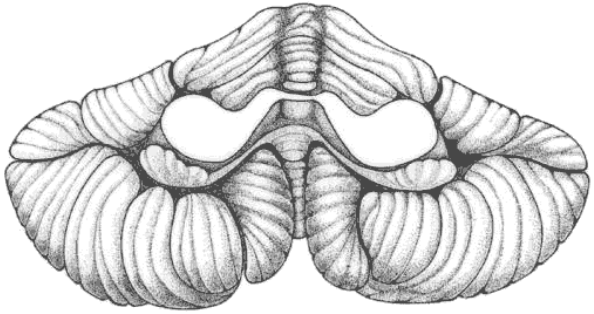
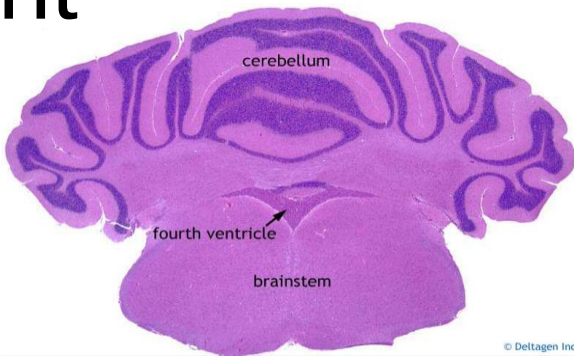
UNIVERSITÉ DE STRASBOURG

INSTITUT DE GENETIQUE ET DE BIOLOGIE MOLECULAIRE ET CELLULAIRE
I G B M C

cnrs

The clinical approach to the ataxia patient



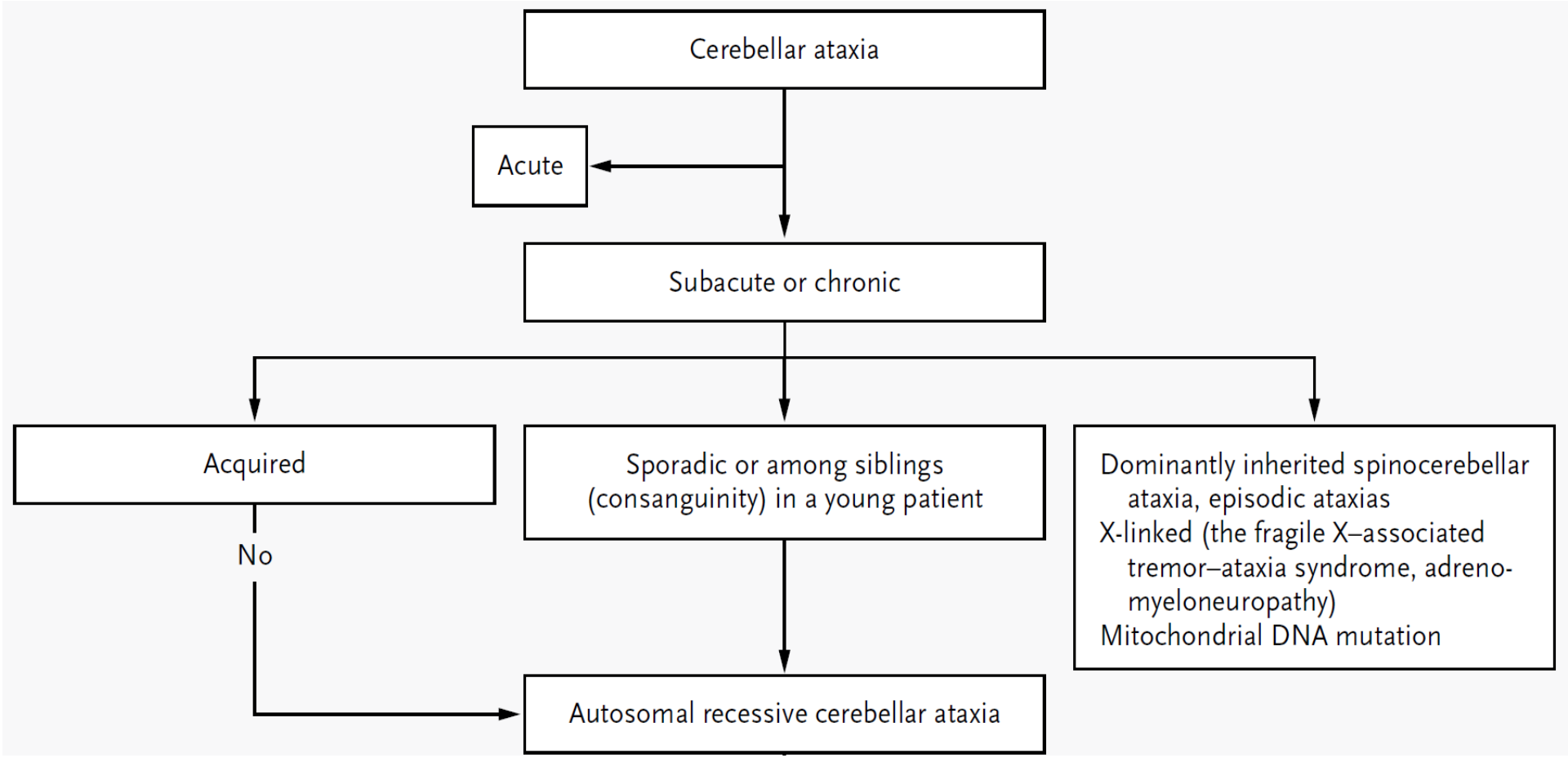


Mathieu Anheim

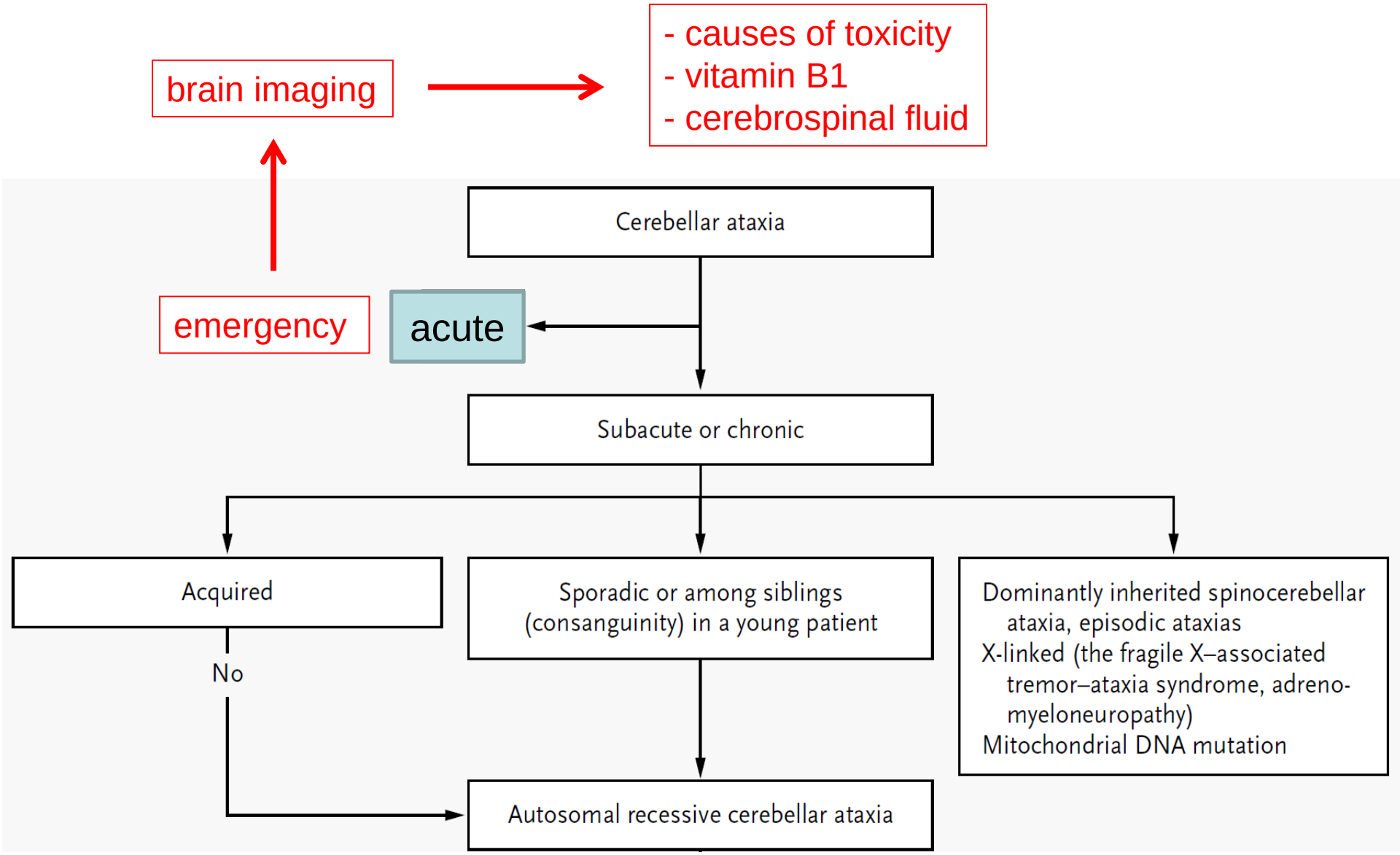
Department of Neurology, Movement Disorders Unit
Referral Center for Ataxia
University Hospital of Strasbourg, France

The Ariadne's thread

Mancuso et al., J Neurol, 2014



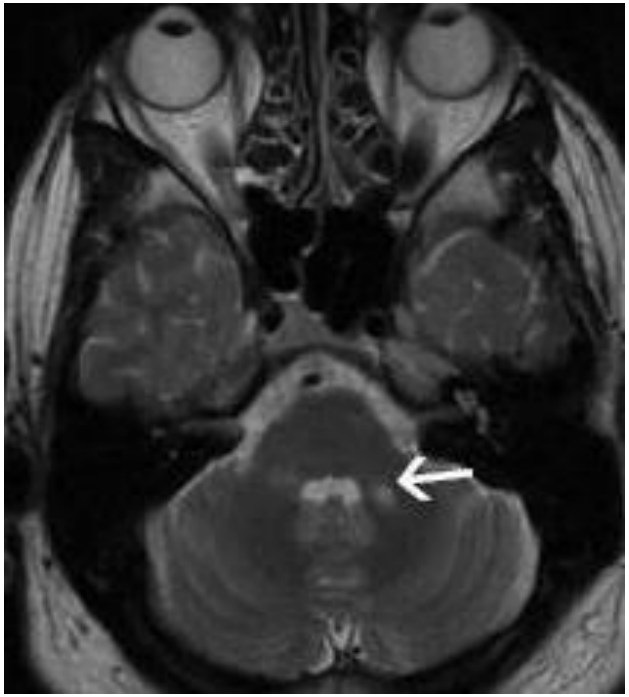
Anheim et al., N Engl J Med, 2012



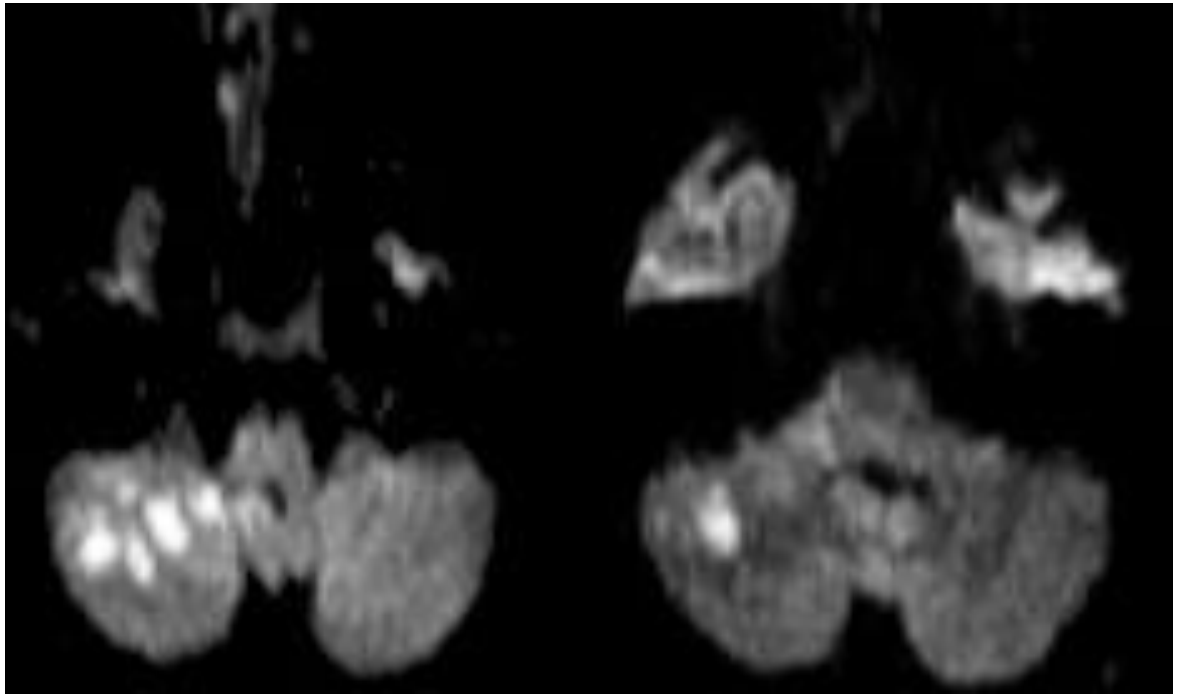
Anheim et al., N Engl J Med, 2012

Abnormal brain imaging

Multiple sclerosis relapse



Cerebellar stroke

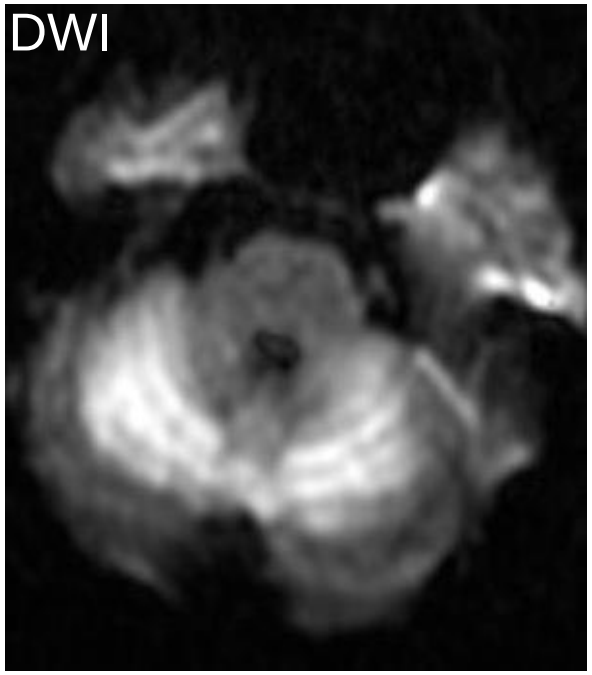


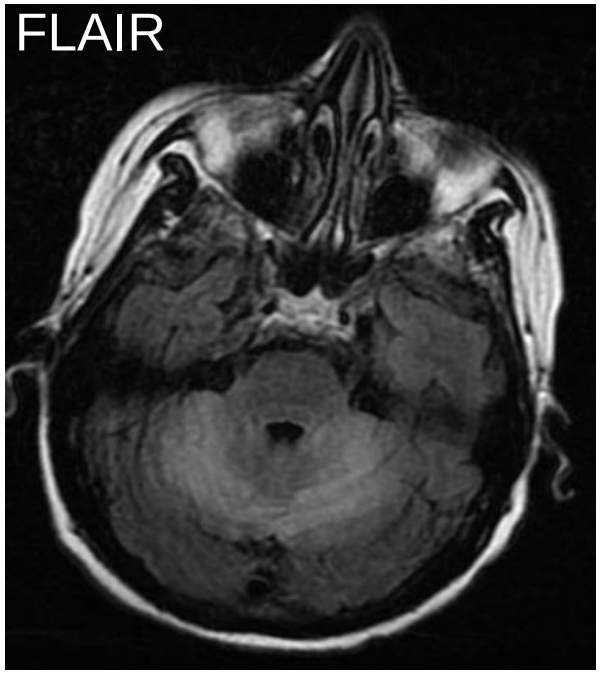
Infections

- viral cerebellitis (VZV, HIV…)
- cryptococcosis
- cerebellar abcess

Abnormal brain imaging

Wernicke encephalopathy





- alcohol consumption / vomiting / bypass / absorption disorder
- marked ataxic gait, paresis, confusion within two days
- vitamin B1 deficiency
- early treatment with high doses of vitamin B1

