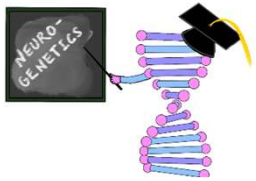
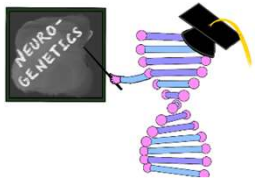
Movement 3:
Ataxia and Cerebellar Disorders

MODULE 7



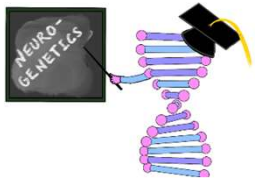
Learning Objectives

- Use the appropriate diagnostic work-up for acquired and treatable causes of chronic progressive ataxias
- Design a testing strategy tailored to the differential diagnosis of a patient presenting with ataxia
- List which ataxias have biochemical markers
- Explain the limitations of exome sequencing in detecting repeat expansion disorders



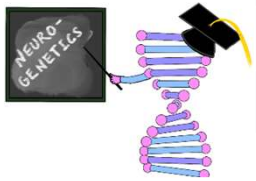
Chief Complaint

- 19-year-old young man with slowly progressive gait unsteadiness starting at age 14



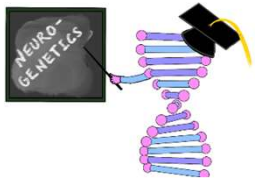
Differential Diagnosis - Interactive

Gene/ Condition	Biochemical Marker	Treatment/ Unique features



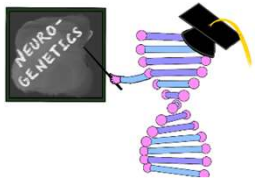
DDx: Chronic/Progressive Ataxias

- Developmental defects/syndromes
- Ataxic cerebral palsy
- Tumors
- Paraneoplastic/autoimmune
- Vitamin deficiencies
- Infectious
- Heavy metal exposure
- Genetic/metabolic



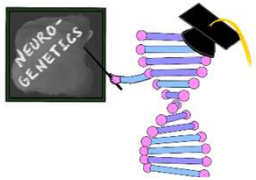
Ataxia

- Inability to generate a normal or expected voluntary movement or trajectory that cannot be attributed to weakness or involuntary muscle action
  - Examples: chorea, dystonia, myoclonus, tremor about the affected joint
- Caused by dysfunction of the cerebellum, proprioception, or vestibular systems



An Approach to Ataxia

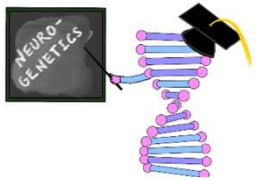
- Careful history of timing of onset and antecedent events are key in framing the differential
- Is this ataxia?
  - Acute, subacute, or insidious/chronic onset?
  - Chronic/progressive course?
  - Episodic?



Differential Diagnosis - Genetic

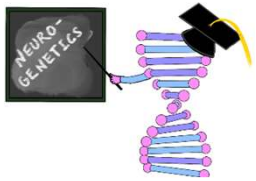
- <u>Disorders with prominent ataxia</u>
  - Leukodystrophies
    - Metachromatic leukodystrophy
  - Mitochondrial disorders
    - Kearns-Sayre
    - MERRF
    - MELAS
  - Niemann-Pick C
  - Wilson disease
  - GLUT1 deficiency
  - Refsum disease

- <u>Primary ataxias</u>
  - Autosomal dominant
    - Repeat expansions
      - SCA1, 2, 3, 6, 7, …
    - Conventional variants
      - SCA29, EA2, …
  - Autosomal recessive
    - Repeat expansions
      - FA
      - CANVAS
    - Conventional variants
      - A-T, AOA1, AOA2, ARSACS, …



