CI, 2.1-6.4; $P < .001$). At 6 months, the aerobic and balance groups had changes in SARA scores of −2.4 points (95% CI, −3.1 to −1.80) and −0.9 points (95% CI, −1.5 to −0.2), respectively. For the aerobic group, individuals who continued training maintained benefits in SARA score (change from baseline, −3.81 points; 95% CI, −2.2 to −5.4), whereas those who limited or stopped training had benefits trend back to baseline levels (change from baseline, 0.4 points; 95% CI, −0.4 to 1.2) at 1 year.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, home high-intensity aerobic training improved ataxia symptoms, fatigue, and aerobic fitness more than dose-matched home balance training among individuals with cerebellar ataxias. Individuals in the aerobic group who continued to train regularly maintained benefits at 1 year.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05002218

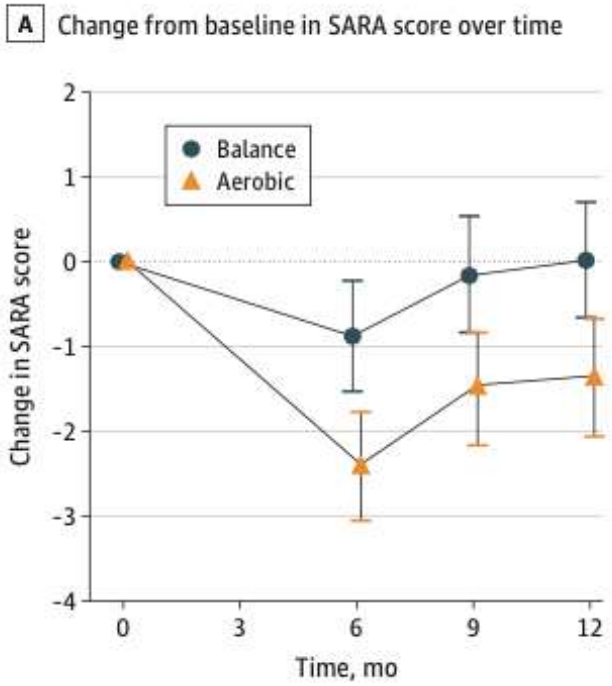
JAMA Neurology | Original Investigation

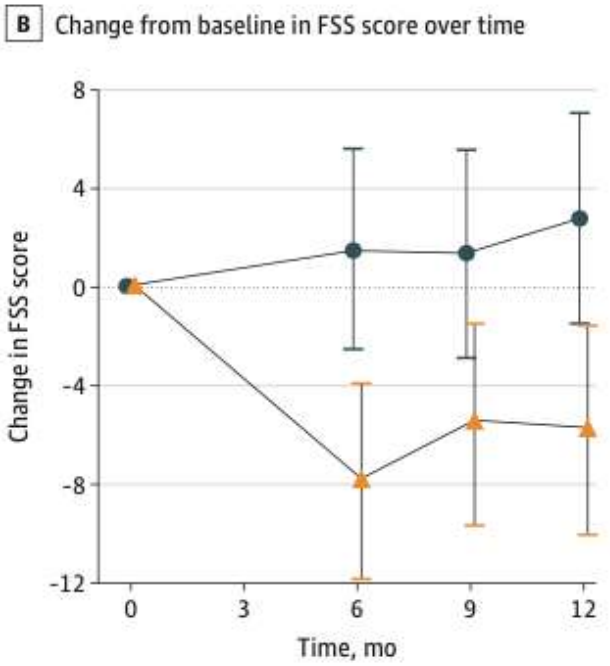
JAMA Neurol. 2025;82(11):1162-1170

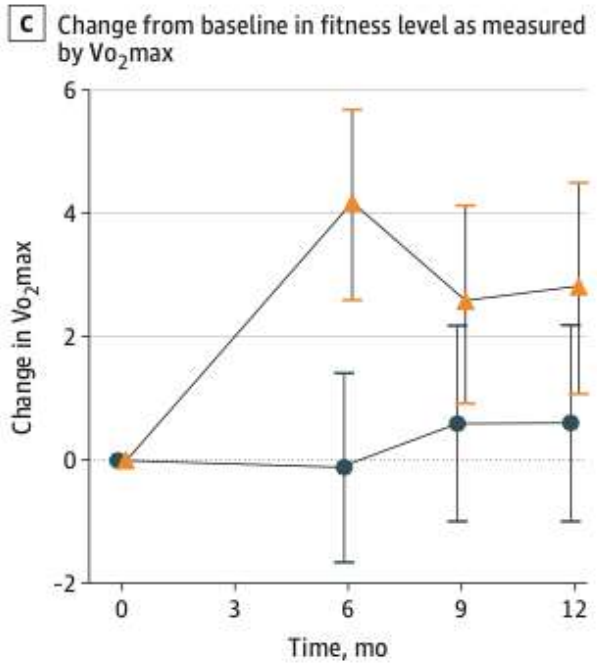
Home Training for Cerebellar Ataxias
A Randomized Clinical Trial

Scott Barbuto, MD, PhD; Seonjoo Lee, PhD; Joel Stein, MD; Sheng-Han Kuo, MD; Lori Quinn, PT, EdD; Michael Spinner, MS; Yaakov Stern, PhD

- 62 patients (SCAs, MSA-C, idiopathic), intervention 6 mo, F/u 9 & 12 mo
- Adherence (80% of goal) - moderate
  - ~76/70% at 6 months, 38/24% at 12 months
- Aerobic training (stationary bike 40 min x 5 days/week, to target HR), but not balance training (exercises to do 30 min x 5 days/week) improved:
  - SARA score
  - Fatigue score
  - VO2 max (~fitness)







Treatment of Cerebellar Ataxias

- No symptomatic treatment is very effective for ataxia
- Always consider inborn errors of metabolism – specific treatments
- Friedreich Ataxia - Omaveloxelone
- Symptomatic treatment for “episodic symptoms” – EAs, SCA27B
  - Acetazolamide; 4-aminopyridine

Treatment of Cerebellar Ataxias

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- ? Others – Ganglioside GM1; N-Acetyl-leucine (NAL) for CACNA1A ataxia
- ? rTMS / tDCS
- ? DBS
- Rehabilitation

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 10 January 2025
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Effects of physiotherapy on degenerative cerebellar ataxia: a systematic review and meta-analysis

Akiyoshi Matsugi[1]*, Kyota Bando[2], Yuki Kondo[2], Yutaka Kikuchi[3], Kazuhiro Miyata[4], Yuichi Hiramatsu[5], Yuya Yamanaka[6], Hiroaki Tanaka[7], Yuta Okuda[3], Koshiro Haruyama[8] and Yuichiro Yamasaki[9]

Conclusion: Physical therapy, especially multi-aspect physical therapy such as muscle strengthening, coordination training, gait training, and ADL training, may reduce DCA symptoms. Further, balance and aerobic training can be added to the program. However, the estimated effect size may change in future studies because of the serious RoB,* very low certainty of evidence, and high heterogeneity with SARA as the primary outcome. High-quality RCTs are required to establish evidence for the effectiveness of physical therapy in patients with DCA.