Normal brain imaging

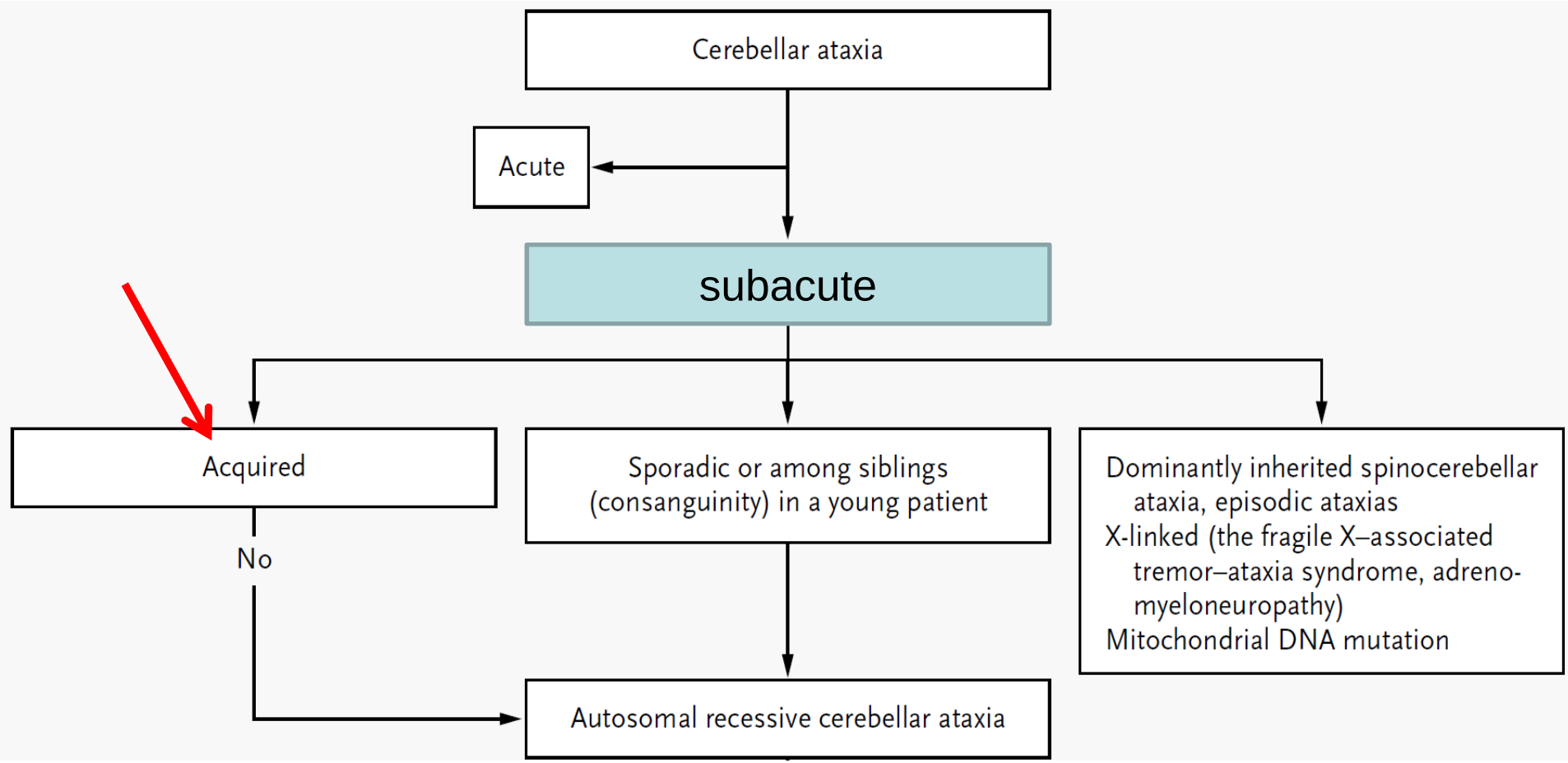
Toxic causes

- acute alcohol consumption

- lithium salts, barbituric, hydantoine, carbamazepine, amiodarone
- 5 fluorouracil, cytarabine

- mercury, lead, manganese, toluene/benzene derivatives, ethyl chloride

Wirth et al., Nat Rev Neurol, 2025



clinical signs in addition to ataxia

brain imaging

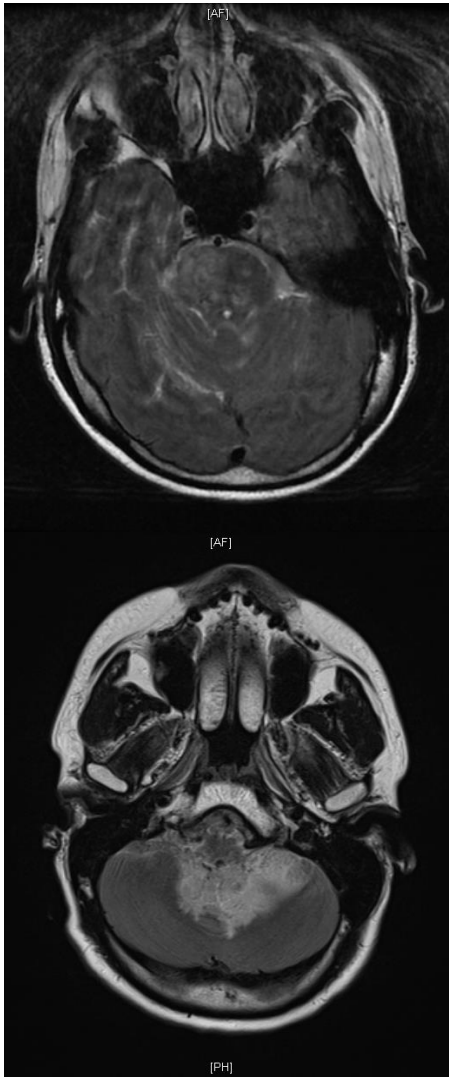
- antineuronal antibodies
- other antibodies
- cerebrospinal fluid

Acquired subacute ataxias

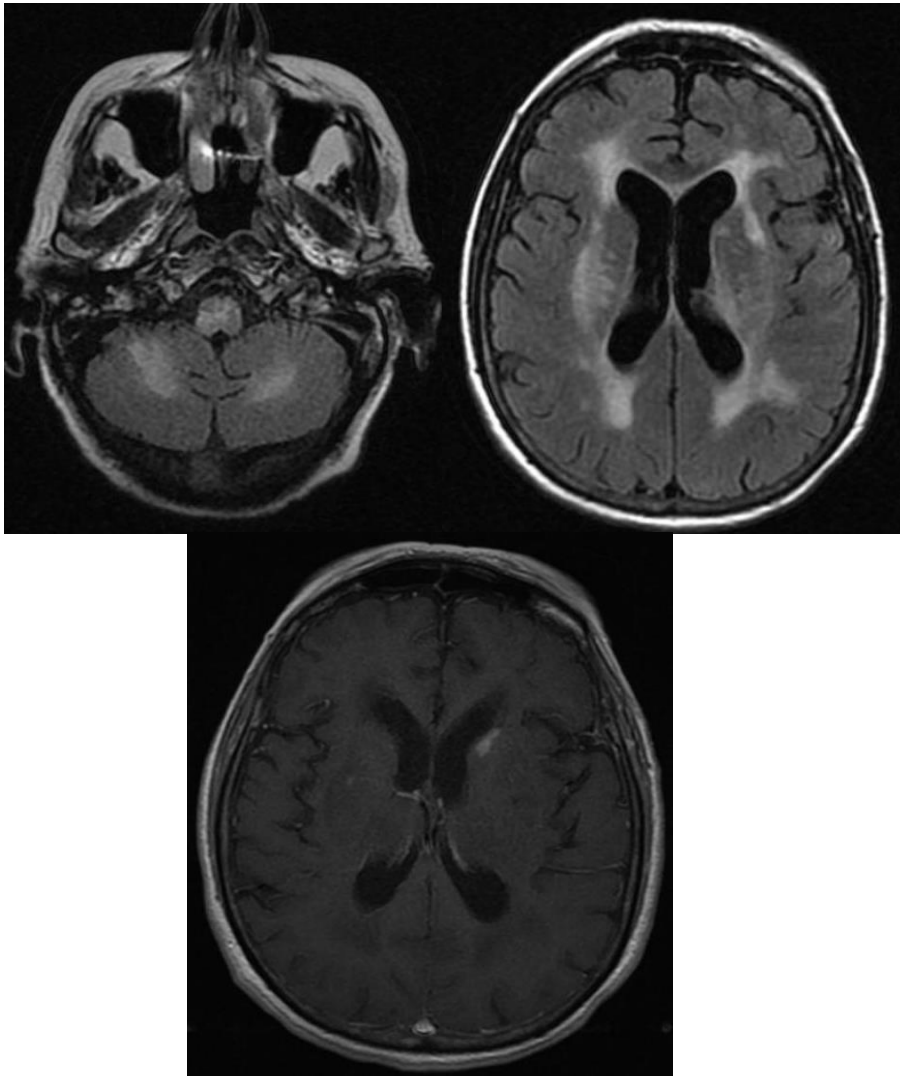
- posterior fossa tumor
  - cancer metastasis
  - primary cancer
- paraneoplastic cerebellar degeneration
- auto-immune and/or inflammatory diseases
  - Sjögren, sarcoidosis, lupus
  - celiac disease / gluten ataxia, stiffman, Hashimoto
- infections
  - tuberculosis
  - JC virus (progressive multifocal leukoencephalopathy)
- Creutzfeldt-Jakob disease

Klockgether, Lancet Neurol, 2007

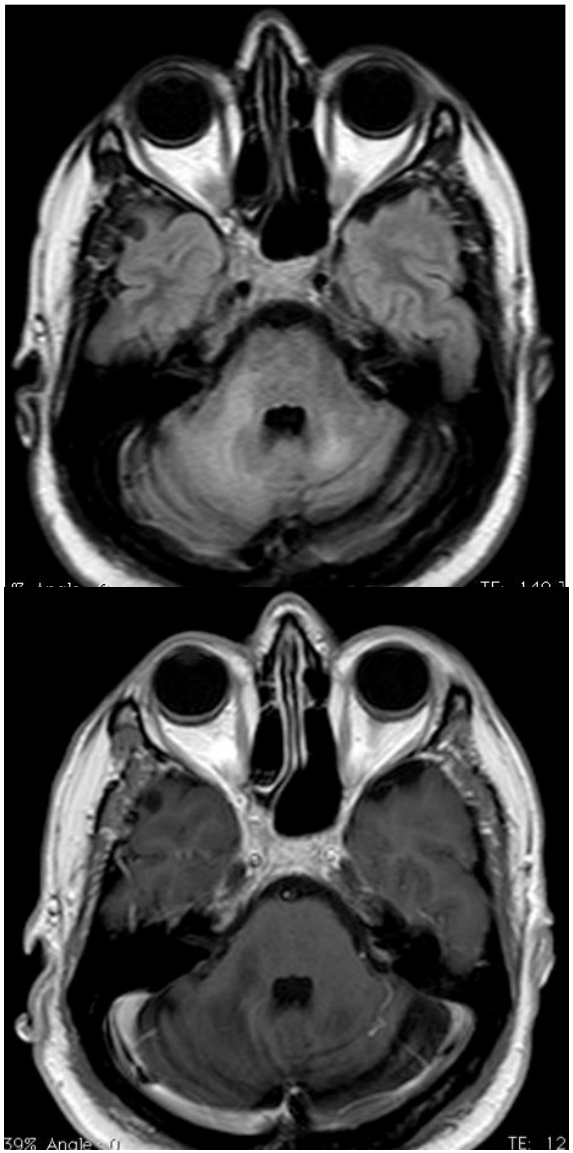
Sarcoidosis



Goujerot syndrome



Multifocal progressive leucoencephalopathy



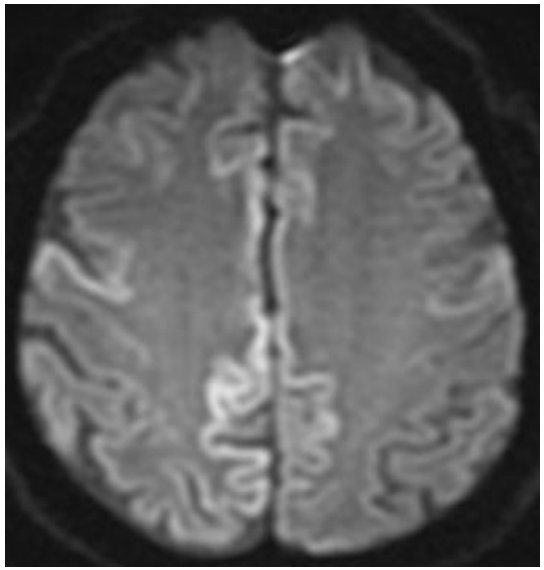
- subacute cerebellar ataxia
- immunodepression
  - natalizumab, HIV, CVID…
- JC virus in CSF
- granule cell neuronopathy

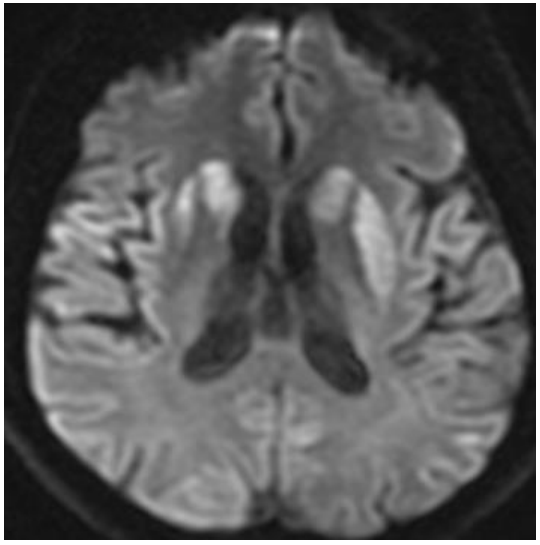
Paraneoplastic cerebellar degeneration

Auto-antibody[a] target	Predominant sex, median age (years)	Cerebellar involvement (%)	Extracerebellar involvement	Typical tumours (frequency, %)
Yo	>95% F, 60	>90	Brainstem, cranial or peripheral neuropathies	Ovary and breast (>90)
Tr (DNER)	70% M, 55	>90	Encephalopathy, sensory neuropathy, optic neuritis	Hodgkin lymphoma (90)
KELCH11[a]	>95% M, 45	85	Brainstem, LE, myeloneuropathy	Testicular (80)
Ri[a]	70% F, 65	50–70	Brainstem, OMS, movement disorders	Breast > lung (>70)
PCA2 (MAP1B)	50% M/F, 70	40	Sensorimotor neuropathy, EM	SCLC, NSCLC, breast (80)
Ma2	70% M, 55	20–30	Limbic–diencephalic–brainstem encephalitis	Testicular, NSCLC (>75)
CV2 (CRMP5)	60% M, 60	20–25	EM, SNN, chorea, uveo-retinal involvement	SCLC, malignant thymoma (>80)
SOX1	60% M, 60	20	LEMS	SCLC (>90)
Amphiphysin	60% F, 65	15	Polyradiculoneuropathy, SNN, EM, SPS	SCLC, breast (80)
Hu	70% M, 65	10–20	SNN, chronic gastrointestinal pseudo-obstruction, EM, LE	SCLC » NSCLC (85)
mGluR1	60% M, 55	>95	Cognitive deficits, behavioural changes	Lymphomas (10)
CASPR2[a]	80% M, 60	30	LE, Morvan syndrome, PNH	Malignant thymoma[b] (90)
IgLON5[a]	50% M/F, 60	30	Sleep disorder, bulbar dysfunction, cognitive deficit	Diverse[c] (<10)
DPPX	70% M, 50	30	Encephalitis with CNS hyperexcitability, PERM	B cell neoplasms (<10)
GlyR	50% M/F, 50	10–20	PERM, LE	Malignant thymoma, Hodgkin lymphoma (<10)
AMPAR	60% F, 60	15	LE, diffuse fulminant encephalitis	SCLC, malignant thymoma (>50)
GABAaR	50% M/F, 40	5–10	Encephalitis with refractory seizures	Malignant thymoma (<30)
GABAbR	60% M, 60	5	LE, rapidly progressive dementia	SCLC (>50)
NMDAR	80% F, 20	5	NMDAR encephalitis	Ovarian teratoma (40)
VGCC	>95% M, 65	<2	LEMS	SCLC (90)
GAD65[a]	50% M/F, 60	30–40	SPS, temporal seizure, LE	Breast, lung, thymoma (10)

