UT Southwestern
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Update on Ataxia

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December 2022

Disclosures

Dr. Shakkottai

Funding through the NIH, National Ataxia Foundation, Seelos Therapeutics, Prior research funding through Biohaven Inc

Formerly advisory board for Cadent (Ataxion) Therapeutics, UniQure Inc.

Royalties from UptoDate Inc. and BMJ

Advisory board for Reata Pharmaceuticals

Inventor on patent filed by the University of Michigan for drug combination in ataxia US Pat # 11382897

Dr. Vernino

Consultant for Alterity, Argenx, Amneal

Research Support from Takeda, BioHaven, UCB, Grifols, Dysautonomia International, NIH

Will mention off-label use of immunotherapies for autoimmune ataxia

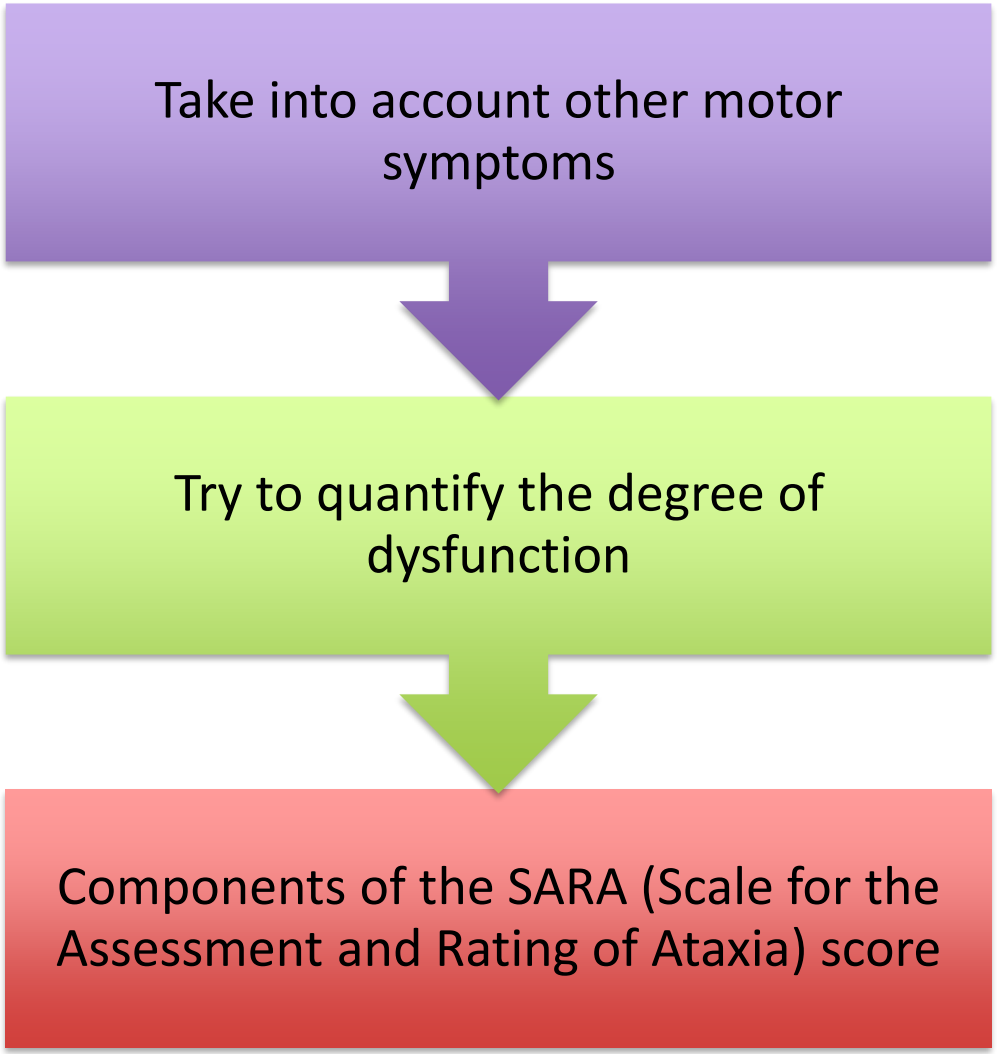
Objectives:

- Identify ataxia, its various causes, and the diagnostic approach
- Be familiar with the common forms of genetic ataxia
- Understand the concept of autoimmune/paraneoplastic disease including autoimmune ataxia and PCD
- Identify ataxia as a presentation of neurodegenerative disorder, MSA, type C
- Recognize features of different forms of progressive ataxia

What is ataxia?

- “A-taxia” or “loss of order”: Group of conditions with problems with coordination
- Can involve gait, coordination of the arms and speech
- Anatomically ataxia can be localized to the cerebellum or its connections

How to make a diagnosis?



SARA

1) Gait

Participant is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
1 Slight difficulties, only visible when walking 10 consecutive steps in tandem
2 Clearly abnormal, tandem walking >10 steps not possible
3 Considerable staggering, difficulties in half-turn, but without support
4 Marked staggering, intermittent support of the wall required
5 Severe staggering, permanent support of one stick or light support by one arm required
6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
8 Unable to walk, even supported

Score _____

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

0 Normal, able to stand in tandem for > 10 s
1 Able to stand with feet together without sway, but not in tandem for > 10s
2 Able to stand with feet together for > 10 s, but only with sway
3 Able to stand for > 10 s without support in natural position, but not with feet together
4 Able to stand for >10 s in natural position only with intermittent support
5 Able to stand >10 s in natural position only with constant support of one arm
6 Unable to stand for >10 s even with constant support of one arm

Score: _____

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

0 Normal, no difficulties sitting >10 sec
1 Slight difficulties, intermittent sway
2 Constant sway, but able to sit > 10 s without support
3 Able to sit for > 10 s only with intermittent support
4 Unable to sit for >10 s without continuous support

Score _____

4) Speech disturbance

Speech is assessed during normal conversation.