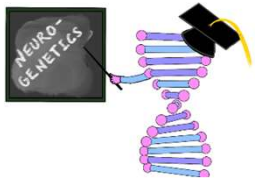
Causes of Ataxia

Disorder	Tests	Treatment options
Vitamin deficiency (B12, B1, folate, E)	Vitamin levels	Supplementation
Coenzyme Q10 deficiency	Measure levels (only accurate in muscle)	Supplementation
Wilson disease	Ceruloplasmin, serum copper, 24-hour urine copper	Dietary copper restriction, chelation
Refsum disease	Phytanic acid (VLCFA)	Diet
Cerebrotendinous xanthomatosis	Cholestanol (sterols)	Chenodeoxycholic acid
GLUT1 deficiency	CSF/serum glucose	Ketogenic diet
Aceruloplasminemia	↑ ferritin, ↓ serum iron and ceruloplasmin, accumulation on SWI	Chelation



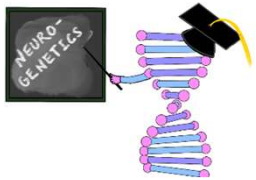
Causes of Ataxia

Disorder	Tests	Treatment options
Abetalipoproteinemia	Acanthocytes on peripheral smear, ↓ cholesterol	High dose vitamin E, dietary changes to LCFA, MCT, EFA
Superficial siderosis	SWI	Remove source of bleeding
Mitochondrial disorders	↑ lactate, alanine/glycine ratio , CSF protein	
Niemann-Pick C	Filipin staining in fibroblasts	Miglustat
Chronic CNS infection: Syphilis, Lyme, Whipple		
Heavy metal exposure		
Autoimmune/ paraneoplastic		



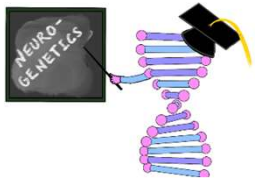
Diagnostic Evaluation for Chronic Progressive Ataxia

- Clinical evaluation
  - Detailed history of symptoms
  - Comprehensive neurological examination
  - Complete family history
  - MRI of brain
- Non-genetic laboratory evaluation
  - Screen for acquired causes of ataxia
  - Test for specific ataxias with serum biomarkers
- Genetic testing



Diagnostic Laboratory Investigations: First Tier

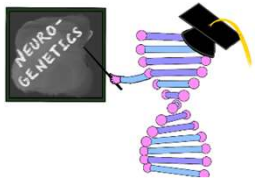
- Common neuro labs
  - CBC
  - CMP
  - TSH, fT4
  - RPR
  - ANA
  - ESR
  - HbA1c
- Metabolic/biochemical
  - Vitamin B12
  - Vitamin B1 (thiamin)
  - Folate
  - Vitamin E
  - Homocysteine
  - MMA
  - Lactate
  - PAA/UOA
  - Copper
  - Ceruloplasmin



Diagnostic Laboratory Investigations: Second Tier

- Common neuro labs
  - Lipid panel
  - SPEP + IFE
  - Lyme
- Metabolic/biochemical
  - Ammonia
  - CK
  - Lysosomal enzymes
  - VLCFA
  - Acylcarnitine profile

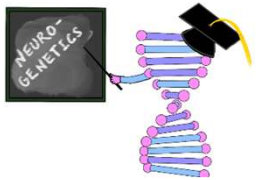
CSF studies



- Urine studies
  - Urine heavy metals
  - UPEP + IFE
- Infectious
  - HTLV I/II
- Immunological studies
  - Paraneoplastic panel
  - Celiac antibodies
  - Thyroid autoantibodies
  - Anti-GAD65
  - SSA/SSB

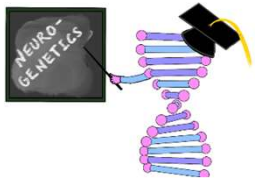
Diagnostic Laboratory Investigations: Other

- Zinc
- Alpha-fetoprotein
- Ferritin
- Coenzyme Q10
- Sterols (cholestanol)
- Lipoprotein electrophoresis
- CDG