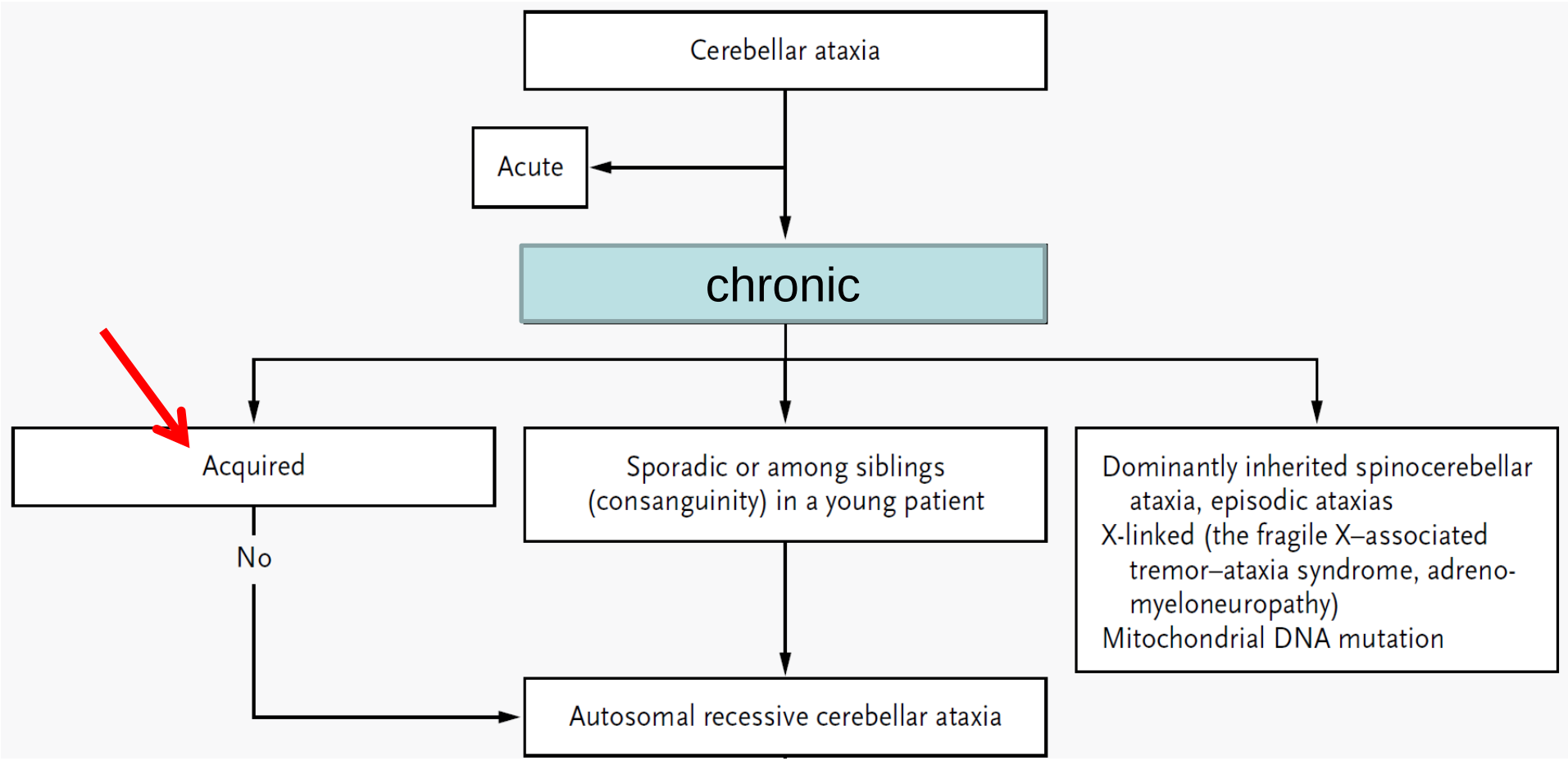
Wirth et al., Nat Rev Neurol, 2025

Sporadic Creutzfeldt Jakob disease





- positive 14 3 3 protein in CSF
- abnormal EEG



Associated clinical signs

Vitamin E, TSH, HIV, TPHA/VDRL

Brain MRI

CSF: oligoclonal bands, PCR Whipple

Question 1

- Facing a 52 years old patient complaining with a twelve months history of progressively worsening imbalance and staggering with urinary emergencies, what do you consider first ?

1. Creutzfeldt-Jakob disease
2. SCA27b (*FGF14* expansion)
3. Multiple system atrophy of cerebellar type
4. Superficial siderosis
5. Very-late onset Friedreich disease

Question 1

- Facing a 52 years old patient complaining with a twelve months history of progressively worsening imbalance and staggering with urinary emergencies, what do you consider first ?

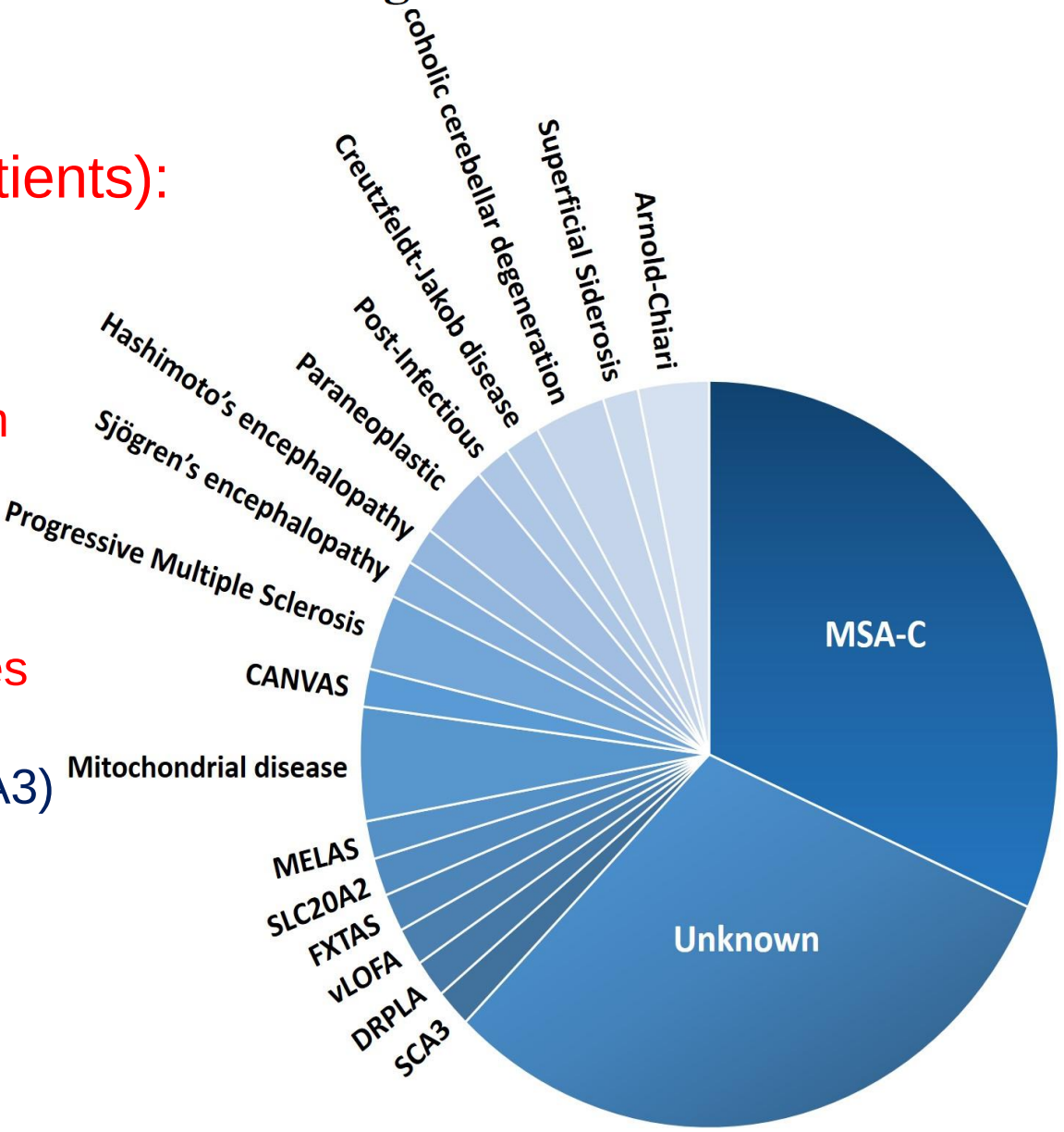
1. Creutzfeldt-Jakob disease
2. SCA27b (*FGF14* expansion)
3. Multiple system atrophy of cerebellar type
4. Superficial siderosis
5. Very-late onset Friedreich disease

Deciphering the causes of sporadic late-onset cerebellar ataxias: a prospective study with implications for diagnostic work

- STARAC cohort (400 patients):
  - late-onset (>40 years)
  - sporadic
  - progressive ataxia
  - standardized examination
  - genetic analysis
  - re-appraisal

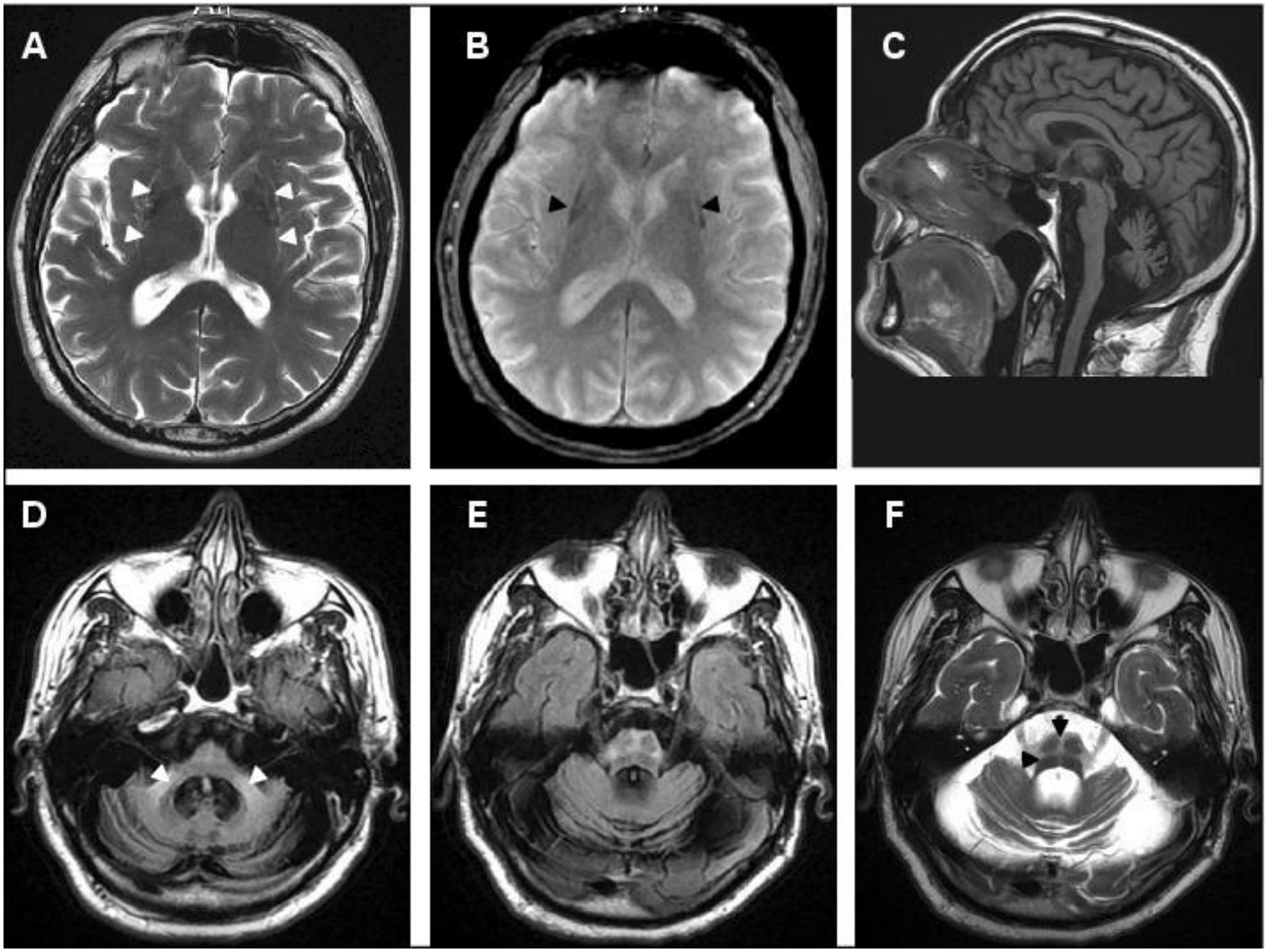
  - several genetic aetiologies
    SPG7, CANVAS, vLOFA
  - even SCA (SCA27b, SCA3)

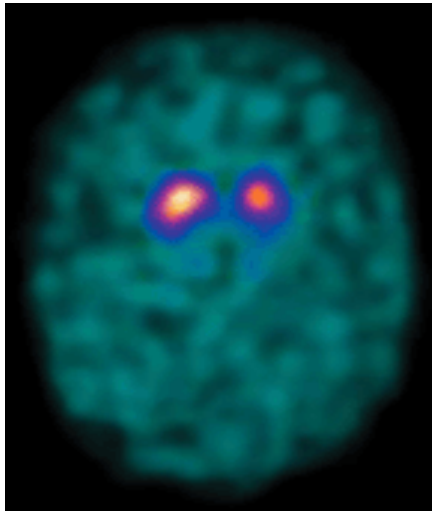
  - 30% remain unknown



Gebus et al., J Neurol, 2017 ; Bogdan et al., J Neurol, 2022

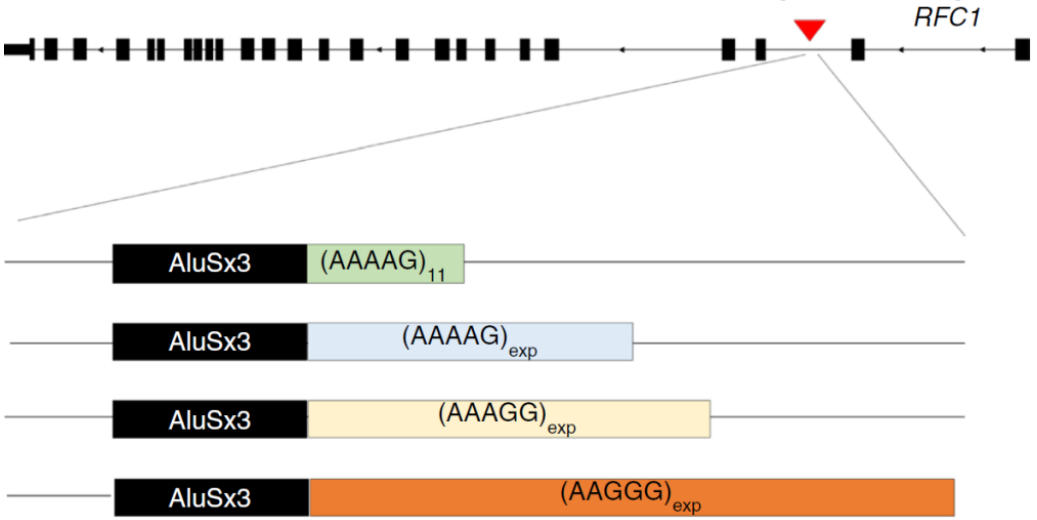
Multiple System Atrophy – type C

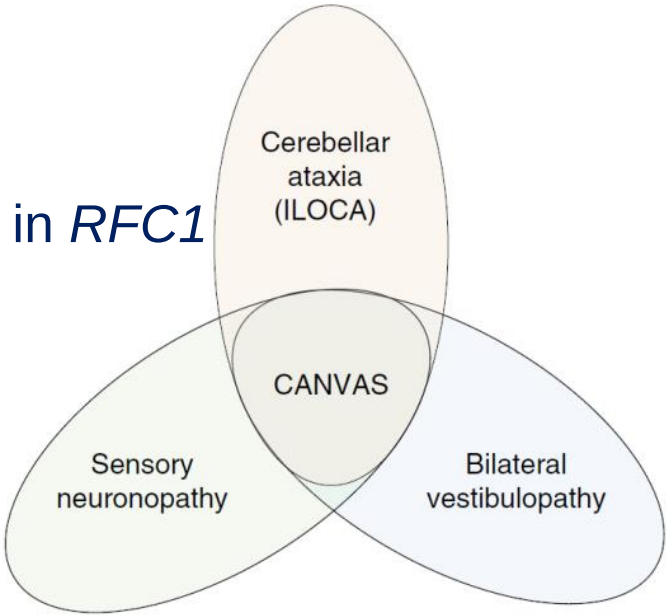




Biallelic expansion of an intronic repeat in *RFC1* is a common cause of late-onset ataxia

- unlocking CANVAS
  - Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome
    - late-onset ataxia with cerebellar atrophy (≈50 y)
    - sensory neuronopathy (100%)
    - bilateral vestibular areflexia (50%)
    - dysautonomia, and/or cough (50%)
  - genome sequencing
    - biallelic intronic AAGGG repeat expansion in *RFC1*





Cortese et al., Nat Genet, 2019

Question 2

66 years-old patient with a 4-years history of cerebellar ataxia with episodic worsening of ataxia with dysarthria, diplopia and vertigo. What is the diagnosis ?