0 Normal
1 Suggestion of speech disturbance
2 Impaired speech, but easy to understand
3 Occasional words difficult to understand
4 Many words difficult to understand
5 Only single words understandable
6 Speech unintelligible / anarthria

Score: _____

SARA

5) Finger chase

Rated separately for each side

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

0 No dysmetria
1 Dysmetria, under/ overshooting target <5 cm
2 Dysmetria, under/ overshooting target < 15 cm
3 Dysmetria, under/ overshooting target > 15 cm
4 Unable to perform 5 pointing movements

Score Right _____ Left _____

Mean of both sides (R+L)/2 _____

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

0 No tremor
1 Tremor with an amplitude < 2 cm
2 Tremor with an amplitude < 5 cm
3 Tremor with an amplitude > 5 cm
4 Unable to perform 5 pointing movements

Score Right _____ Left _____

Mean of both sides (R+L)/2 _____

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

0 Normal, no irregularities (performs <10s)
1 Slightly irregular (performs <10s)
2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s
3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
4 Unable to complete 10 cycles

Score Right _____ Left _____

Mean of both sides (R+L)/2 _____

TOTAL SCORE _____

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

0 Normal
1 Slightly abnormal, contact to shin maintained
2 Clearly abnormal, goes off shin up to 3 times during 3 cycles
3 Severely abnormal, goes off shin 4 or more times during 3 cycles
4 **Unable to perform the task**

Score Right _____ Left _____

Mean of both sides (R+L)/2 _____

/40

Eye Movements

Gaze evoked nystagmus

Downbeat nystagmus in primary gaze

Saccadic overshoot

Saccadic undershoot

Etiology of Cerebellar Ataxia

- Sporadic
  - Congenital
  - Degenerative: Kuru, CJD, Superficial Siderosis
  - Nutritional/toxic: EtOH, Mercury, Vitamin E, Vitamin B12, Iatrogenic-AEDs, Amiodarone
  - Infectious/post-infectious: Ebstein-Barr, Enterovirus, HTLV1 /HIV/Syphilis, Lyme disease, Measles, Rubella, Varicella, Prion disease, Whipple's disease
  - Inflammatory/Immune: MS, Stiff person syndrome, Gluten-sensitive enteropathy associated, Hashimoto's encephalopathy, Primary Sjogren's disease
  - Paraneoplastic
  - Ischemic
  - Neoplastic
  - Idiopathic

Etiology of Cerebellar Ataxia

- Inherited
  - Autosomal dominant:
    SCA, DRPLA, episodic ataxia
    Other dominant: FXTAS
  - Recessive:
    Friedreich ataxia, RFC1 CANVAS, Ataxia telangiectasia

Acute or subacute onset

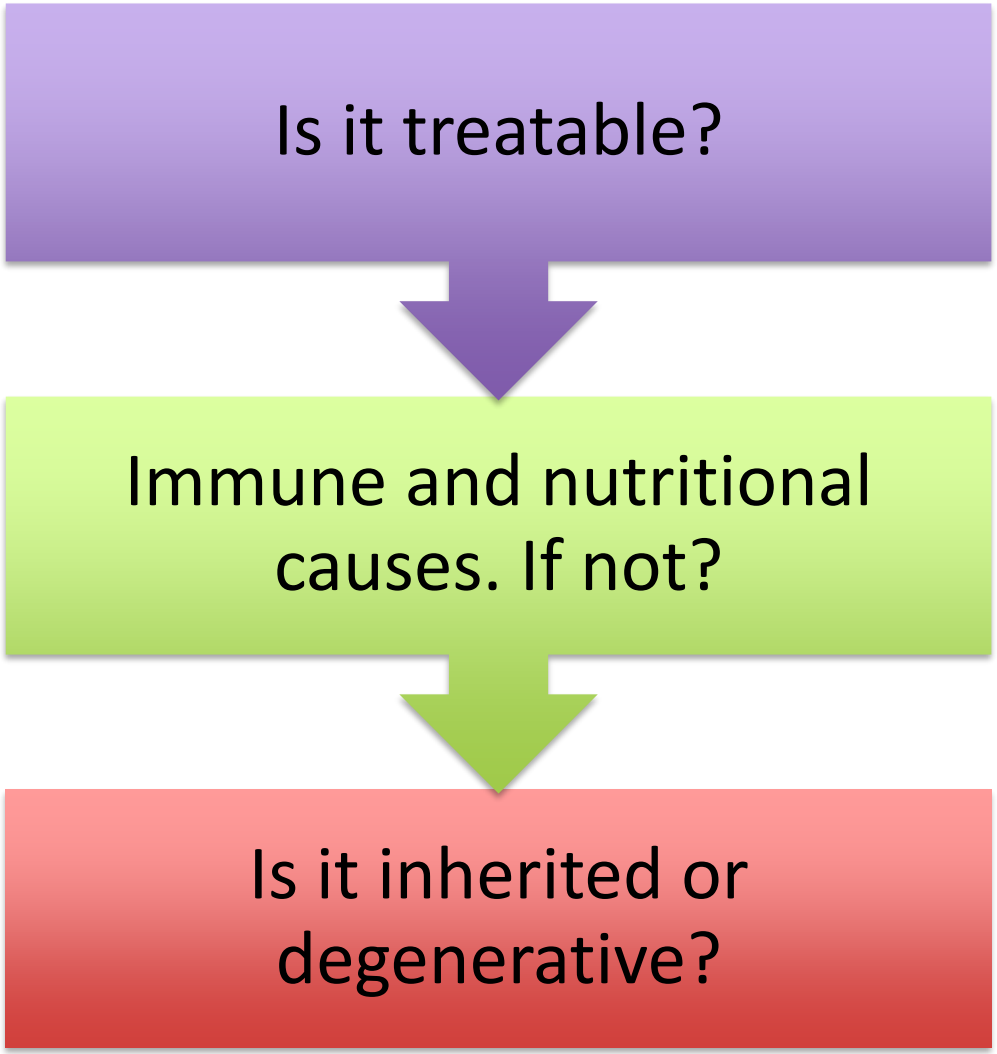
- Intoxication (e.g., phenytoin, lead, alcohol)
- Hemorrhage
- Ischemic stroke
- Trauma
- Tick paralysis poisoning
- Tumor, posterior fossa or cerebellum
- Brainstem encephalitis
- Occult neuroblastoma (opsoclonus/myoclonus)
- Miller Fisher variant of GuillainBarre´ syndrome
- Conversion reaction
- Multiple sclerosis
- Vasculitis (e.g., Kawasaki)
- Metabolic (e.g., pyruvate dehydrogenase, maple syrup urine
- disease, and Hartnup disease)