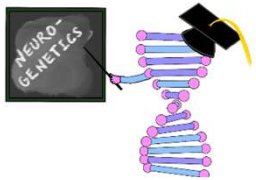
HPI

- Started having balance issues at 14 years of age
- Ataxia has been worsening and has led to recurrent falls
- PT not helping
- Symptoms worse in AM
- Feet can turn inward when walking
- Pt sad/anxious about disability

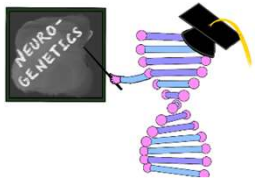


Exam

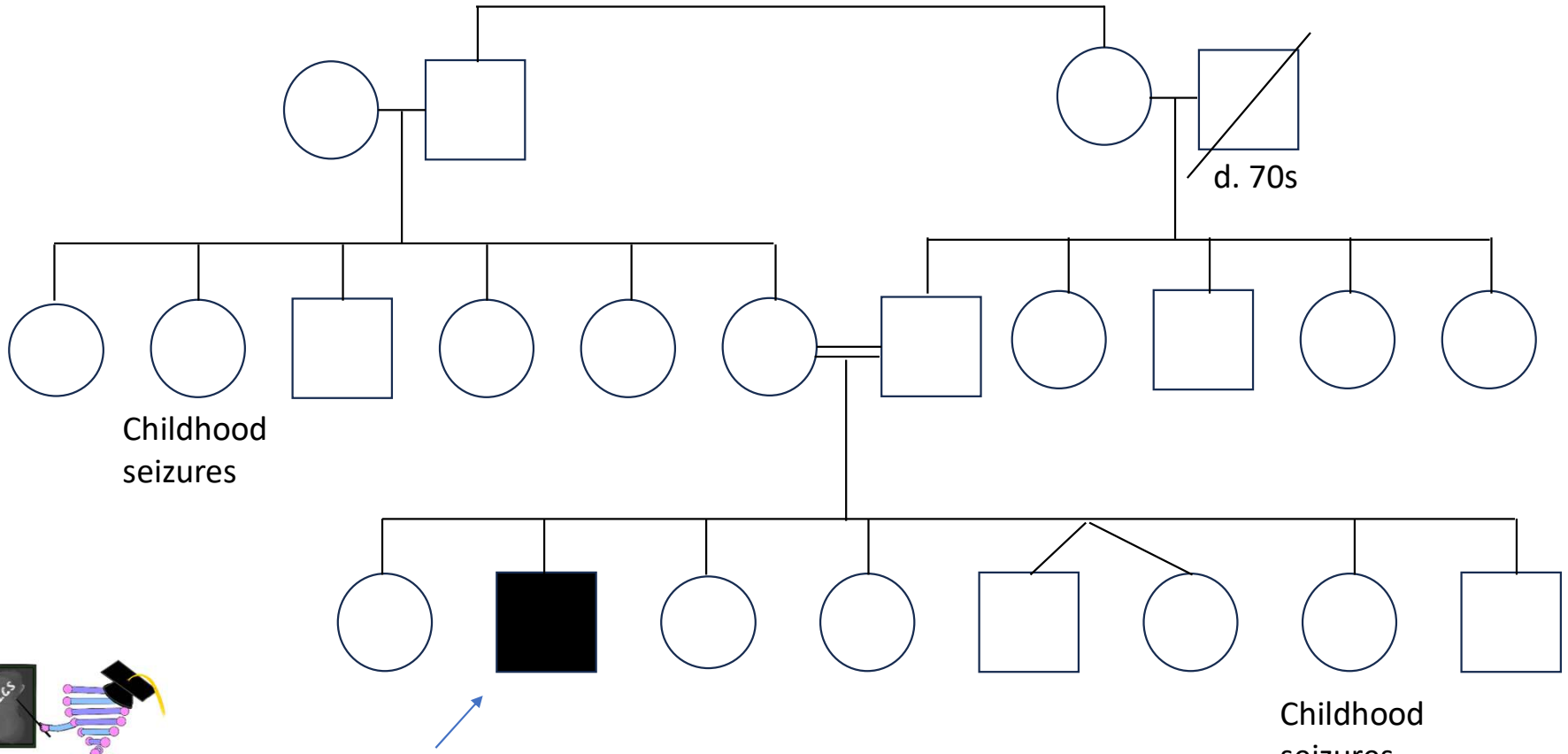
- Normal mental status
- Horizontal and vertical nystagmus, disconjugate gaze, hypermetric saccades
- Mild atrophy in calves, no weakness
- Impaired vibration and proprioception
- Absent reflexes
- Toes mute