1. Paraneoplastic ataxia
2. Multiple system atrophy
3. SCA27b (*FGF14* expansion)
4. CLIPPERS
5. SPG7

Wirth et al., Mov Disord, 2023

FGF14 CAG triplet repeat SCA27b

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

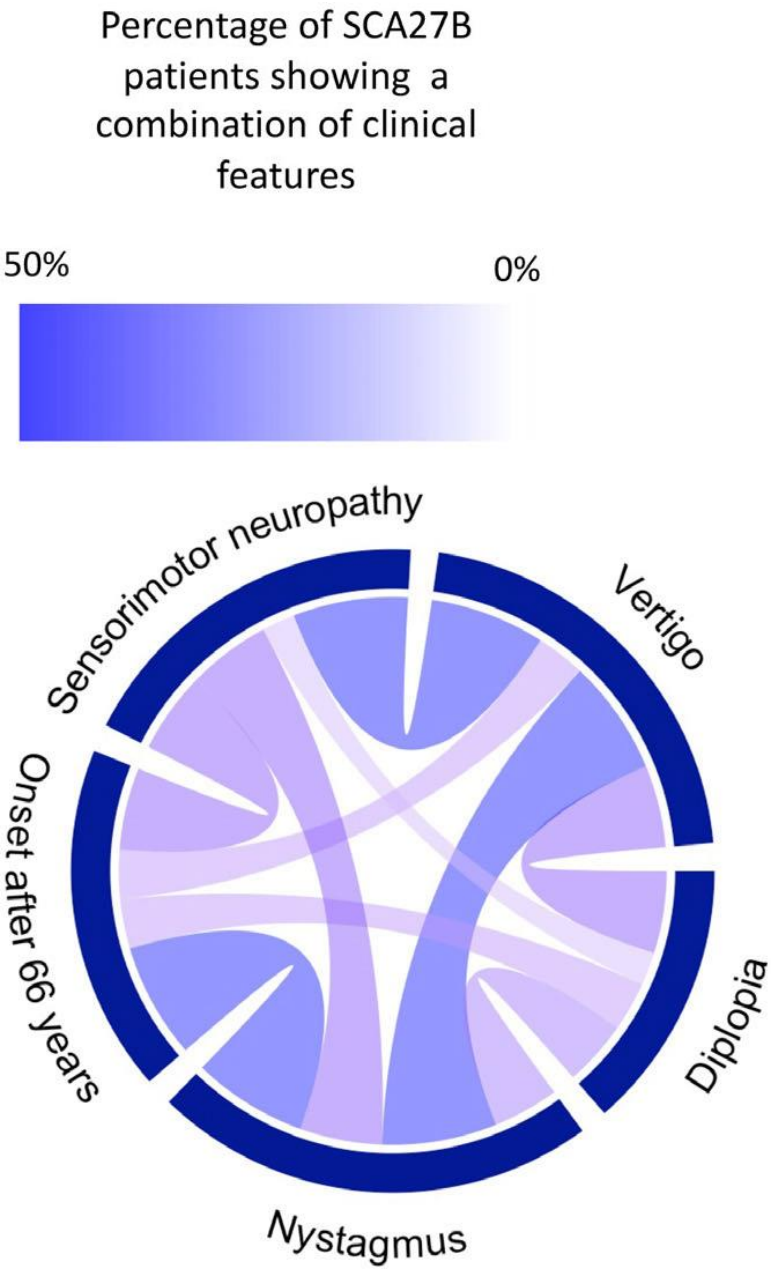
D. Pellerin, M.C. Danzi, C. Wilke, M. Renaud, S. Fazal, M.-J. Dicaire, C.K. Scriba, C. Ashton, C. Yanick, D. Beijer, A. Rebelo, C. Rocca, Z. Jaunmuktane, J.A. Sonnen, R. Larivière, D. Genís, L. Molina Porcel, K. Choquet, R. Sakalla, S. Provost, R. Robertson, X. Allard-Chamard, M. Tétreault, S.J. Reiling, S. Nagy, V. Nishadham, M. Purushottam, S. Vengalil, M. Bardhan, A. Nalini, Z. Chen, J. Mathieu, R. Massie, C.H. Chalk, A.-L. Lafontaine, F. Evoy, M.-F. Rioux, J. Ragoussis, K.M. Boycott, M.-P. Dubé, A. Duquette, H. Houlden, G. Ravenscroft, N.G. Laing, P.J. Lamont, M.A. Saporta, R. Schüle, L. Schöls, R. La Piana, M. Synofzik, S. Zuchner, and B. Brais

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

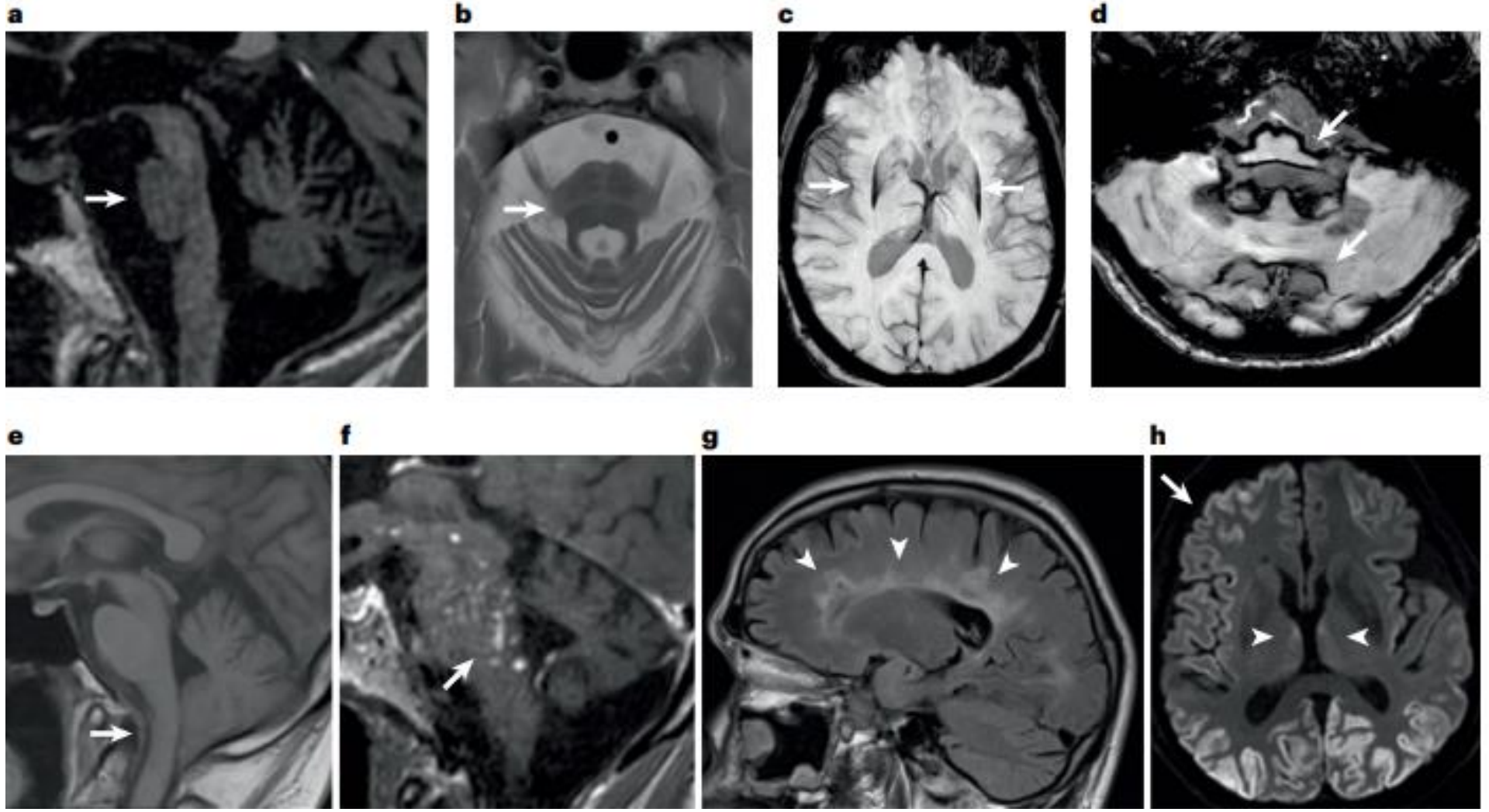
Carlo Wilke,[1,2] David Pellerin,[3] David Mengel,[1,2] Andreas Traschütz,[1,2] Matt C. Danzi,[4] Marie-Josée Dicaire,[3] Manuela Neumann,[2,5] Holger Lerche,[6] Benjamin Bender,[7] Henry Houlden,[8] RFC1 study group, Stephan Züchner,[4] Ludger Schöls,[2,9] Bernard Brais[3] and Matthis Synofzik[1,2]

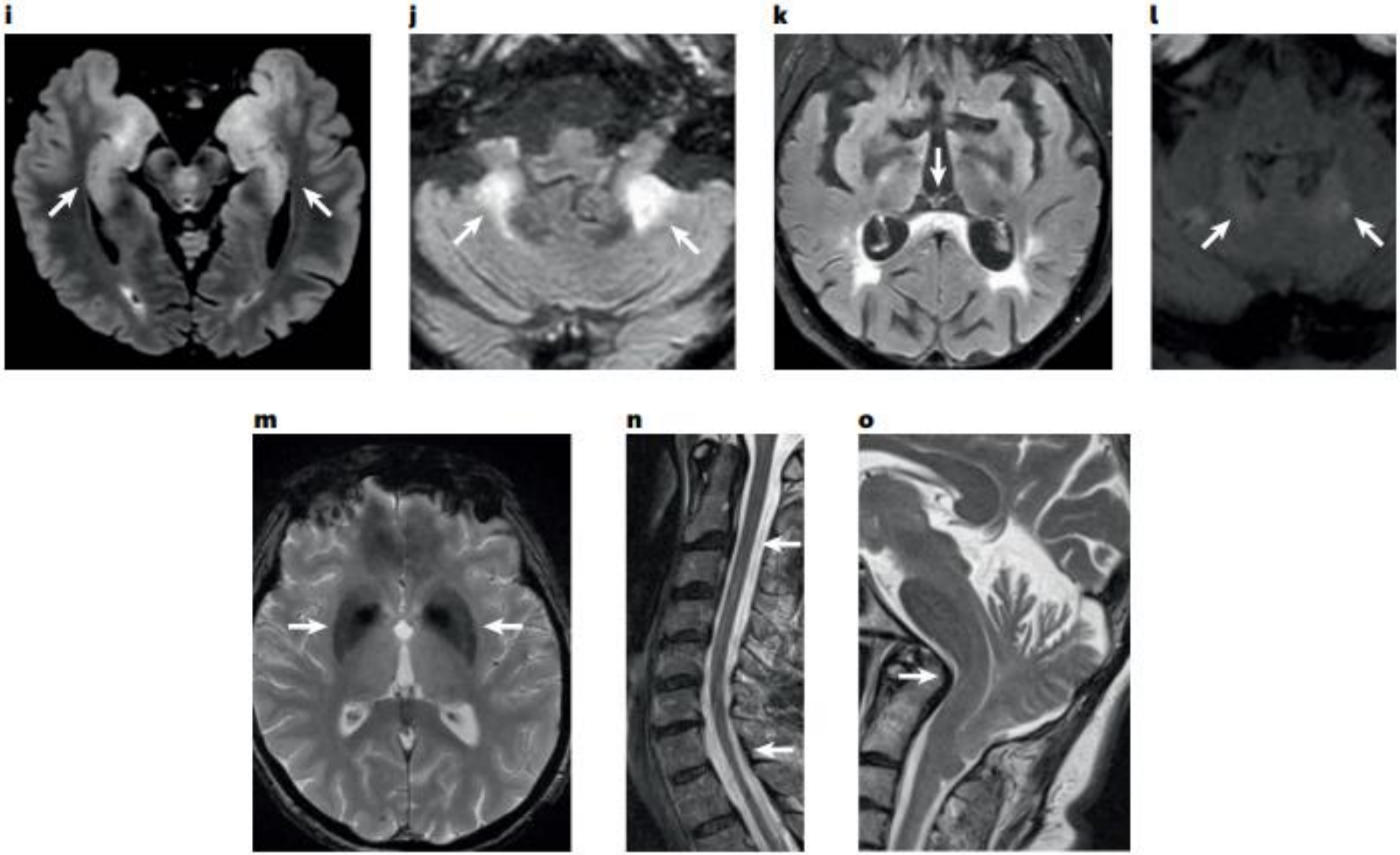
Characteristic	Overall (N = 122)
Male sex — no. (%)	62 (51)
Inheritance — no./total no. (%)	
Sporadic	36/118 (31)
Familial	82/118 (69)
Episodic features — no./total no. (%)	56/121 (46)
Mean age at onset of episodes — yr	55±13
Mean age at onset of permanent ataxia — yr	59±11
Signs and symptoms — no./total no. (%)	
Nystagmus	
Downbeat nystagmus	50/119 (42)
Gaze-evoked horizontal nystagmus	65/119 (55)
Diplopia or visual blurring	57/120 (48)
Cerebellar dysarthria	63/118 (53)
Gait ataxia	113/118 (96)
Appendicular ataxia	94/118 (80)
Vertigo or dizziness	33/114 (29)
Postural tremor	18/114 (16)
Cerebellar atrophy on MRI — no./total no. (%)	67/91 (74)