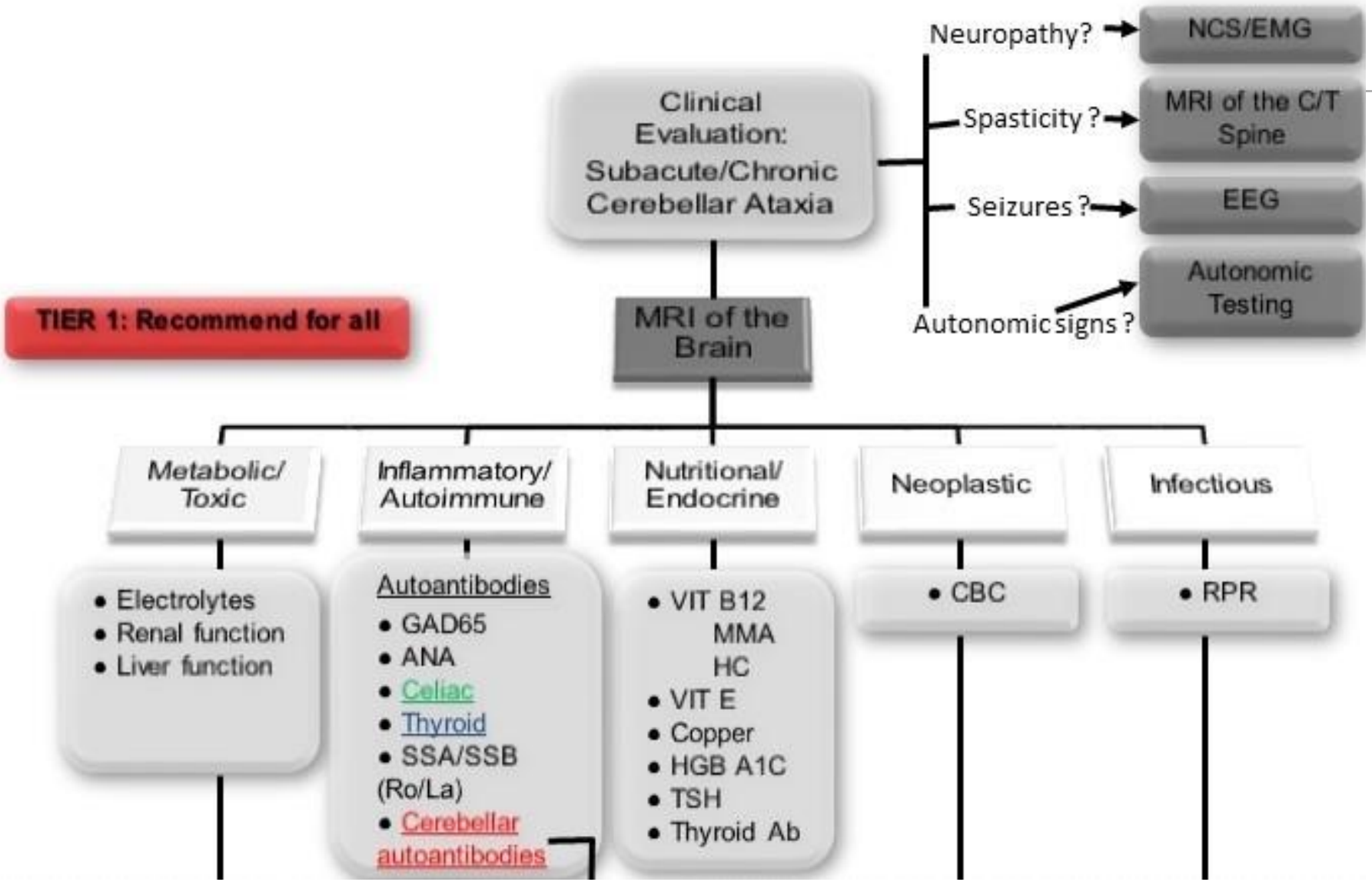
Handbook of Clinical Neurology, Vol. 112 (3rd series)
Pediatric Neurology Part II

Chronic

- Cerebellar aplasia or hypoplasia, DandyWalker or Chiarimalformations
- Autosomal dominant: spinocerebellar ataxias, dentatorubralpallidoluysian atrophy (DRPLA)
- Autosomal recessive: Friedrich's ataxia, ataxia with oculomotor apraxia, ataxia-telangiectasia, abetalipoproteinemia, cerebrotendinous xanthomatosis,autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS)
- X-linked: fragile X-associated tremor and ataxia, sideroblasticanemia and ataxia
- Maternal: mitochondrial disorders such as KearnsSayre, NARP (neuropathy, ataxia, and retinitis pigmentosa), MERRF (myoclonic epilepsy with ragged red fibers)
- Leukodystrophies
- Vitamin E deficiency, vitamin B12 deficiency
- Metabolic disorders (e.g., Refsum disease, sulfatide lipidoses, and metabolic causes of acute ataxia)
- Marinesco Sjogren syndrome
- Ramsay Hunt syndrome