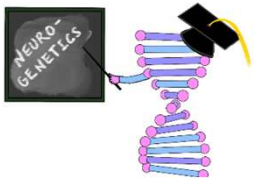


Family History – Interactive: Role Play



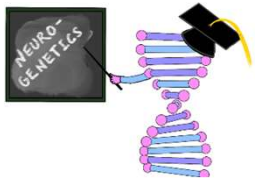
Family History - Interactive



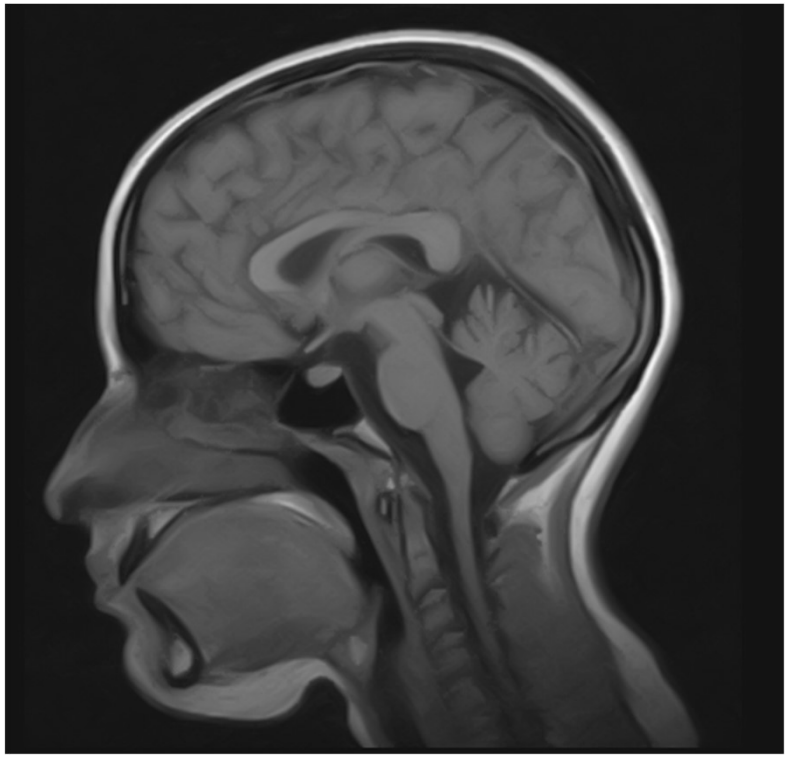


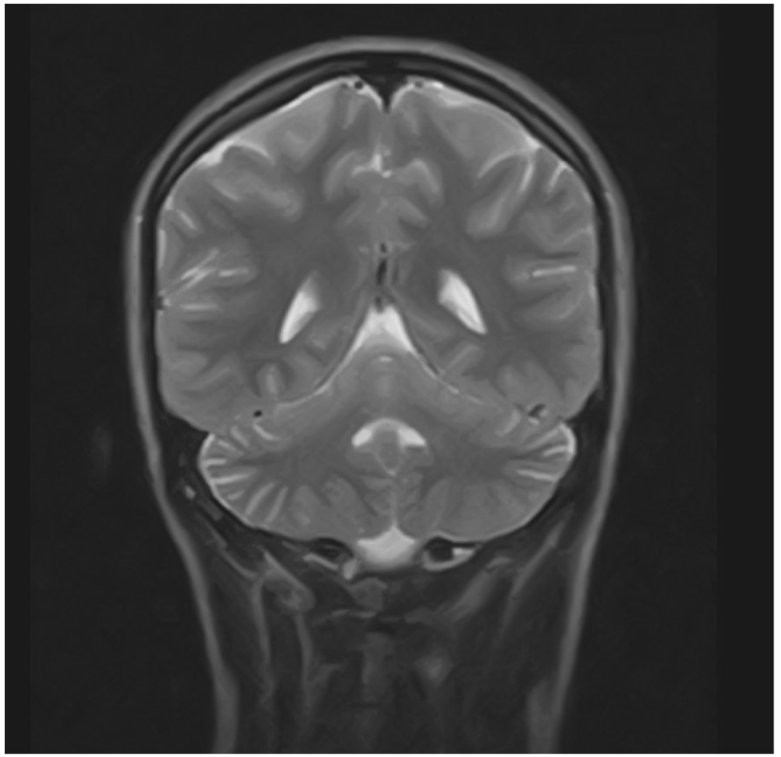
Differential Diagnosis for AR Ataxia with Sensorimotor Neuropathy

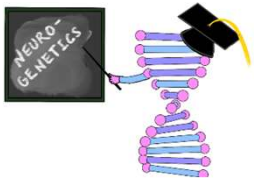
Disorder	Gene
Friedreich ataxia	FXN
Spinocerebellar ataxia with axonal neuropathy-1	TDP1
Ataxia with vitamin E deficiency	TTPA
Ataxia with oculomotor apraxia type 1	APTX
Ataxia with oculomotor apraxia type 2	SETX
Coenzyme Q10 deficiency	ADCK
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	SACS



Brain MRI







Nerve Conduction Studies

Sensory NCS

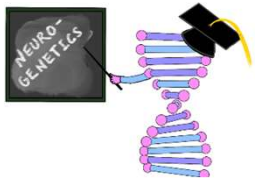
Nerve / Sites	Rec. Site	Latency ms	Ampl µV	Distance cm	Velocity m/s
R Median					
Dig II	Wrist	NR	NR	12	NR
Mid palm	Wrist	NR	NR	6	NR
				6	NR
R Ulnar					
Dig V	Wrist	NR	NR	10	NR
R Radial					
Forearm	Wrist	NR	NR	11	NR
R Sural					
Calf	Lat Mall	NR	NR	11	NR

Motor NCS

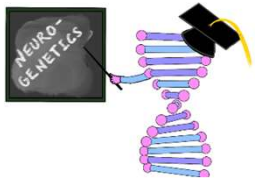