Pellerin et al., NEJM, 2023



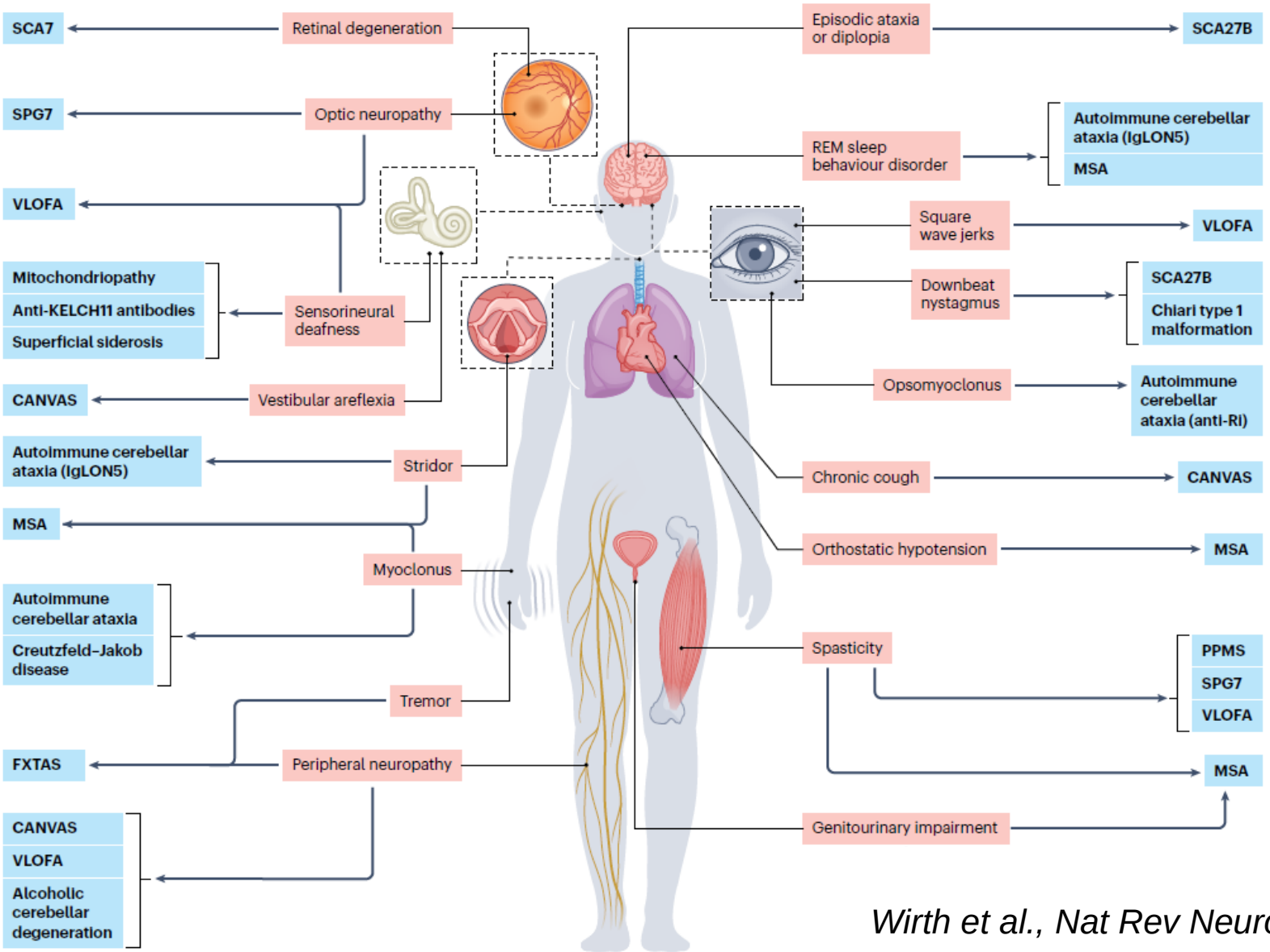
Wirth et al., Mov Disord, 2023


a
b
c
d
e
f
g
h

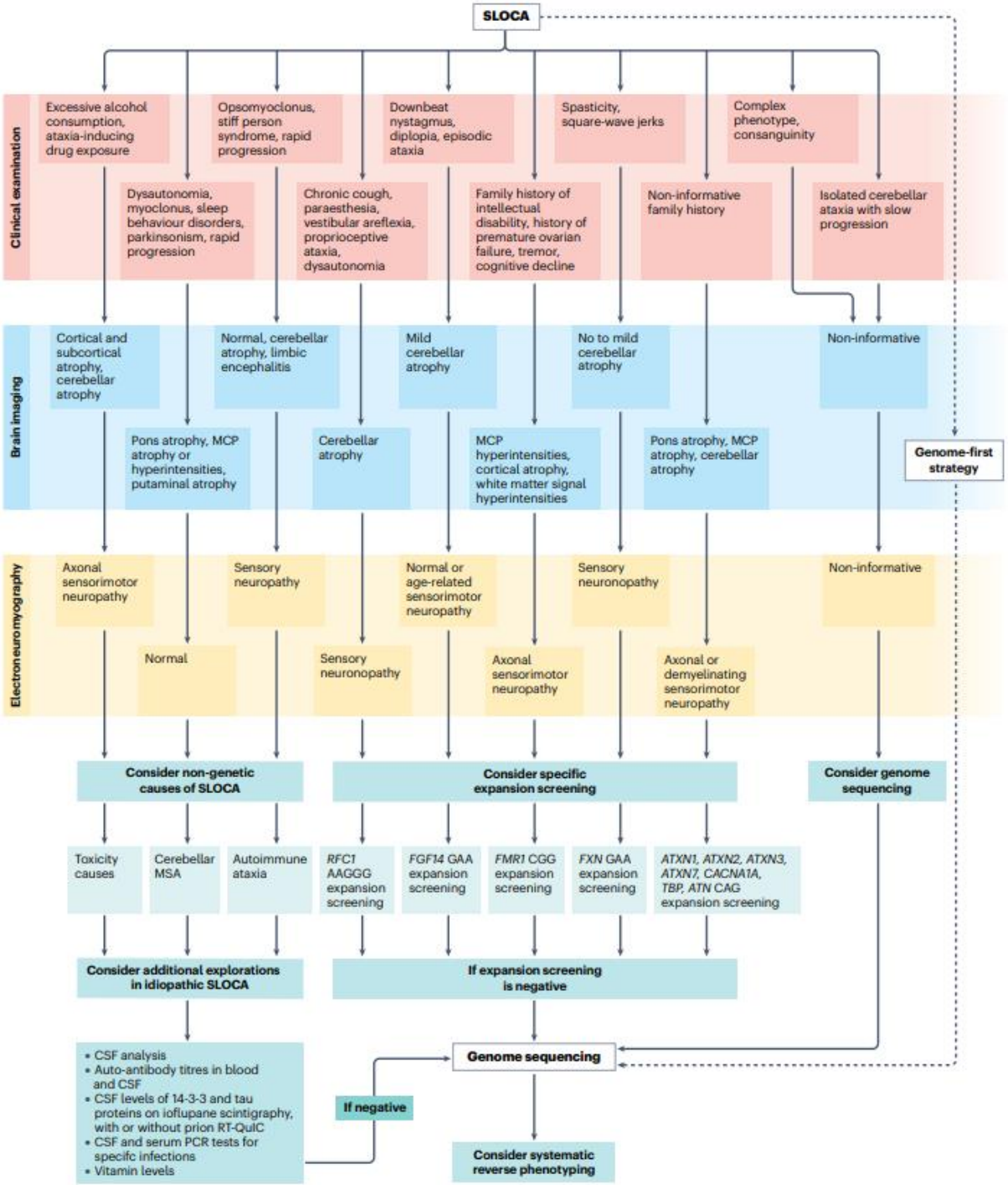

i
j
k
l
m
n
o

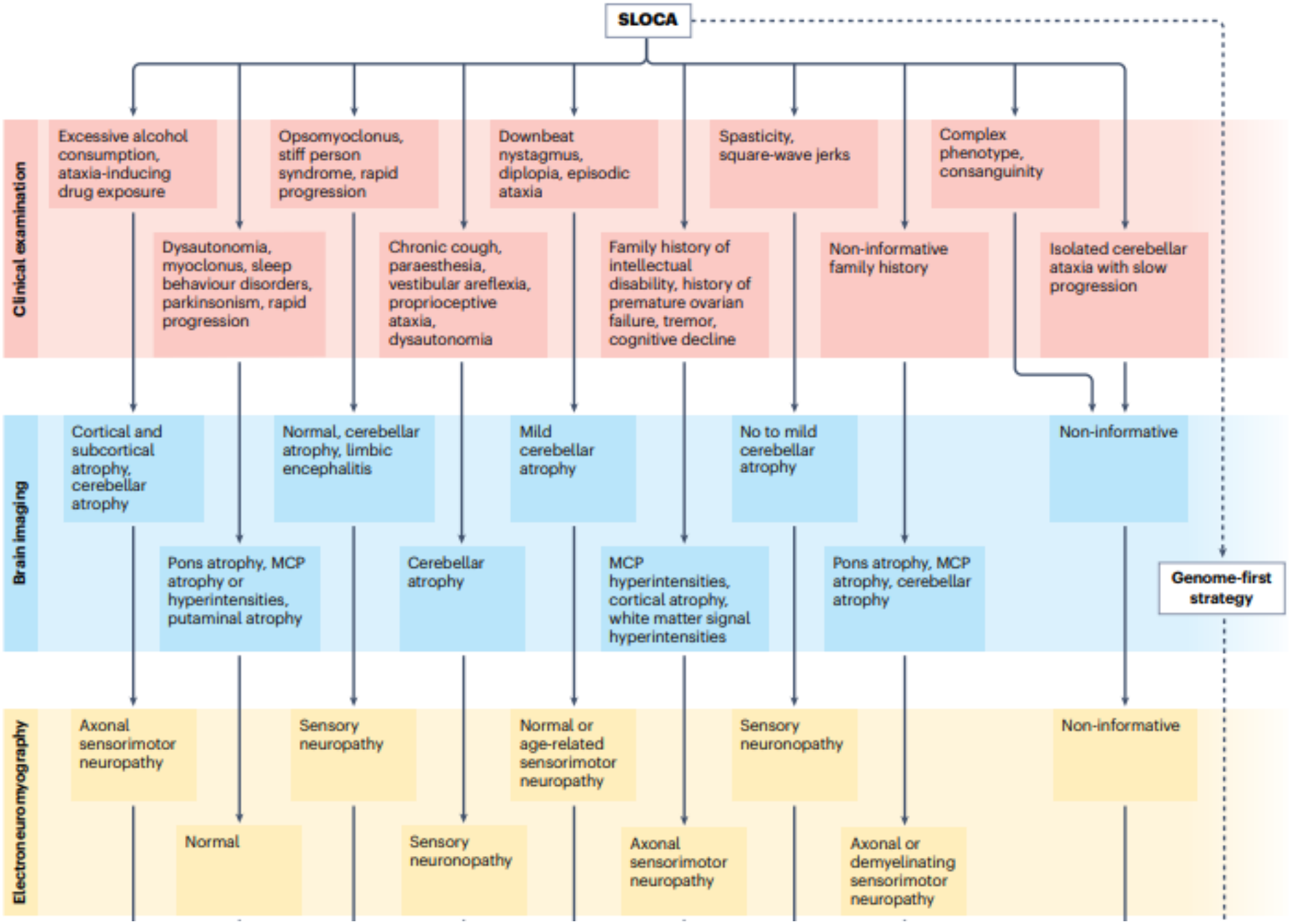
Progress and challenges in sporadic late-onset cerebellar ataxias

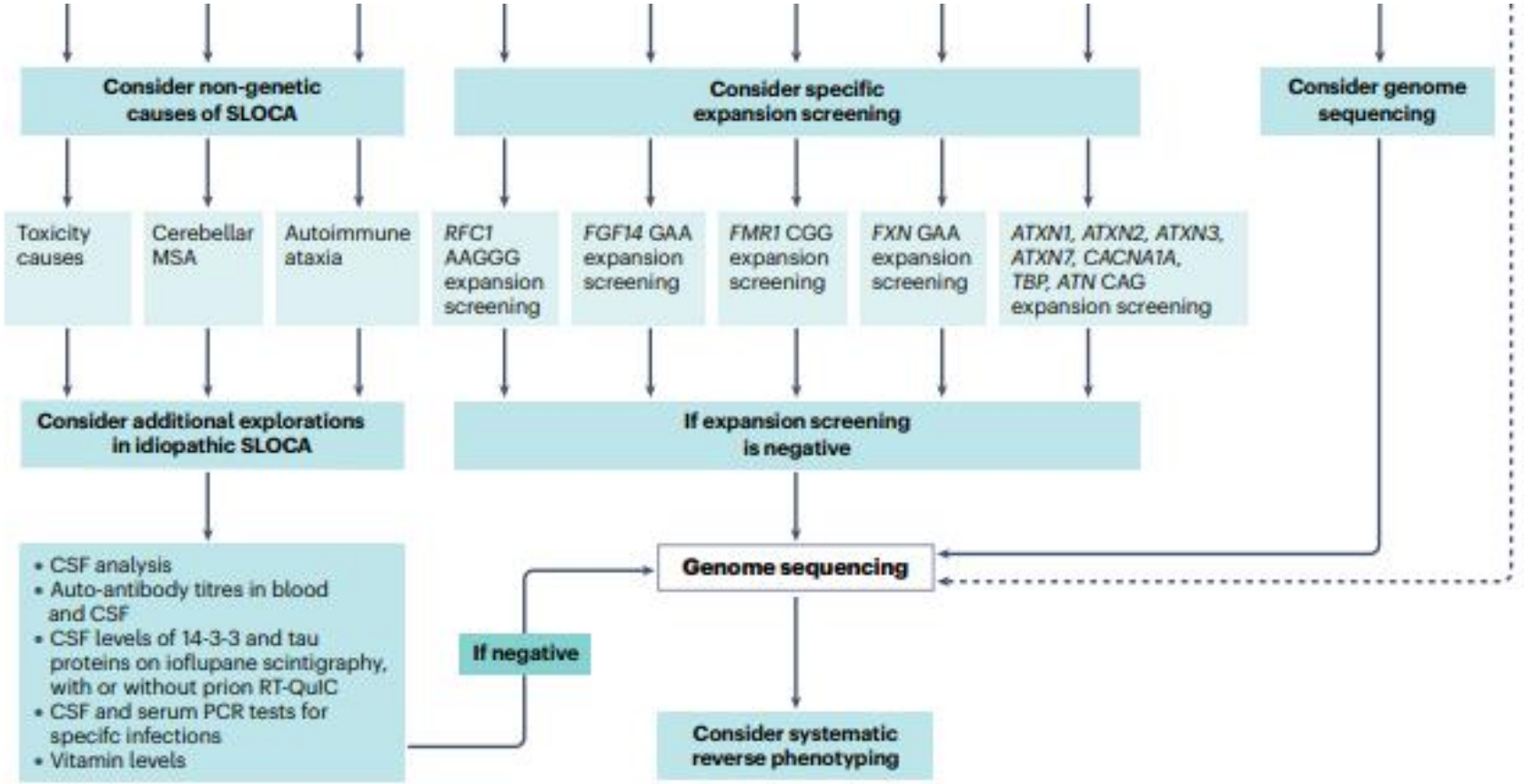
Thomas Wirth[1,2,3], Jennifer Faber[4,5], Christel Depienne[6], Emmanuel Roze[7], Jérôme Honnorat[8,9], Wassilios G. Meissner[10,11,12,13], Paola Giunti[14,15], Christine Tranchant[1,2,3], Thomas Klockgether[4,5] & Mathieu Anheim[1,2,3]