Major categories

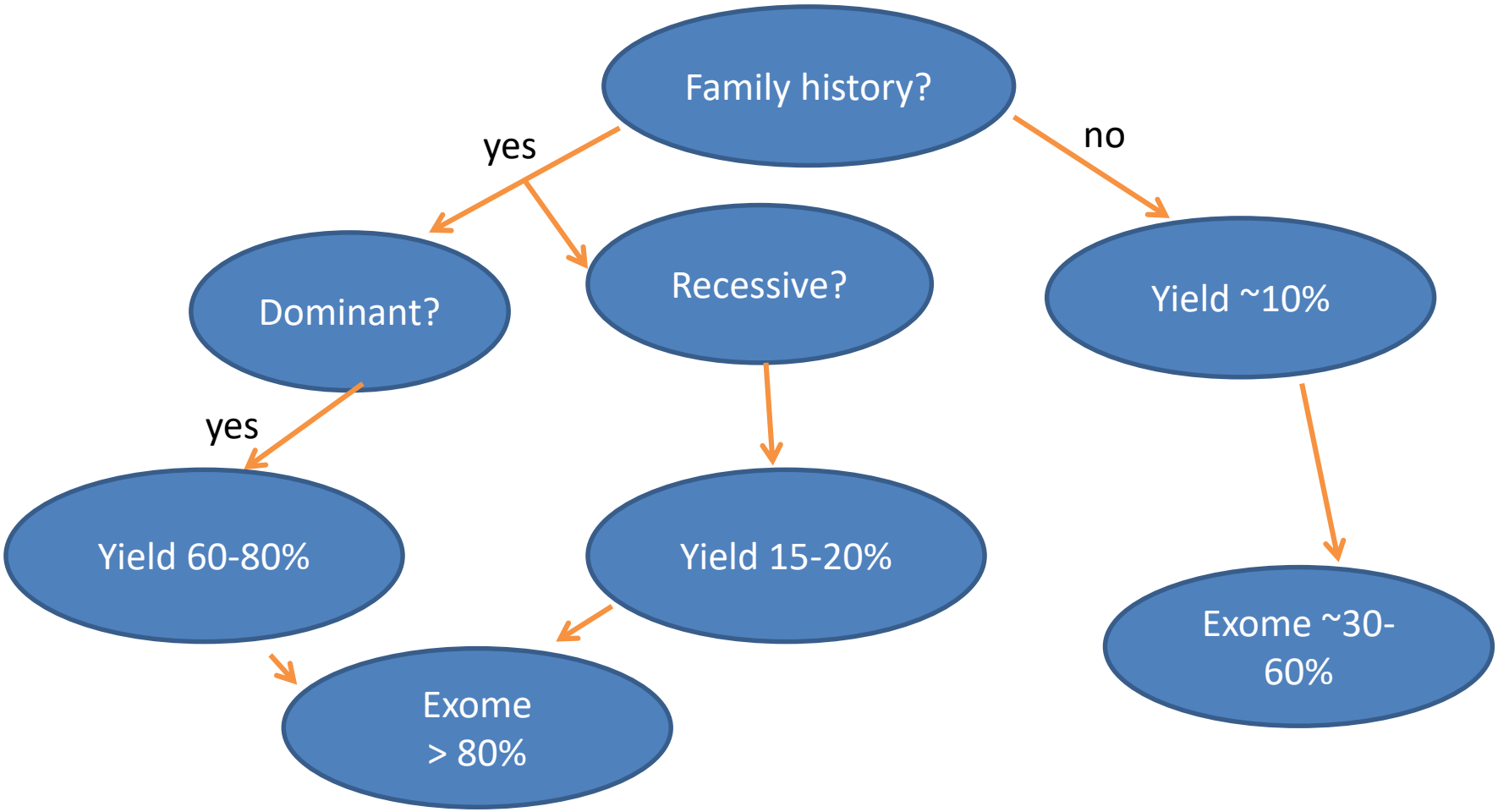



Clinical Evaluation: Subacute/Chronic Cerebellar Ataxia
Neuropathy?
NCS/EMG
Spasticity ?
MRI of the C/T Spine
Seizures ?
EEG
Autonomic signs ?
Autonomic Testing
TIER 1: Recommend for all
MRI of the Brain
Metabolic/ Toxic
Inflammatory/ Autoimmune
Nutritional/ Endocrine
Neoplastic
Infectious
• Electrolytes
• Renal function
• Liver function
Autoantibodies
• GAD65
• ANA
• Celiac
• Thyroid
• SSA/SSB (Ro/La)
• Cerebellar autoantibodies
• VIT B12
MMA
HC
• VIT E
• Copper
• HGB A1C
• TSH
• Thyroid Ab
• CBC
• RPR

Genetic testing?

- How is it useful?
- What is the yield?

Diagnostic decision tree



Mosely et al. Neurology. Volume 51, December 1998,1666-1671

Value of genetic testing

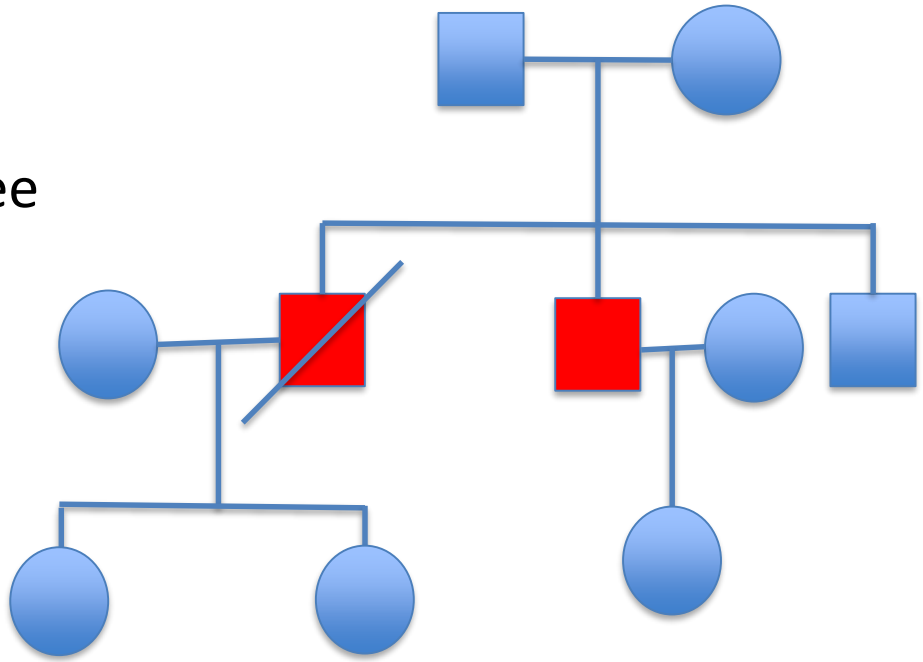
- Predicting natural history
- Planning family
- Avoiding unnecessary treatment
- Ongoing trials for specific inherited forms of ataxia
- Potential gene specific treatment is imminent

Case 1

- 60-yr old with 5-year history of balance impairment
- Started having changes in speech with the onset of balance impairment
- History of excess alcohol use but stopped at least 3 years ago.
- Sibling who died at age 70 who had cerebellar atrophy with Purkinje neuron loss at autopsy.
- Has another sibling in his 60s in good health.
- Parents were in good health.
- Complains of a cough even with mildly spicy food for many years.

Case 1

- What is this pedigree?
  - Classic recessive pedigree



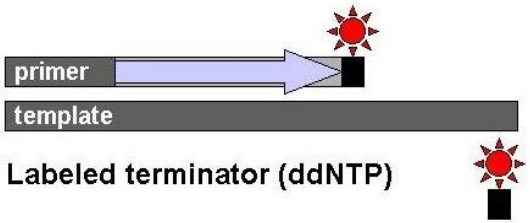
- Examination reveals mild hyperreflexia and vibration loss at the toes.

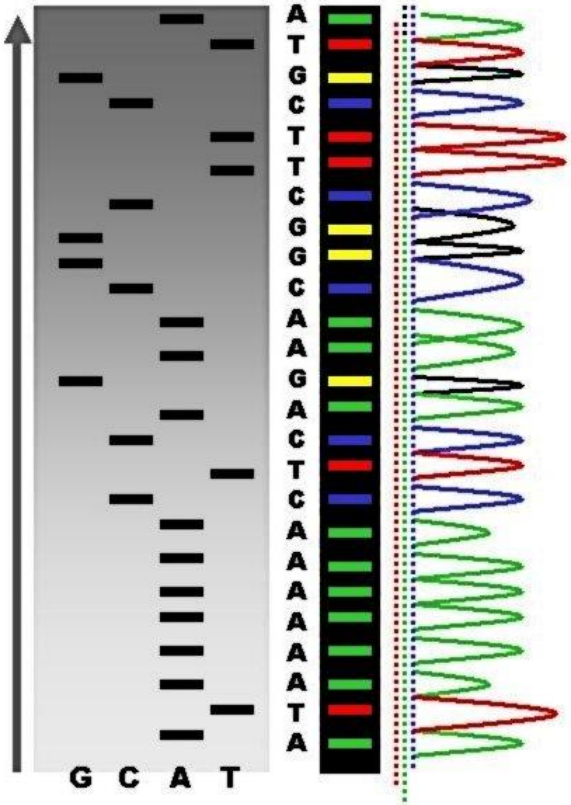
Which genetic test to get?