Nerve / Sites	Muscle	Lat ms	Amp mV	Rel Amp %	Dist cm	Vel m/s	Area mVms	Rel Area %	Dur ms	Rel Dur %
R Median - APB										
Wrist	APB	2.4	11.0	100			36.2	100	6.3	100
Elbow	APB	6.8	10.1	91.4	24	56	34.2	94.4	7.0	112
R Peroneal - EDB										
Ankle	EDB	3.2	3.1	100			9.7	100	5.5	100
B Fib Head	EDB	12.3	2.3	73.2	31	34	5.8	59.8	5.7	103

F Wave

Nerve	F Lat ms
R Peroneal - EDB	47.9
R Median - APB	24.8

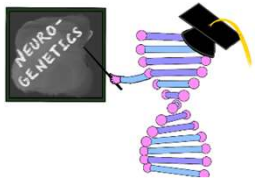


Case Summary (Interactive)



Investigations (Metabolic)

- CBC, CMP
- Vit E, AFP, CK, lipid panel, CoQ10
- Lactate, PAA, UOA
- Frataxin level



Investigations (Metabolic)

- CBC, CMP
- Vit E, AFP, CK, lipid panel, CoQ10
- Lactate, PAA, UOA
- Frataxin level

Frataxin, Quant, WB

Reason for Referral MGR

Not provided

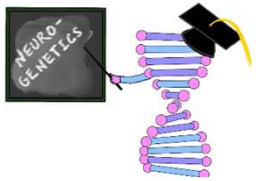
Frataxin MGR

⚠ 8 ng/mL

Low

Reference Value

≥21



Investigations (Genomic)

note, this assay cannot rule out the possibility of larger repeat sizes in other tissues, such as the central nervous system, due to somatic mosaicism.