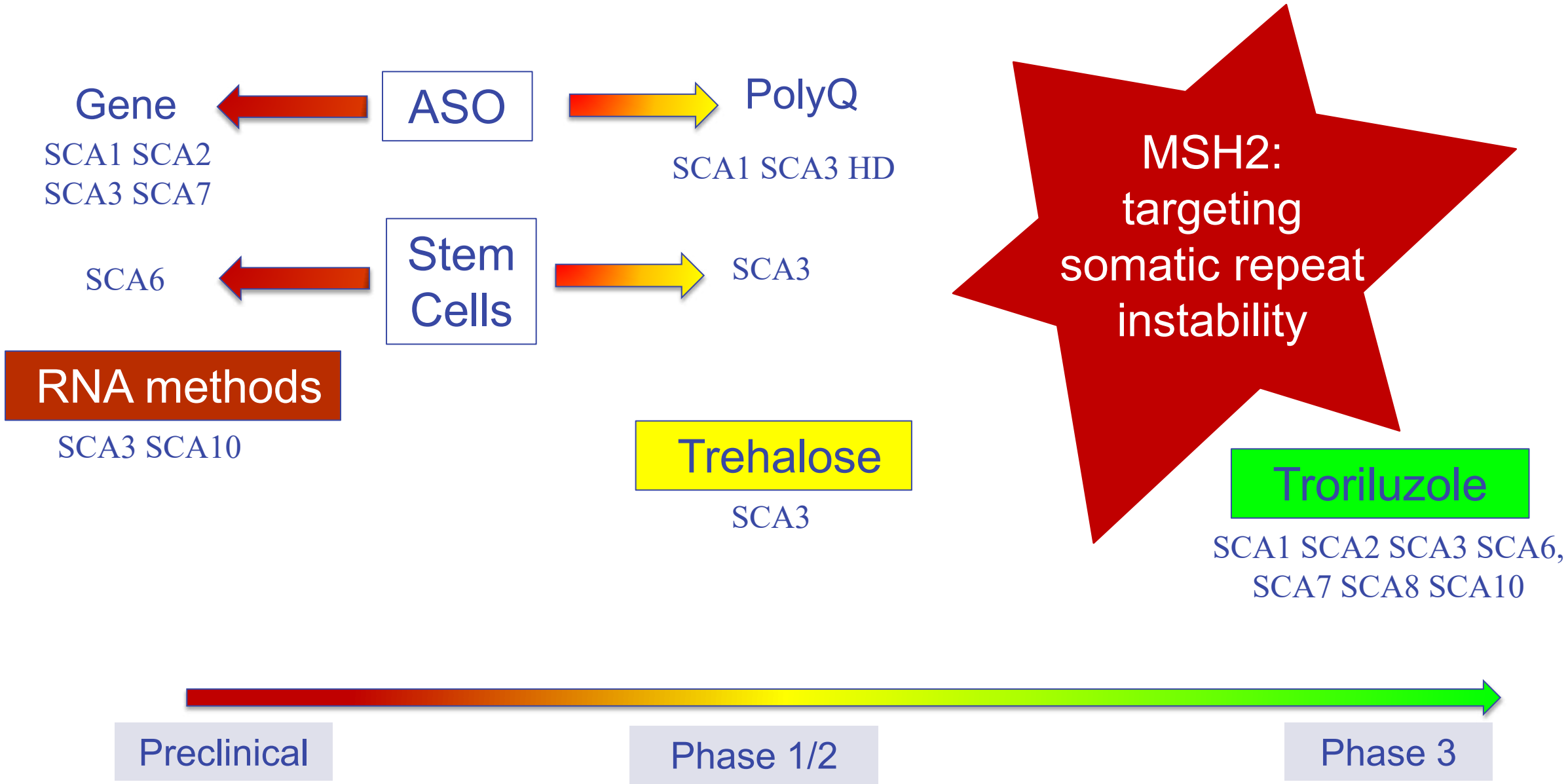
Goal-Directed Rehabilitation Versus Standard Care for Individuals with Hereditary Cerebellar Ataxia: A Multicenter, Single-Blind, Randomized Controlled Superiority Trial

Sarah C Milne, PhD,[1,2,3,4] Melissa Roberts, GCertG&RStud,[1,2] Shannon Williams, MNR,[5,6] Jillian Chua, BAppSc(Physio),[7] Alison C Grootendorst, MPH,[8] Genevieve Agostinelli, BPhysio,[8] Anneke C Grobler, PhD,[4,9] Hannah L Ross, BPhysio,[2] Amy Robinson, BAppSc(Physio),[10] Kristen Grove, BSc(Physio),[5,6] Gabrielle Modderman, BPhysio,[11] Annabel Price, BPhysio,[10] Megan Thomson, MPhysio,[2] Libby Massey, MPH,[8,12] Christina Liang, PhD,[13,14] Kishore R Kumar, PhD,[15,16,17] Kim Dalziel, PhD,[18] Joshua Burns, PhD,[19] Carolyn M Sue, PhD,[20,21,22] Pubudu N Pathirana, PhD,[23] Malcolm Horne, PhD,[24,25] Nikki Gelfand, PostGradDipGenCounss,[26] Helen Curd, MGenCoun,[26] David Szmulewicz, PhD,[24,27,28] Louise A Corben, PhD,[1,4,29] and Martin B Delatycki, PhD[1,4,30]