- Use a stratified approach
  - Test repeat-associated ataxias first-SCA3, SCA2, SCA6, and SCA1 account for 50-60% of dominant ataxia.
  - Friedreich ataxia: 5-10%
  - RFC1 associated ataxia may be as common as FA
- Most cost-effective is to then proceed with exome sequencing

Mosely et al. Neurology. Volume 51, December 1998,1666-1671
Synofzik et al. J Med Genet 2011 48, 407-12

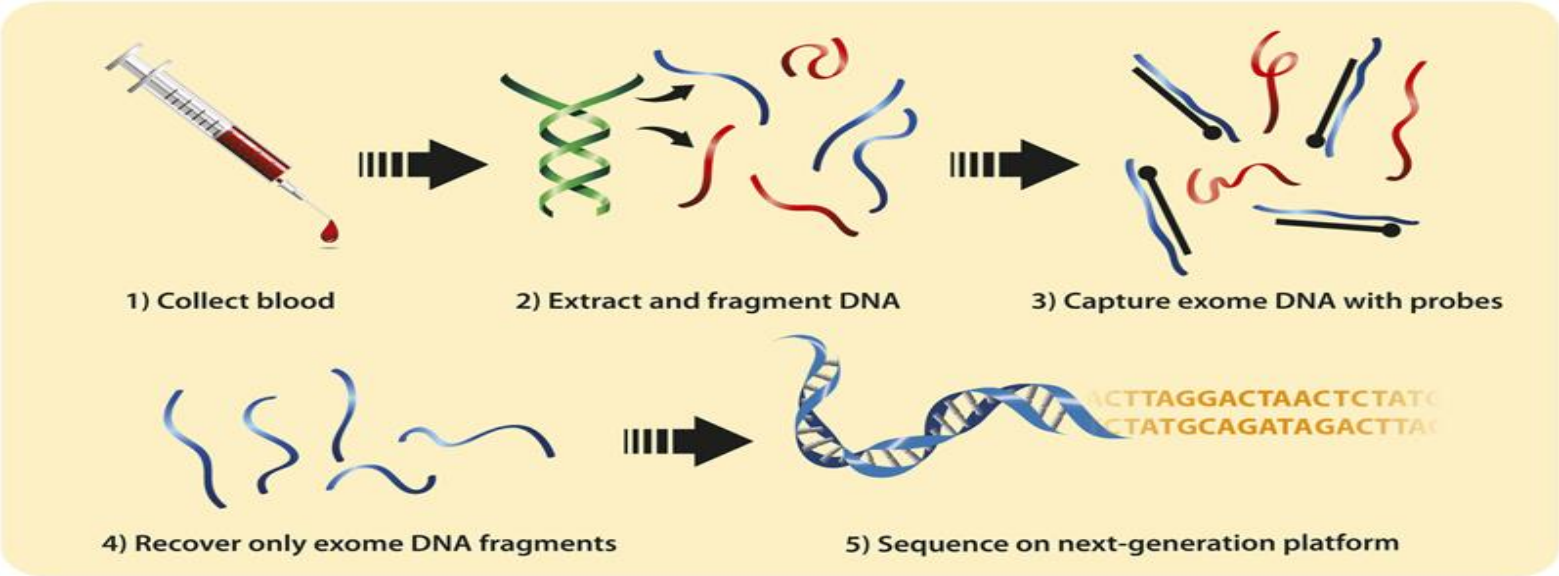
Gene sequencing





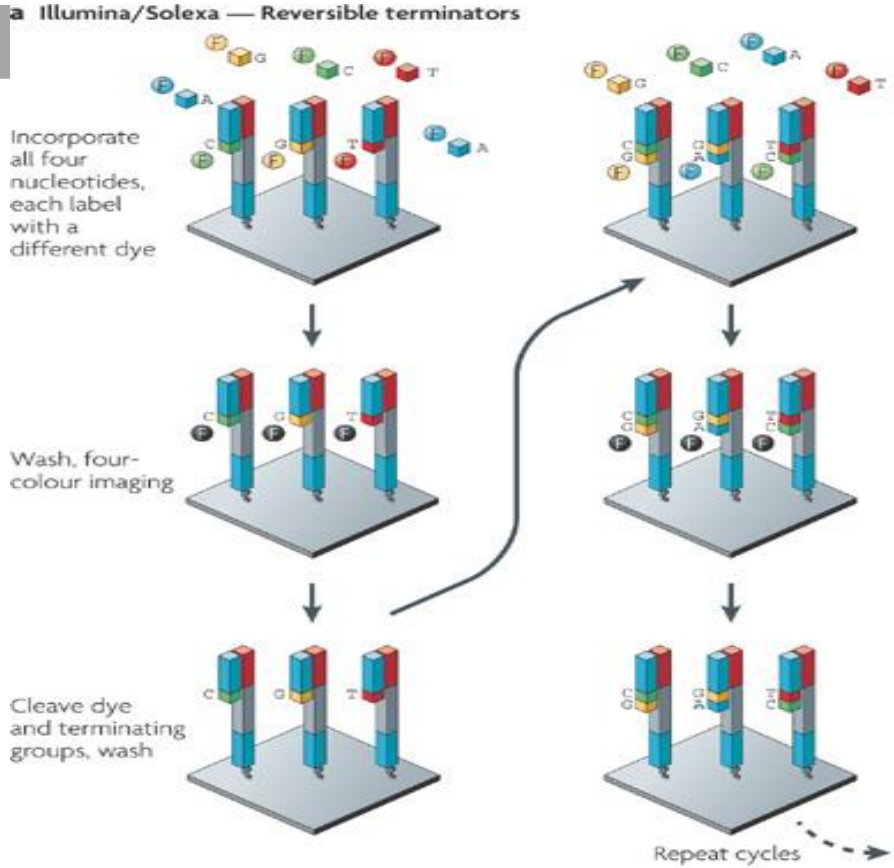
Wikimedia commons