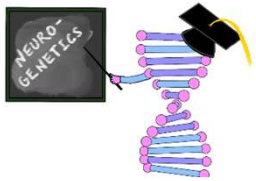
As full penetrance alleles were detected in this individual, genetic testing of at risk family members could be considered. If appropriate, genetic testing should be offered to this individual's reproductive partner to further clarify the risk of having a child affected with FA.

A genetic consultation may be of benefit.

variants (eg, sequence variants, deletions, and duplications).

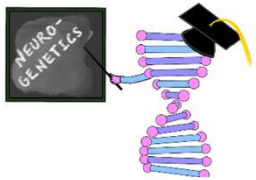
It is strongly recommended that patients undergoing genetic testing receive genetic counseling.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data, such as frataxin concentrations (see FFRWB / Friedreich Ataxia, Frataxin, Quantitative, Blood and FFRBS / Friedreich Ataxia, Frataxin, Quantitative, Blood Spot). Errors in test interpretation may occur if the provided information is inaccurate or incomplete.



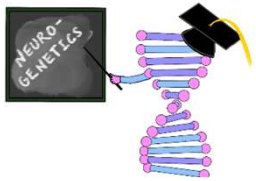
Exercise: Genetic Testing

1. What is the name of the condition caused by pathogenic changes in this gene? What is the mode of inheritance?
2. What testing would you have sent if the frataxin level had been normal?
3. What testing would you consider if this could have been *de novo* or if there had been an AD pattern of inheritance?
4. What commercially-available gene panels would catch trinucleotide repeats in *FXN*?



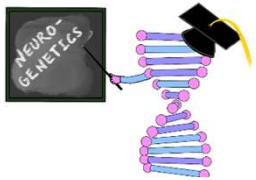
Frataxin and *FXN*

- Expressed in tissues with high metabolic rate
- Involved in the assembly of iron-sulfur complexes in mitochondria
- 98% of patients with biallelic expanded GAA repeats in intron 1 of *FXN*



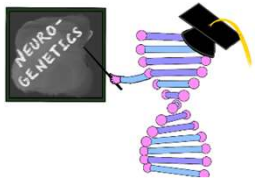
What if the Frataxin Level Had Been Normal?

- Options for further testing:
  - Exome sequencing
  - Complete (AR and AD) ataxia panel