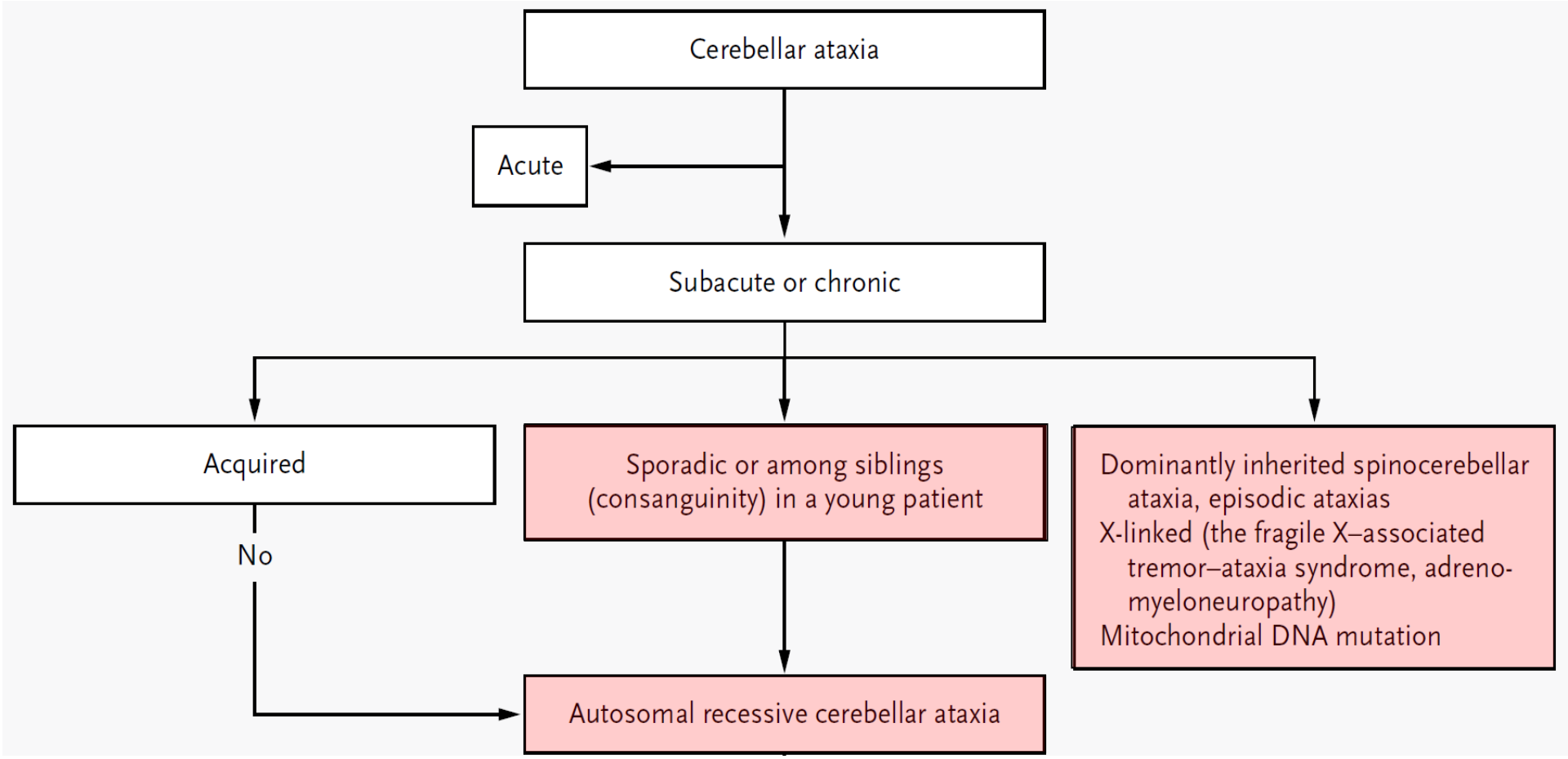
Wirth et al., Nat Rev Neurol, 2025


SLOCA
Clinical examination
Excessive alcohol consumption, ataxia-inducing drug exposure
Opsomyoclonus, stiff person syndrome, rapid progression
Downbeat nystagmus, diplopia, episodic ataxia
Spasticity, square-wave jerks
Complex phenotype, consanguinity
Dysautonomia, myoclonus, sleep behaviour disorders, parkinsonism, rapid progression
Chronic cough, paraesthesia, vestibular areflexia, proprioceptive ataxia, dysautonomia
Family history of intellectual disability, history of premature ovarian failure, tremor, cognitive decline
Non-informative family history
Isolated cerebellar ataxia with slow progression
Brain imaging
Cortical and subcortical atrophy, cerebellar atrophy
Normal, cerebellar atrophy, limbic encephalitis
Mild cerebellar atrophy
No to mild cerebellar atrophy
Non-informative
Pons atrophy, MCP atrophy or hyperintensities, putaminal atrophy
Cerebellar atrophy
MCP hyperintensities, cortical atrophy, white matter signal hyperintensities
Pons atrophy, MCP atrophy, cerebellar atrophy
Genome-first strategy
Electroneuromyography
Axonal sensorimotor neuropathy
Sensory neuropathy
Normal or age-related sensorimotor neuropathy
Sensory neuronopathy
Non-informative
Normal
Sensory neuronopathy
Axonal sensorimotor neuropathy
Axonal or demyelinating sensorimotor neuropathy
Consider non-genetic causes of SLOCA
Consider specific expansion screening
Consider genome sequencing
Toxicity causes
Cerebellar MSA
Autoimmune ataxia
RFC1 AAGGG expansion screening
FGF14 GAA expansion screening
FMR1 CGG expansion screening
FXN GAA expansion screening
ATXN1, ATXN2, ATXN3, ATXN7, CACNA1A, TBP, ATN CAG expansion screening
Consider additional explorations in idiopathic SLOCA
If expansion screening is negative
• CSF analysis
• Auto-antibody titres in blood and CSF
• CSF levels of 14-3-3 and tau proteins on ioflupane scintigraphy, with or without prion RT-QuIC
• CSF and serum PCR tests for specifc infections
• Vitamin levels
If negative
Genome sequencing
Consider systematic reverse phenotyping

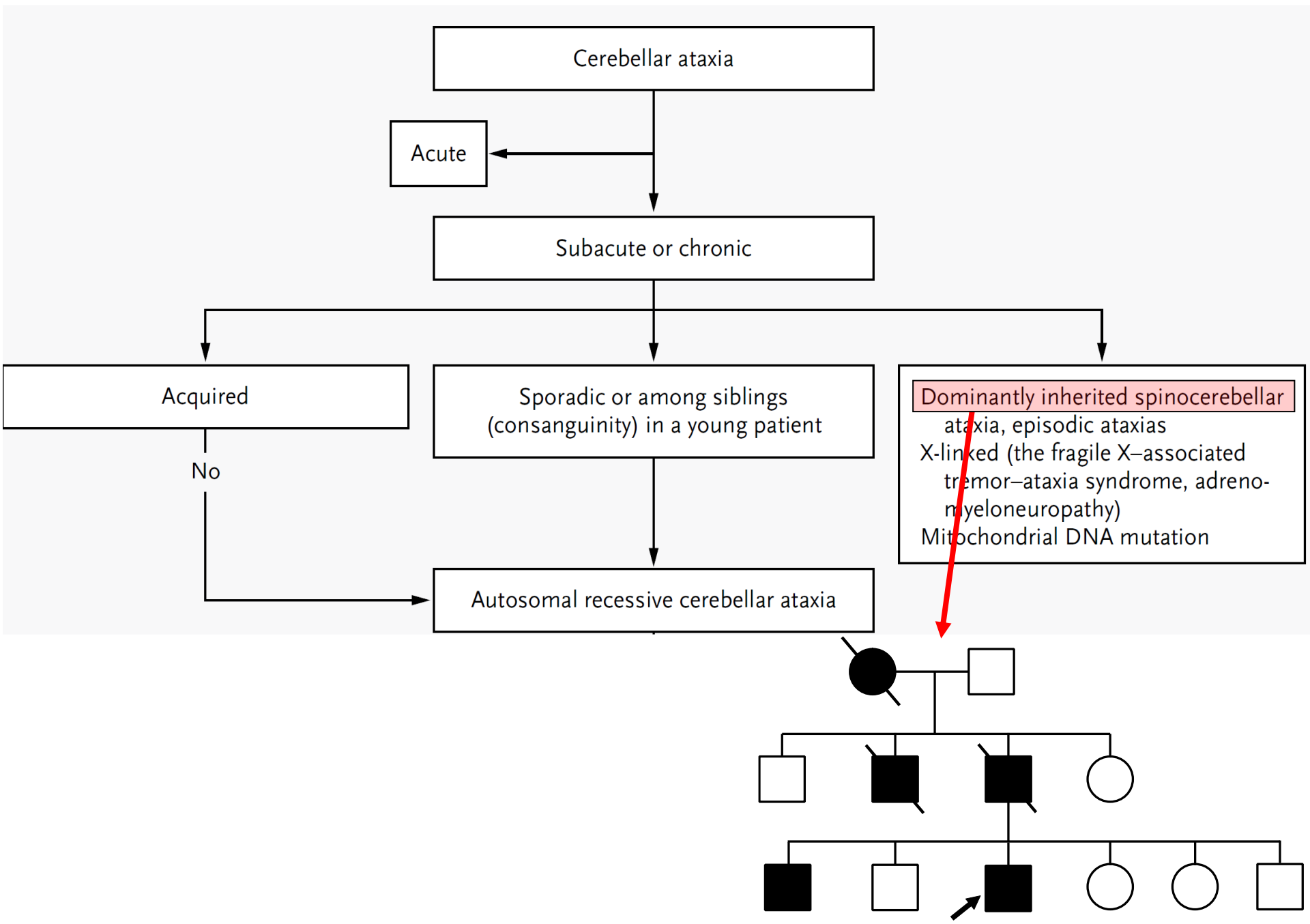

SLOCA
Clinical examination
Excessive alcohol consumption, ataxia-inducing drug exposure
Opsomyoclonus, stiff person syndrome, rapid progression
Downbeat nystagmus, diplopia, episodic ataxia
Spasticity, square-wave jerks
Complex phenotype, consanguinity
Dysautonomia, myoclonus, sleep behaviour disorders, parkinsonism, rapid progression
Chronic cough, paraesthesia, vestibular areflexia, proprioceptive ataxia, dysautonomia
Family history of intellectual disability, history of premature ovarian failure, tremor, cognitive decline
Non-informative family history
Isolated cerebellar ataxia with slow progression
Brain imaging
Cortical and subcortical atrophy, cerebellar atrophy
Normal, cerebellar atrophy, limbic encephalitis
Mild cerebellar atrophy
No to mild cerebellar atrophy
Non-informative
Pons atrophy, MCP atrophy or hyperintensities, putaminal atrophy
Cerebellar atrophy
MCP hyperintensities, cortical atrophy, white matter signal hyperintensities
Pons atrophy, MCP atrophy, cerebellar atrophy
Genome-first strategy
Electroneuromyography
Axonal sensorimotor neuropathy
Sensory neuropathy
Normal or age-related sensorimotor neuropathy
Sensory neuronopathy
Non-informative
Normal
Sensory neuronopathy
Axonal sensorimotor neuropathy
Axonal or demyelinating sensorimotor neuropathy



Wirth et al., Nat Rev Neurol, 2025



Anheim et al., N Engl J Med, 2012

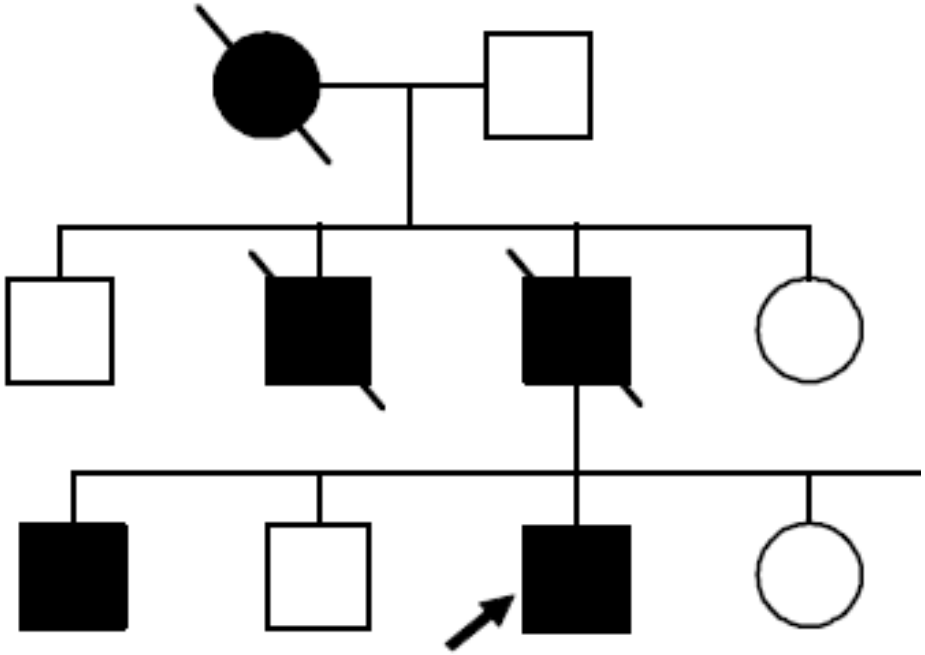

Cerebellar ataxia
Acute
Subacute or chronic
Acquired
No
Sporadic or among siblings (consanguinity) in a young patient
Dominantly inherited spinocerebellar ataxia, episodic ataxias
X-linked (the fragile X–associated tremor–ataxia syndrome, adrenomyeloneuropathy)
Mitochondrial DNA mutation
Autosomal recessive cerebellar ataxia

Autosomal Dominant Cerebellar Ataxias (=SCAs)

<u>Group 1:</u>
Complex
(SCA 1, 2, 3, 17, DRPLA)
- opthalmoparesis
- dystonia
- parkinsonism
- cognitive decline
- peripheral neuropathy

Severe progression

<u>Group 2:</u>
Macular progressive dystrophy (SCA7)



<u>Group 3:</u>
Pure cerebellar ataxia (SCA6)

<u>Group 4:</u>
Ataxia +
Epilepsy
Intellectual deficiency
Peripheral neuropathy (SCA18, SCA25)

Durr, Lancet Neurol, 2010 ; Coarelli, Lancet Neurol, 2023

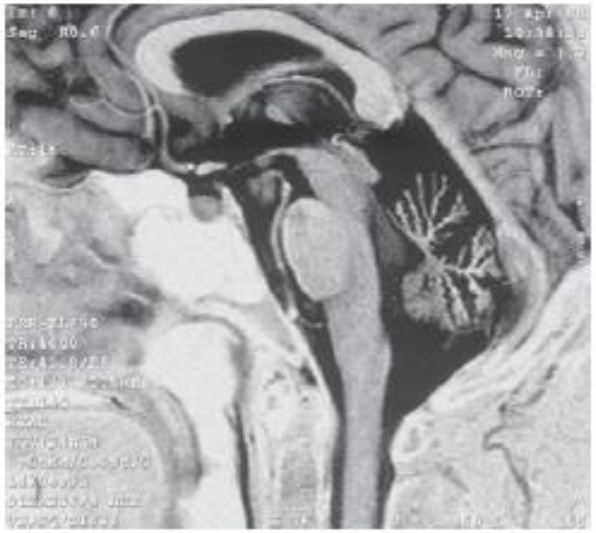
Autosomal Dominant Cerebellar Ataxias (=SCAs)

	Associated signs	Locus	Chrom	Mutation
I	Variable: ophtalmoplegia, optic atrophy, dementia, extrapyramidal signs, amyotrophy	SCA1	6p	Translated CAG expansion
		SCA2	12q	Translated CAG expansion
		SCA3/MJD	14q	Translated CAG expansion
		SCA4	16q	?
		SCA14 PKCγ	19q	**Missense mutation**
		SCA17/TBP	6q	Translated CAG expansion
		SCA16	8q	?
		SCA19/SCA22	1p	?
		SCA21	7p	?
II	Progressive macular dystrophy	SCA7	3p	Translated CAG expansion
III	« Pure » form	SCA5/Spectrin	11cen	**Missense mutation**
		SCA6/CACNAA	19p	Translated CAG expansion
		SCA8	13q	Non coding CTG expansion
		SCA11	15q	?
		SCA12	5q	Non coding CTG expansion
		SCA15	3p	?
		FGF14	13q	**Missense mutation**
		SCA23	20p	?
		SCA26	19p	?
IV	Ataxia + epilepsy	SCA10	22q	ATTCT expansion
	Ataxie + M retardation	SCA13/KCNC3	19q	**Missense mutations**
	Ataxie + SM neuropathy	SCA18/SMNA	7q	?
	Ataxia + S neuropathy	SCA25	2p	?
	Dentatorubropallidoluysian atrophy	DRPLA	12p	Translated CAG expansion