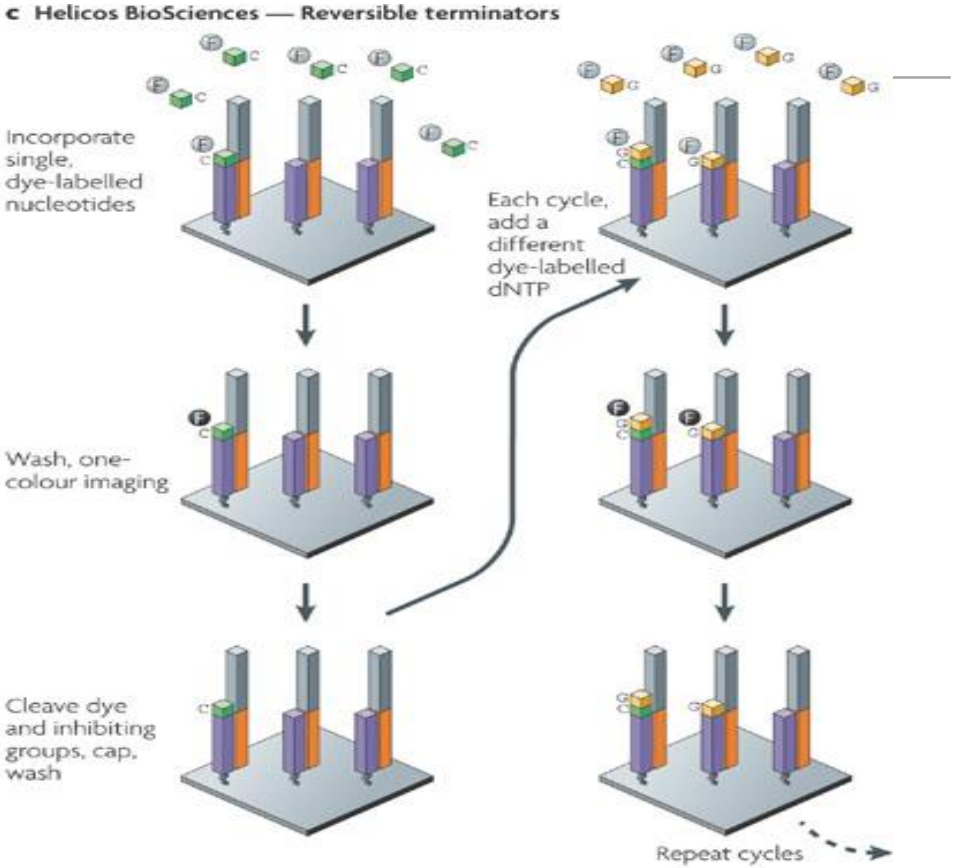
Whole exome sequencing

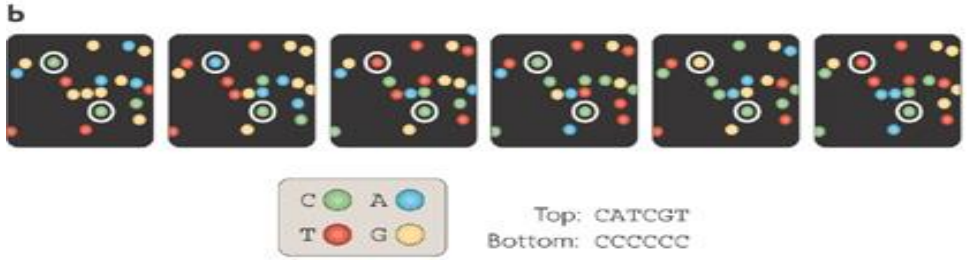


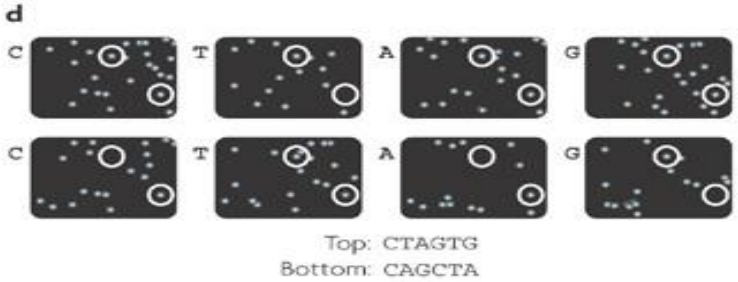
Paria N, Copley LA, Herring JA, Kim HK, Richards BS, Sucato DJ, Wise CA, Rios JJ. (2013) **Whole-exome sequencing: discovering genetic causes of orthopaedic disorders.** *J Bone Joint Surg Am* 95(23), e1851-8

NGS platforms

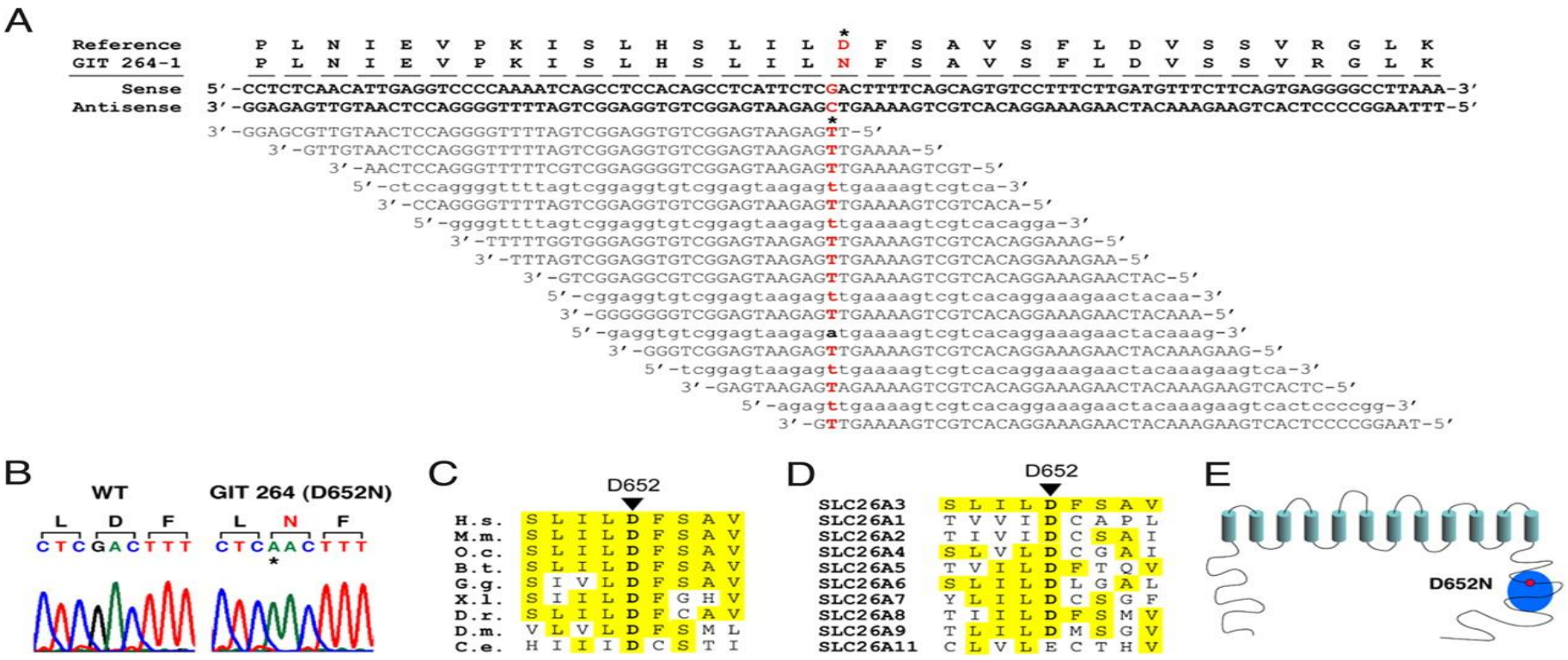








WES



Choi et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. PNAS 2009

ADCA (SCA)