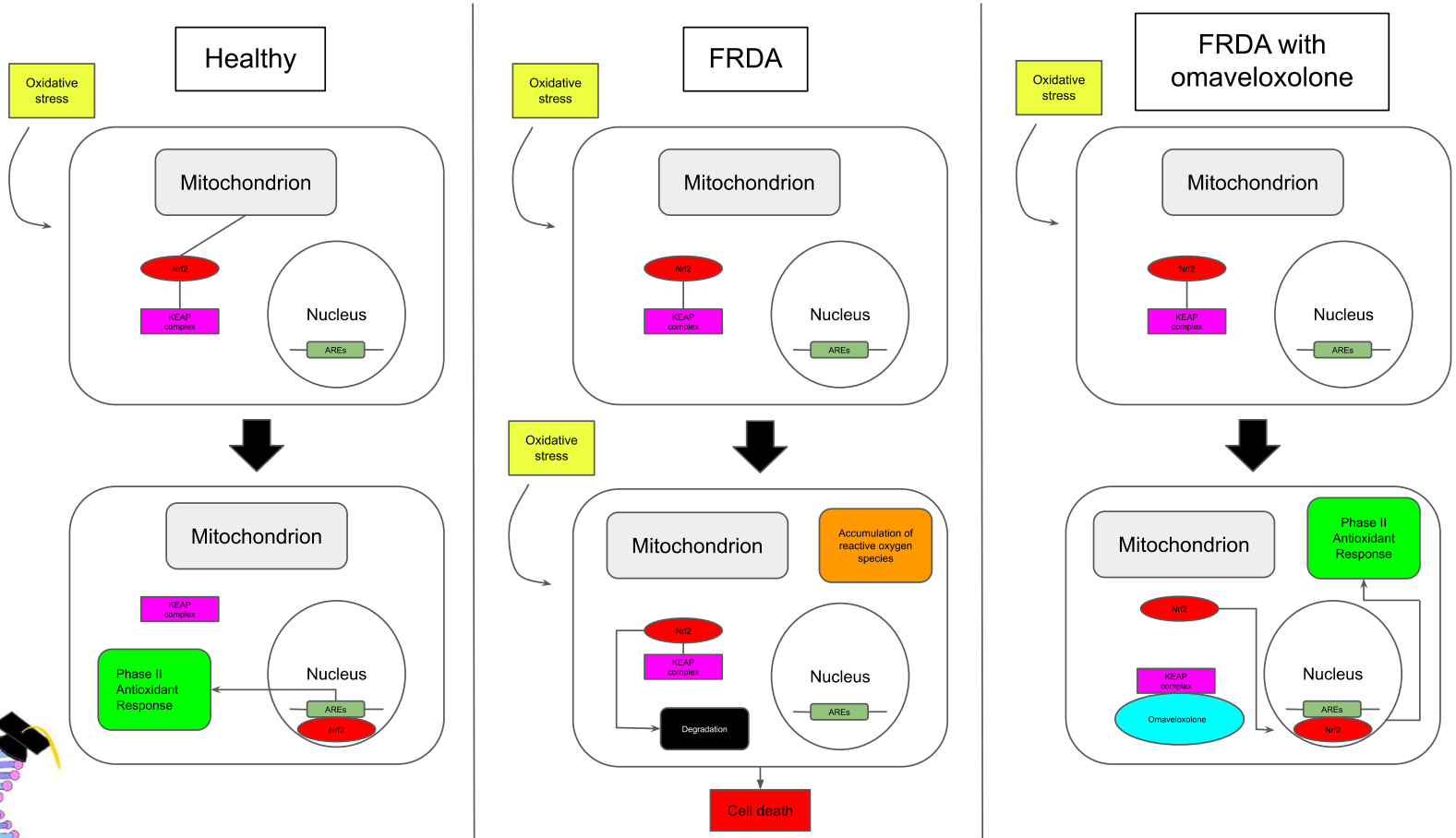


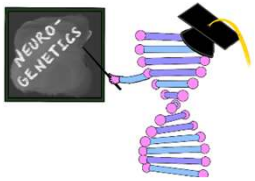
Friedreich Ataxia

- Most common AR ataxia
- Onset typically by age 25 (mean 10-15 years)
- Typically associated with dysarthria, muscle weakness, spasticity, scoliosis, loss of reflexes, loss of proprioception and vibratory sense
- 2/3rd with cardiomyopathy
- 30% with Diabetes Mellitus (DM)
- Recent FDA approval of omaveloxolone



Omaveloxolone

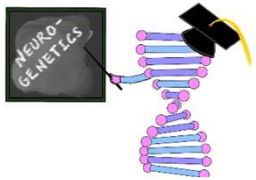




https://www.gimopen.org/article/S2949-7744(23)00841-5/fulltext

Suggested Reading

- Curefa.org
- Ataxia.org
- Lynch DR, Chin MP, Delatycki MB, et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study) [published correction appears in Ann Neurol. 2023 Dec;94(6):1190]. *Ann Neurol*. 2021;89(2):212-225. doi:10.1002/ana.25934



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