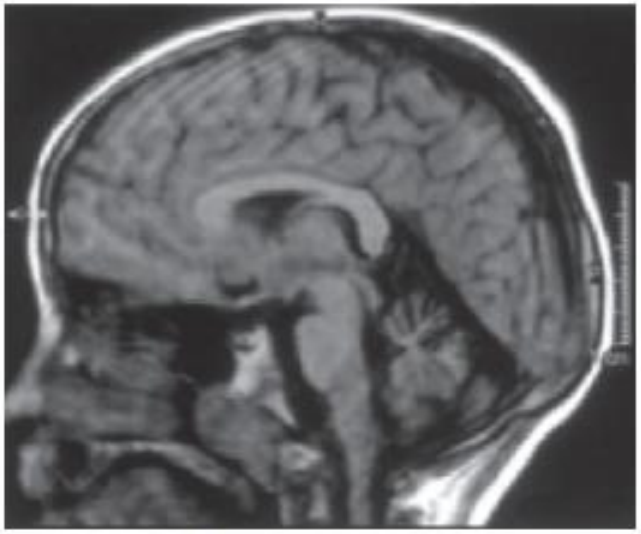
Genotype-phenotype correlations

	Polyglutamine expansion SCAs	Conventional mutation SCAs
Age at onset	Variable (intrafamilial); anticipation	Variable (often in childhood); no anticipation
Disease progression	Progressive, often fatal and juvenile cases are more severe than late-onset cases	Slowly progressive, childhood onset is not associated with a more severe disease course
Clinical features	Multisystemic, neurodegenerative widespread lesions that increase with disease duration	Pure cerebellar, congenital features such as stable mental retardation
Neuropatholgy	Widespread neuronal loss	Predominant Purkinje cell loss
Cerebral imaging	Brainstem>cerebellar atrophy	Pure and global cerebellar atrophy

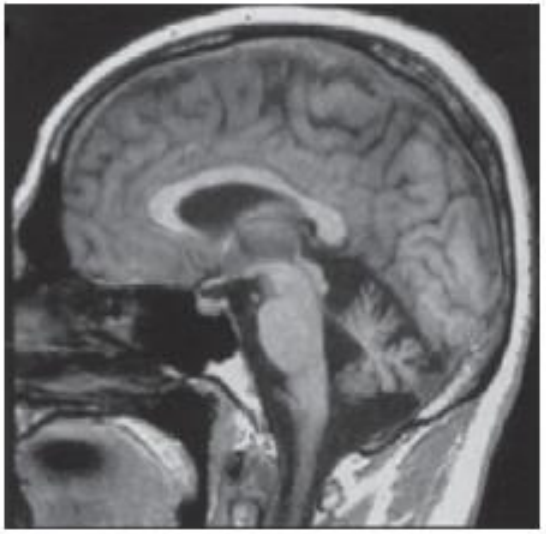
Durr, Lancet Neurol, 2010



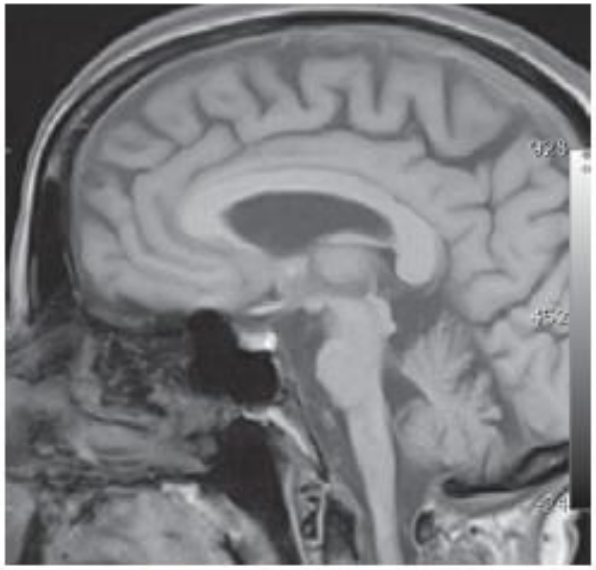
SCA14: AO at 6 years; DD 28 years



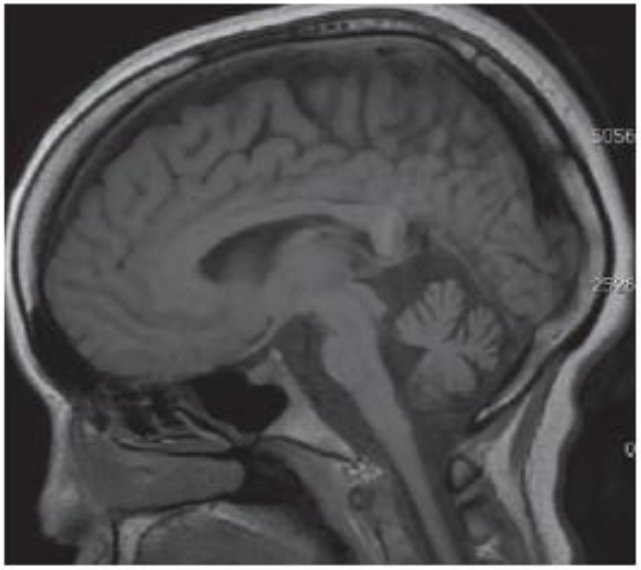
SCA13: AO at 1 year; DD 4 years



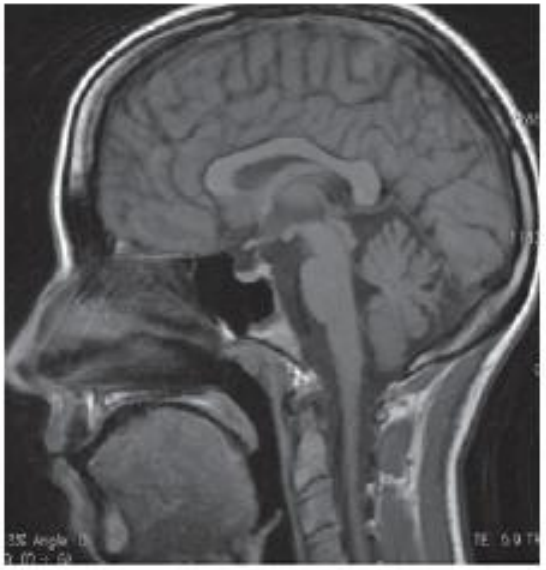
SCA5: AO at 26 years; DD 10 years



SCA3: AO at 36 years; DD 39 years

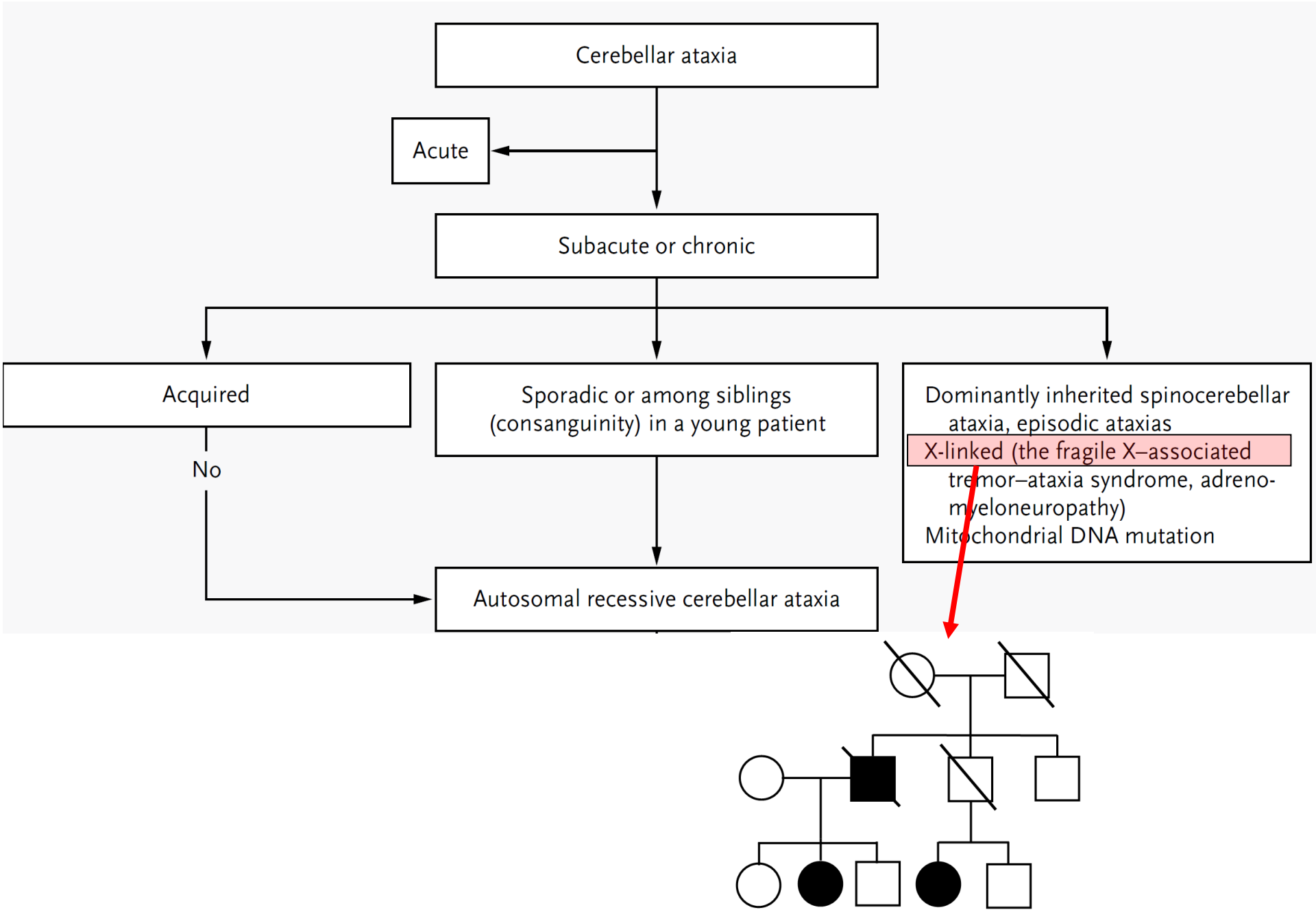


SCA2: AO at 22 years; DD 8 years



SCA7: AO at 20 years; DD 9 years

Durr, Lancet Neurol, 2010



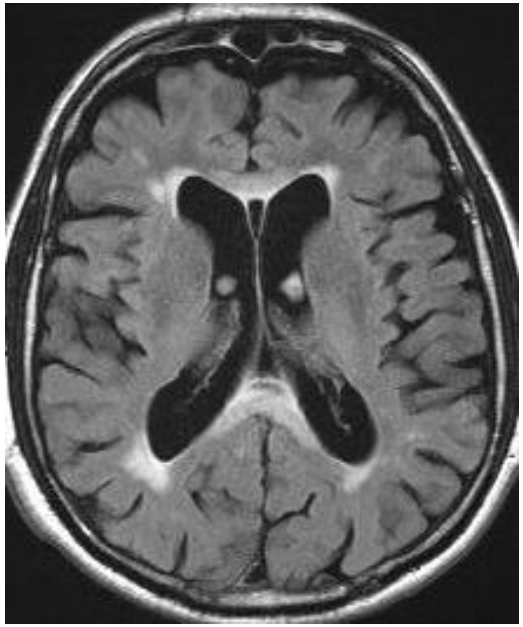
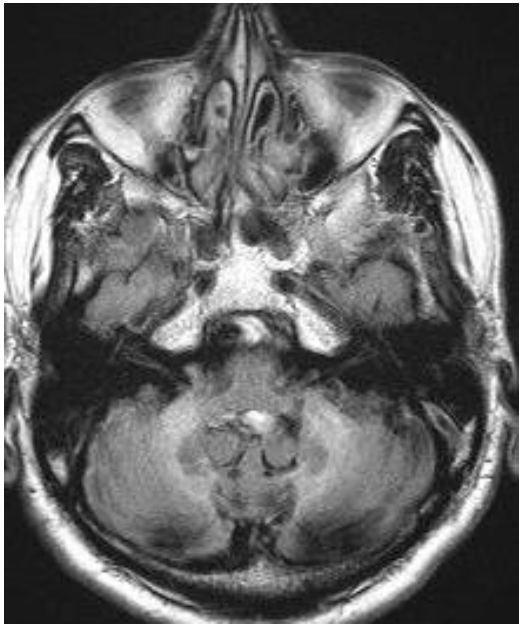
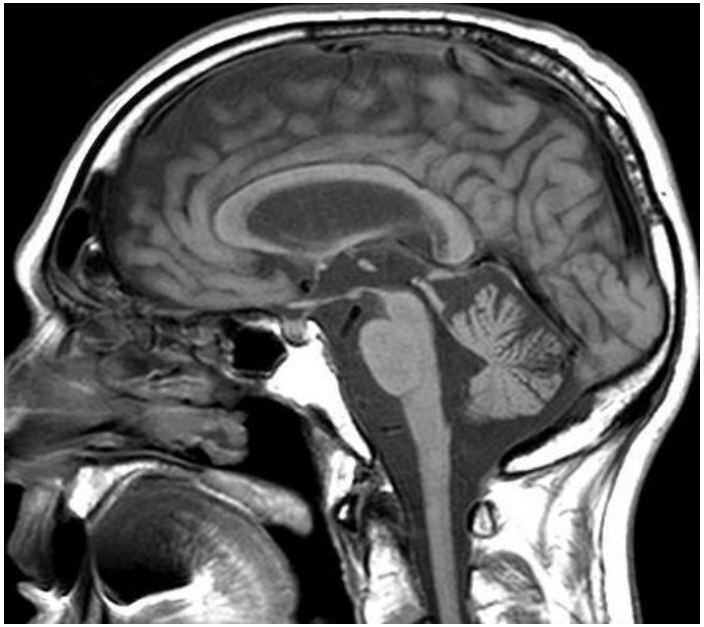
Anheim et al., N Engl J Med, 2012

Fragile X-associated Tremor Ataxia Syndrome

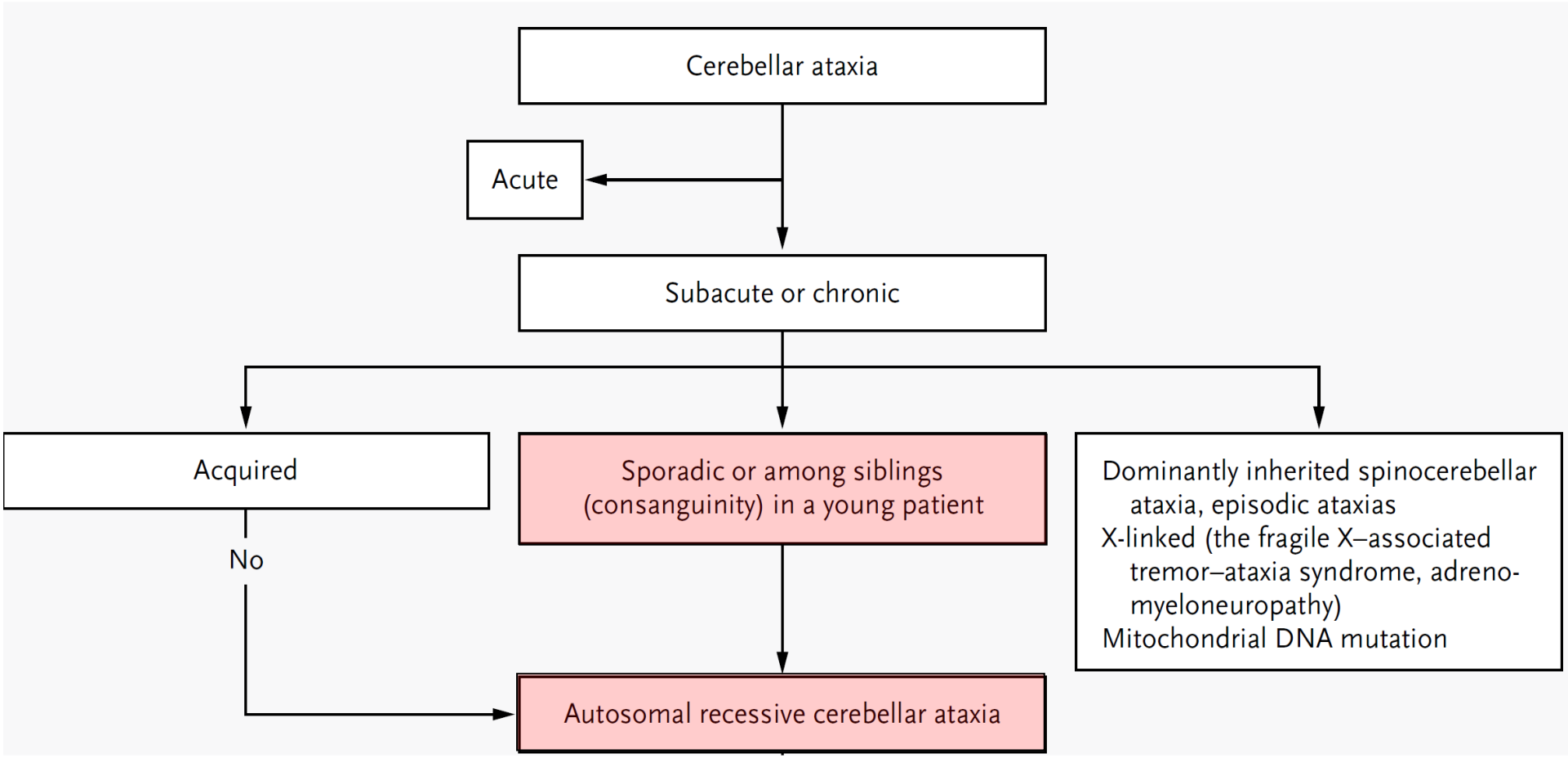
- onset near 55 years of age
- mostly male
- action tremor
- cerebellar ataxia
- cognitive decline
- parkinsonism