- ADCA (Autosomal dominant cerebellar ataxia) or SCA (spinocerebellar ataxia)
  - 30 now identified
  - SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA are CAG repeat disorders
  - Typically late onset conditions with ataxia accompanied by variable amounts of brain stem dysfunction, extrapyramidal symptoms and long tract signs

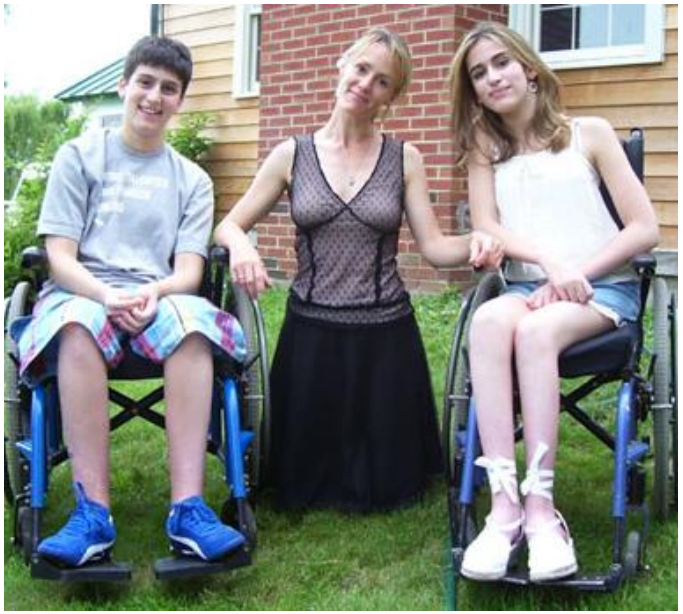
RECESSIVE ATAXIA

Disorder	gene	location	MIM
Friedreich ataxia	Frataxin (FRDA)	9q13	229300
Ataxia telangiectasia	ATM	11q22.3	208900
Ataxia with isolated vitamin E deficiency (AVED)	Alpha-tocopherol transfer protein (α-TTP)	8q13	277460
Abetaliproteinemia	microsomal trygliceride transfer protein (MTP)	4q22-q24	200100
Cerebrotendinous xanthomatosis	sterol 27-hydroxylase (CYP27)	2q33-qter	213700
Ataxia with oculomotor apraxia 1 (AOA1)	Aprataxin (APTX)	9p13	208920
Oculomotor apraxia – ataxia telangiectasia-like (AOA-ATL/AOA2; SCAR1)		9q34	606002
Charlevoix-Saguenay spastic ataxia	Sacsin (SACS)	13q12	270550
Early onset cerebellar ataxia with retained tendon reflexes (EOCARR)		13q11-12	212895
Infantile onset spinocerebellar ataxia (IOSCA)		10q22.3-q24.1	271245
Marinesco-Sjögren syndrome			248800
Classical MSS		5q32	
MSS with myoglobinuria		18qter	
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	Tyrosyl-DNA phosphodiesterase 1 (TDP1)	14q31	607250
Coenzyme Q_{10} deficiency with cerebellar ataxia			607426
Posterior column ataxia and retinitis pigmentosa (PCARP)		1q31	176250
Joubert syndrome		9q34	213300
Cockayne syndrome type I	CKN1	5	216400

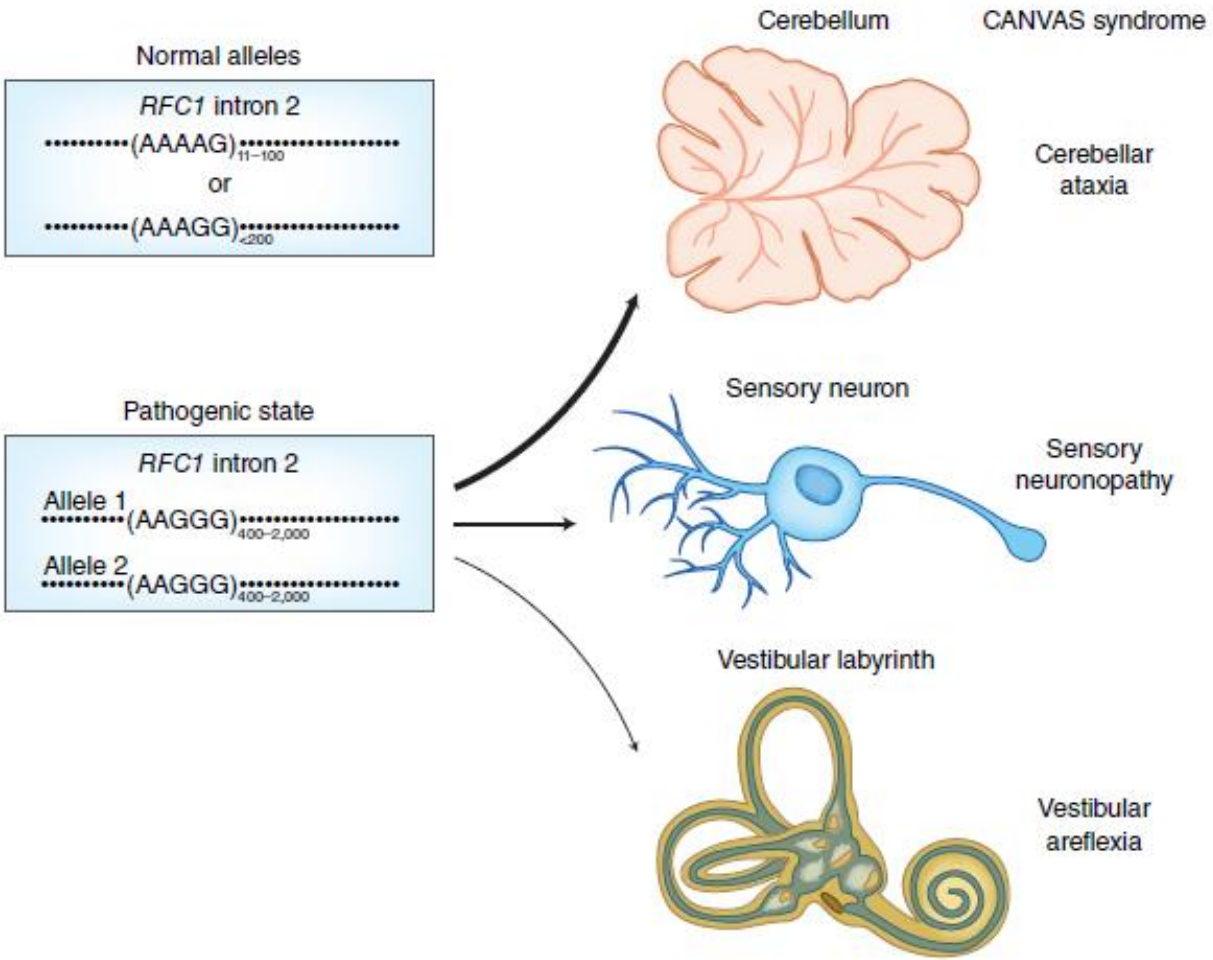
Friedreich ataxia

- Incidence: 1 in 30-50,000
- Neurological features Cerebellar (100%)
- Sensory loss (~80%): Especially vibration & joint position
- Tendon reflexes: Absent (75%) or reduced
- **Corticospinal tract signs and spasticity in late-onset FA**
- Motor Weakness (67% to 88%)
- Optic atrophy (30%): May be no visual impairment
- Hearing loss: Sensorineural (20%)
- Scoliosis, cardiomyopathy and diabetes mellitus