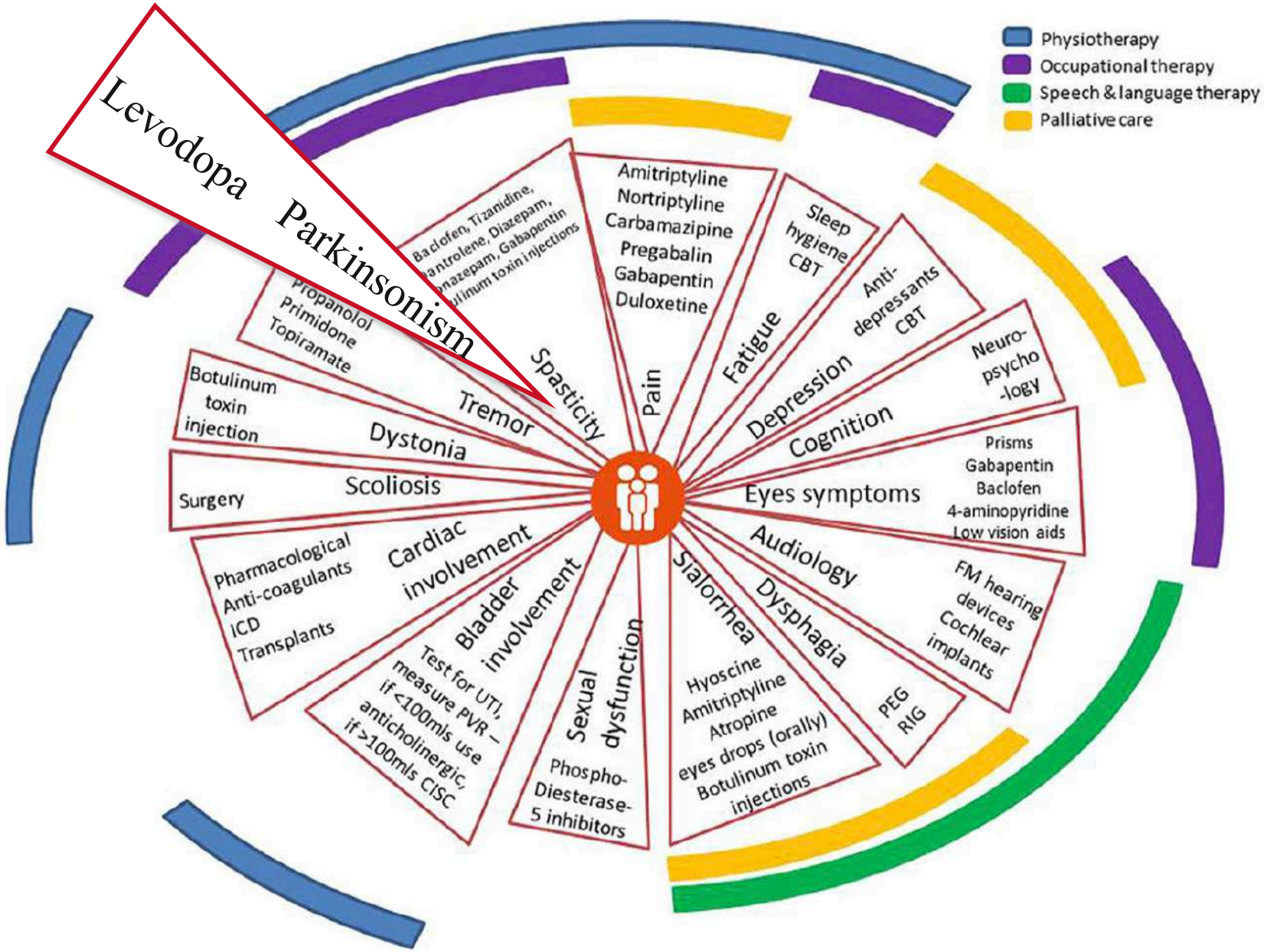
ANN NEUROL 2025;97:409–424

* Risk of Bias

SCA: Future Therapies?



Management: Not Just Ataxia



Thank you!



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