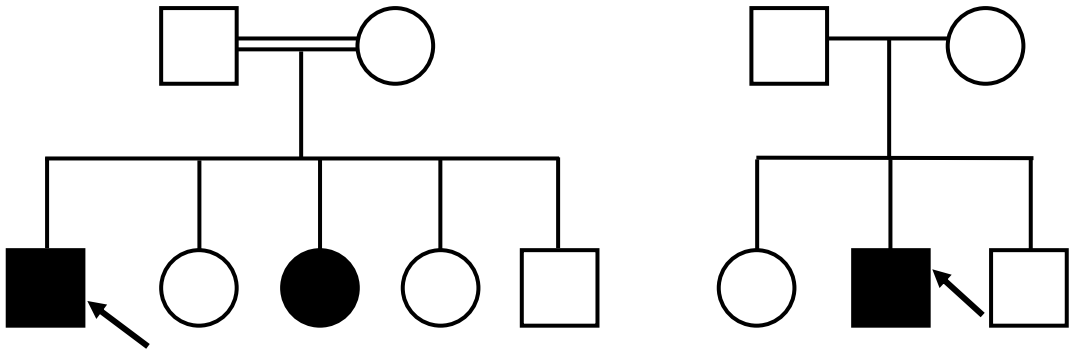
- *FMR1* gene premutation
  < 50 CGG triplets : normal
  60-200 CGG : premutation
  > 200 CGG : complete mutation

- genetic counselling

Berry-Kravis, Mov Disord, 2007
Jacquemont, Lancet Neurol, 2007





early-onset (< 25 years of age)

Friedreich's ataxia (ATX-FXN)

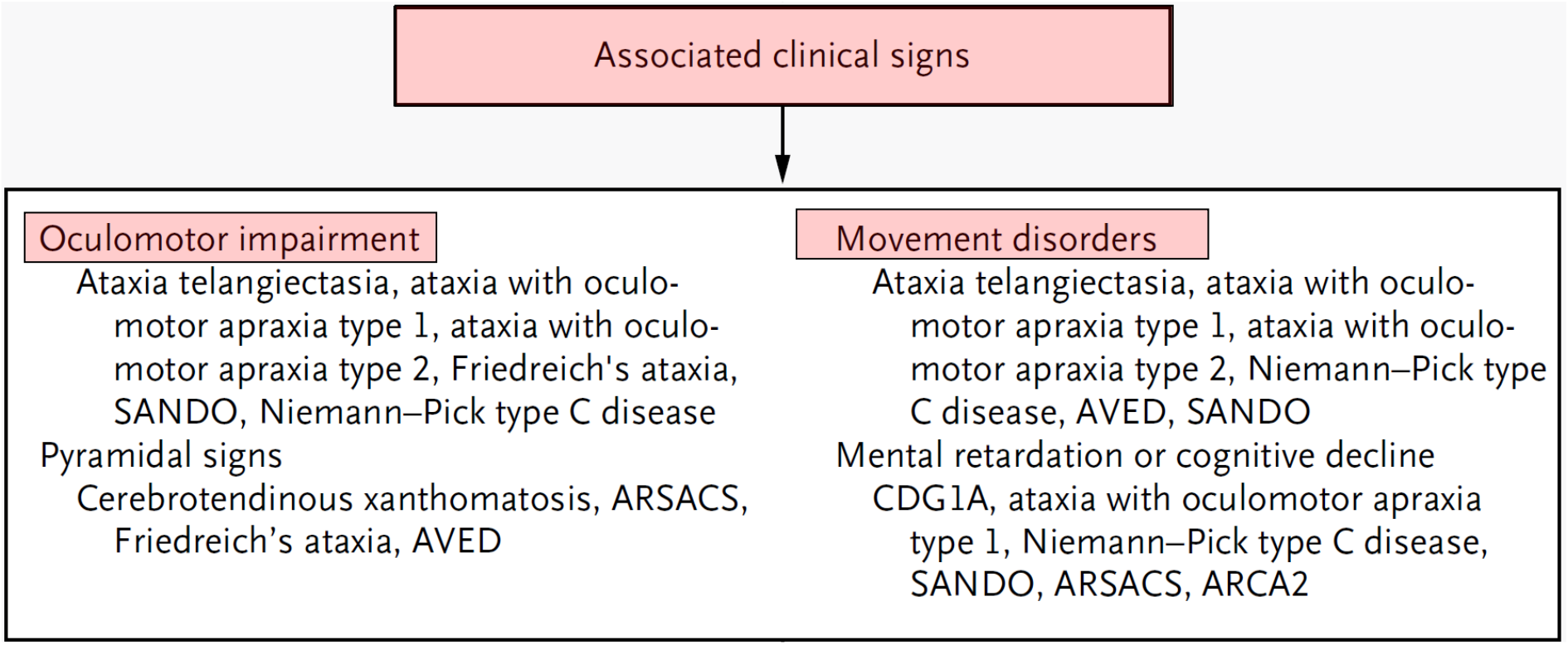
neurological signs
- combined ataxia
- cerebellar dysarthria
- absent tendon reflexes
- hypopallesthesia

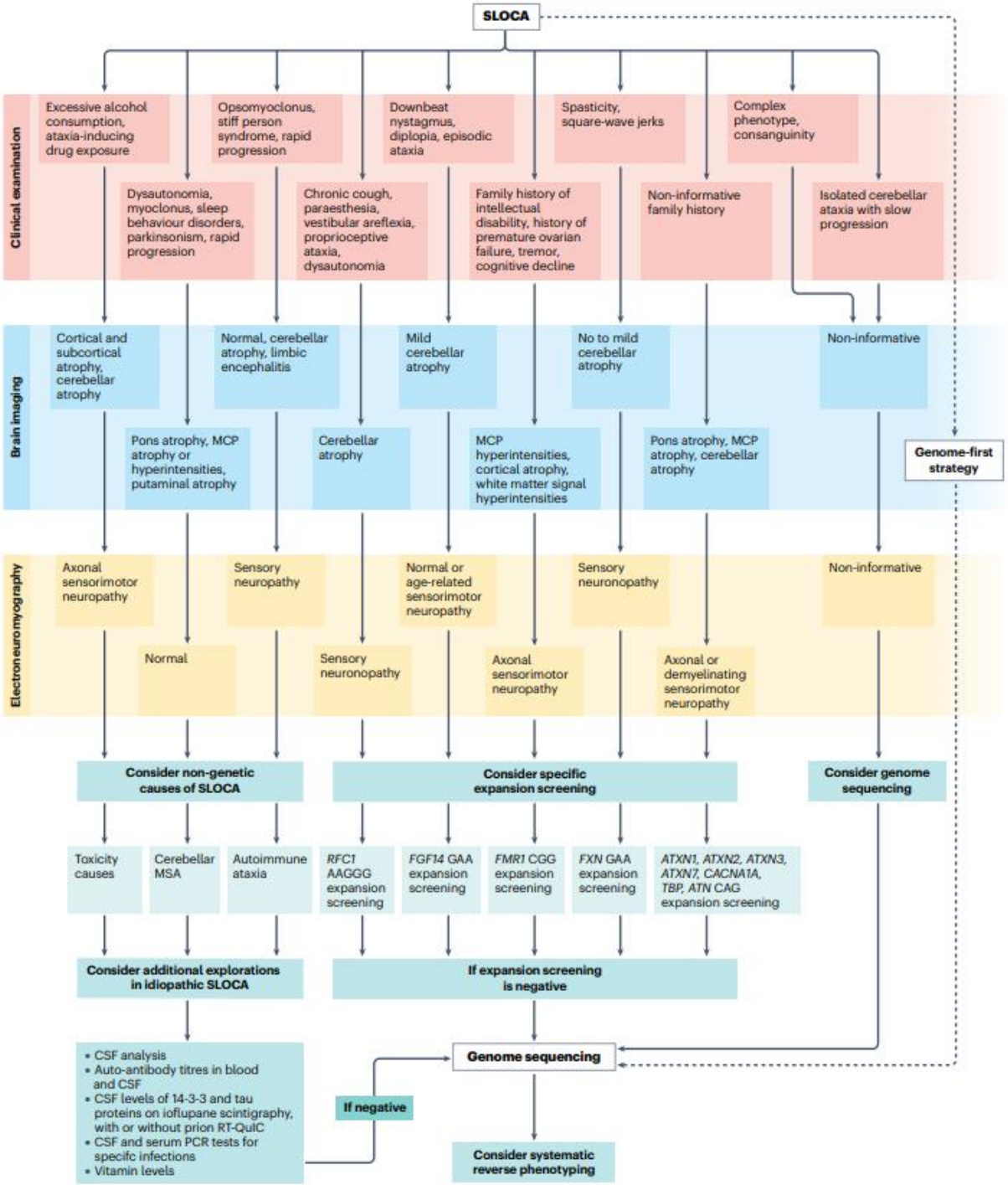
= sensory neuronopathy
- extensor plantar reflexes
- square waves jerks

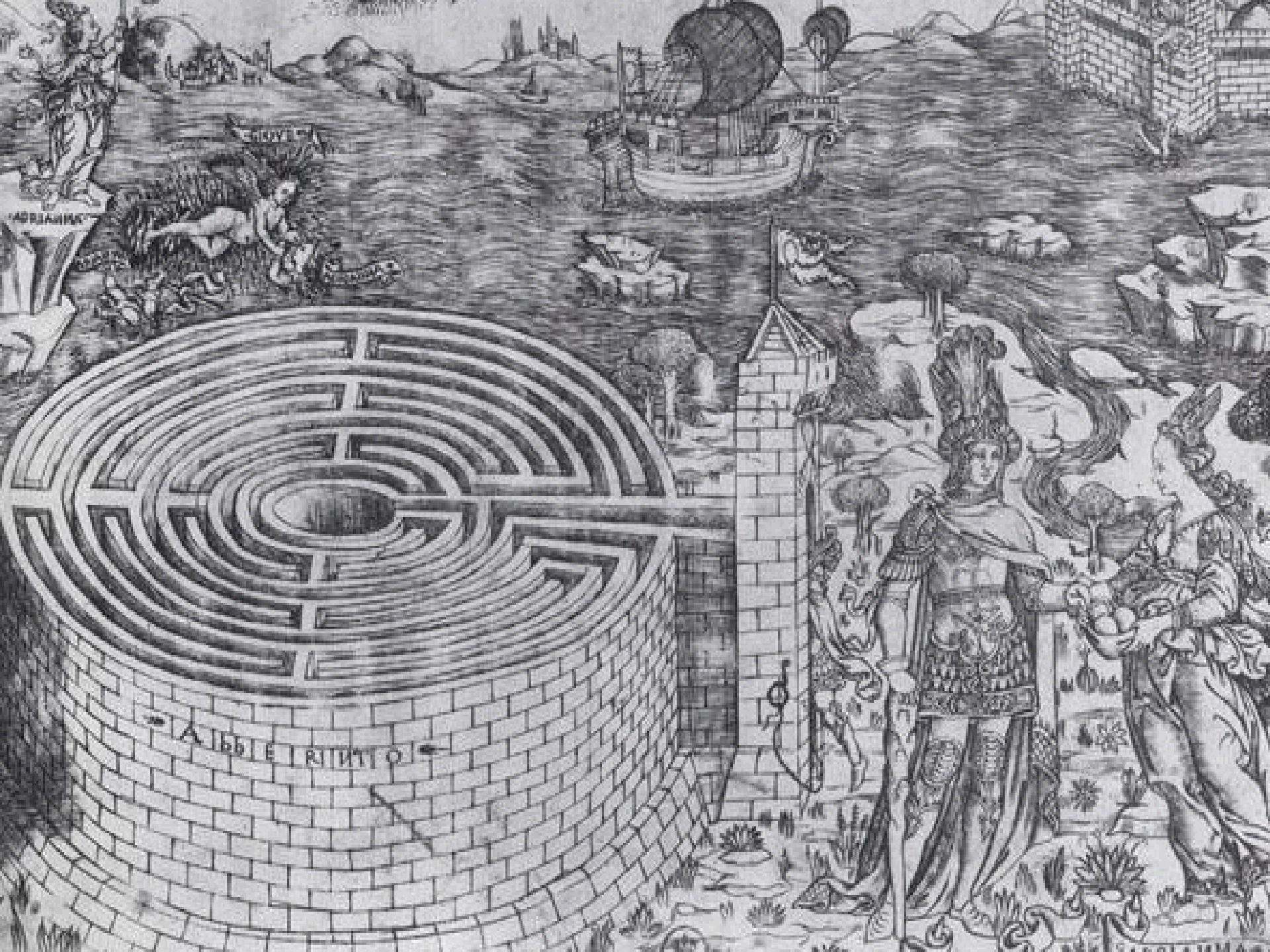
extra-neurological signs
- hypertrophic cardiomyopathy
- scoliosis
- diabetes
- optic neuropathy
- deafness
- pes cavus

Coarelli et al., J Neurol, 2023

Autosomal recessive cerebellar ataxias




SLOCA
Clinical examination
Excessive alcohol consumption, ataxia-inducing drug exposure
Opsomyoclonus, stiff person syndrome, rapid progression
Downbeat nystagmus, diplopia, episodic ataxia
Spasticity, square-wave jerks
Complex phenotype, consanguinity
Dysautonomia, myoclonus, sleep behaviour disorders, parkinsonism, rapid progression
Chronic cough, paraesthesia, vestibular areflexia, proprioceptive ataxia, dysautonomia
Family history of intellectual disability, history of premature ovarian failure, tremor, cognitive decline
Non-informative family history
Isolated cerebellar ataxia with slow progression
Brain imaging
Cortical and subcortical atrophy, cerebellar atrophy
Normal, cerebellar atrophy, limbic encephalitis
Mild cerebellar atrophy
No to mild cerebellar atrophy
Non-informative
Pons atrophy, MCP atrophy or hyperintensities, putaminal atrophy
Cerebellar atrophy
MCP hyperintensities, cortical atrophy, white matter signal hyperintensities
Pons atrophy, MCP atrophy, cerebellar atrophy
Genome-first strategy
Electroneuromyography
Axonal sensorimotor neuropathy
Sensory neuropathy
Normal or age-related sensorimotor neuropathy
Sensory neuronopathy
Non-informative
Normal
Sensory neuronopathy
Axonal sensorimotor neuropathy
Axonal or demyelinating sensorimotor neuropathy
Consider non-genetic causes of SLOCA
Consider specific expansion screening
Consider genome sequencing
Toxicity causes
Cerebellar MSA
Autoimmune ataxia
RFC1 AAGGG expansion screening
FGF14 GAA expansion screening
FMR1 CGG expansion screening
FXN GAA expansion screening
ATXN1, ATXN2, ATXN3, ATXN7, CACNA1A, TBP, ATN CAG expansion screening
Consider additional explorations in idiopathic SLOCA
If expansion screening is negative
• CSF analysis
• Auto-antibody titres in blood and CSF
• CSF levels of 14-3-3 and tau proteins on ioflupane scintigraphy, with or without prion RT-QuIC
• CSF and serum PCR tests for specifc infections
• Vitamin levels
If negative
Genome sequencing
Consider systematic reverse phenotyping


LABIRINTO