Source: FARA



RFC1-related Ataxia



Nature Genetics. 2019 Apr;51(4):580-581

When to suspect RFC1 associated ataxia

- Ask for chronic or familial unexplained cough
- Late onset slowly progressive ataxia

Case 1 follow up

- Late onset recessive pedigree
- Biallelic pathogenic expansions in RFC1 consistent with RFC1-related ataxia

- Allelic frequency of 0.7% for the expanded AAGGG sequence in the European population.
- In a small cohort of late onset ataxia:
- 22% had homozygous expansions at the RFC1 locus
- 62% with sensory neuronopathy
- 92% in individuals exhibiting all three core features of CANVAS

Cortese et al. Nature Genetics **volume 51**, pages649–658 (2019)

Exome sequencing

- SPG7
- ARSACS

- Both are recessive spastic ataxias with variable other neurological signs.

Management

- Symptomatic
- Spasticity
- Parkinsonism may be levodopa responsive
- Physical therapy

Treatment

- Pyruvate dehydrogenase deficiency: ketogenic diet.
- Maple syrup urine disease: thiamine and dietary modifications to exclude branched-chain amino acids.
- Refsum disease: Phytanic acid restriction
- Urea cycle disorders: Diet modification

Treatment

- Cerebellitis: Steroids may hasten recovery.
- Abetalipoproteinemia and hypobetalipoproteinemia are treated with vitamin E.
- Biotinidase deficiency is treated with biotin supplementation
- Cerebrotendinous xanthomatosis responds to chenodeoxycholic acid.
- Coenzyme Q10 deficiency is treated with coenzyme Q10 supplementation
- Hartnup disease may receive nicotinamide.

Physical therapy

Table 1: Overview of high-intensity training studies in degenerative ataxia.

	Physiotherapy combined with occupational therapy [36]	Coordinative Physiotherapy [34, 35]	Exergames training [43]
Number of patients	42	16	10
Type of disease	SCA6 (20), ADCA (6), and IDCA (16)	SCA6 (2), SCA2 (1), ADCA (1), IDCA (6), FRDA (3), SANDO (2),and SN (1)	FRDA (4), arCA (3), AOA2 (1), and ADCA (2)
Age ± SD (range)	62.5 ± 8.0 (range: 40–82)	61.4 ± 11.2 (range: 44–79)	15.4 ± 3.5 (range: 11–20)
Gender	22 males, 20 females	8 males, 8 females	5 males, 5 females
Duration of disease	9.8 ± 6.2 (7 months–30 years)	12.9 ± 7.8 (3–25 years)	
Baseline SARA	11.3 ± 3.8 (5–21.5)	15.8 ± 4.3 (11–24)	10.9 ± 2.3 (7–13.5)
Control	Crossover for short-term effect	Intraindividual controls for short-term effect	Intraindividual controls
Evidence class	Class Ib	Class III evidence	Class III evidence
Intervention	2 hours × 5 days + 1 hour × 2 days per week for 4 weeks	1 hour, 3 days per week for 4 weeks	1 hr × 4 per week for 2 weeks at lab; variable frequency at subjects' own motivation for 6 weeks at home
After training	No	Home-training protocols	No
Outcome measures	SARA, FIM, gait speed, cadence, FAC, and falls	SARA, gait speed, balance, BBS, GAS, and movement analysis	SARA, balance, ABC scale, DGI scale, GAS, and movement analysis
Assessment point	Baseline, post 0, 4, 12, and 24 weeks	4 weeks pre, baseline, and post 0, 8 weeks	2 weeks pre, baseline, and post 0
Main results	SARA and gait improved 12 wks but not 24 wks	SARA and gait improved 8 wks after rehabilitation only in patients with cerebellar ataxia not afferent ataxia	SARA and gait improved directly post rehabilitation; improvement correlated with individual's training intensity at home

SCA: spinocerebellar ataxia; FRDA: Friedreich's ataxia; IDCA: idiopathic cerebellar ataxia; ADCA: autosomal dominant cerebellar ataxia of unknown type; SANDO: sensory ataxic neuropathy with dysarthria and ophthalmoparesis caused by mutations in the polymerase gamma gene; SN: sensory neuropathy with cerebellar degeneration; arCA: autosomal recessive cerebellar ataxia of unknown type; AOA2: ataxia with oculomotor apraxia type 2; SARA: scale for the assessment and rating of ataxia; ABC: activity-specific balance confidence scale; BBS: Berg balance score; GAS: goal attainment scaling [42]; DGI: dynamic Gait index; FIM: functional independence measure [38]; and FAC: functional ambulation categories. Evidence was graded according to the Oxford Center for Evidence Based Medicine (CEBM) classification. This table presents details of the first three clinical studies of motor rehabilitation in larger cohorts in degenerative spinocerebellar disease [34–36, 43].

Review Article

Motor Training in Degenerative Spinocerebellar Disease: Ataxia-Specific Improvements by Intensive Physiotherapy and Exergames

Matthis Synofzik[1,2] and Winfried Ilg[3,4]

Acknowledgements

Ataxia Clinic (UM)

Neurologists:	Peter Todd
	Henry Paulson
Speech Pathology:	Karen Kluin
Social Work:	Selina Quintana, Maneesha Finkle
Physical Therapy:	Liz Schaar, Eitan Daniel, Fritzie
	Funni, Jeanna Welch, Karissa Aktakka
Nursing:	Toni Muirhead

Ataxia Clinic (UTSW)

Neurologists:	Director of Ataxia Clinic: Vikram Shakkottai,
	Movement Disorders: Shilpa Chitnis, Padraig O'Suilleabhain
	Pediatrics: Peter Tsai,
	MSA: Steve Vernino
Physical Therapy:	Egle Bauzaite, Jeanne Vinson, (PM&R) Staci Shearin (School of Allied Health)
Nursing (Movement d/o):	Felicia Berno, Janet Liebman