NARP: BEYOND THE LETTERS

UNDERSTANDING THE GENETICS, RECOGNIZING THE SYMPTOMS & NAVIGATING THE JOURNEY

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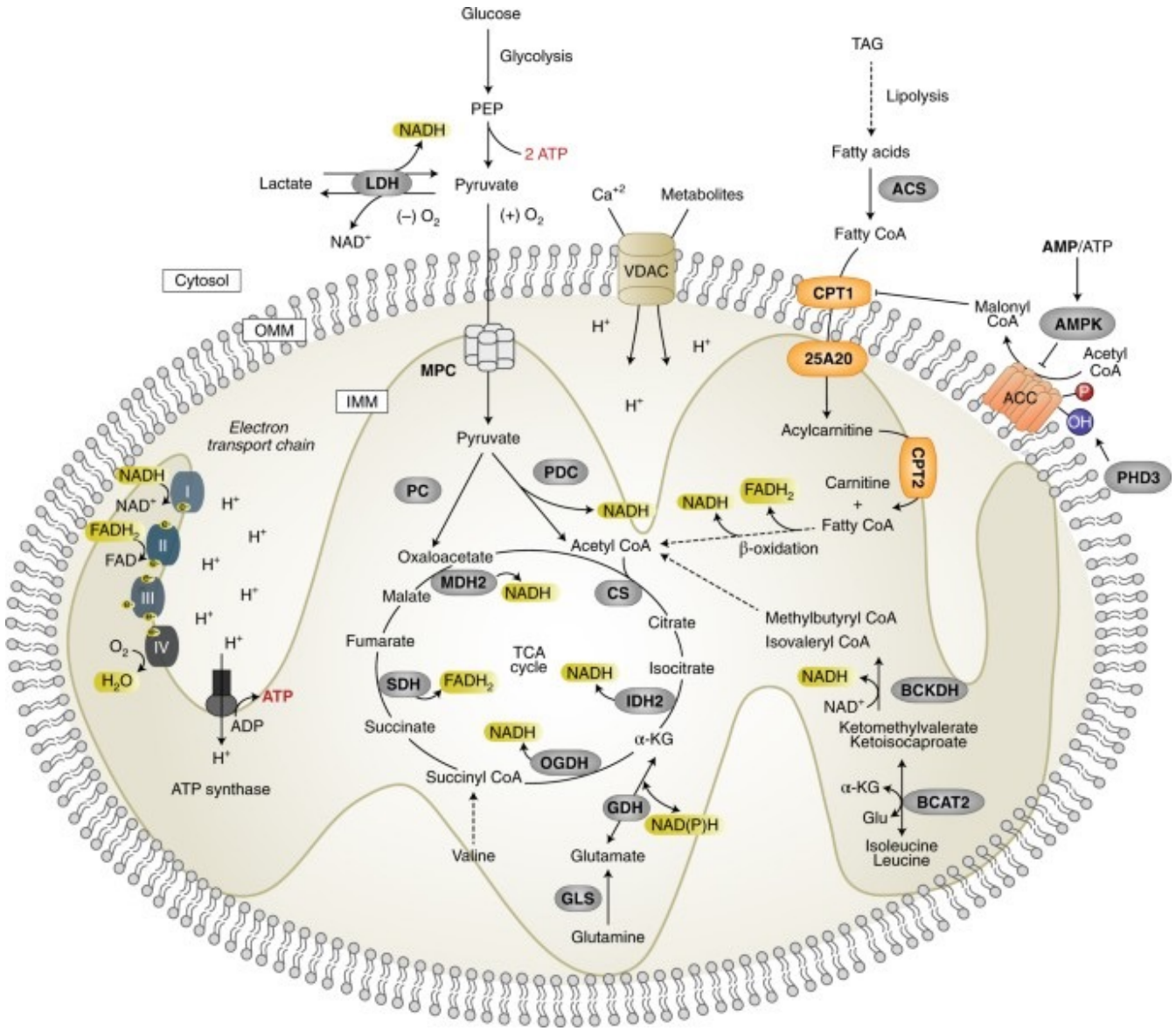
CONFLICTS OF INTEREST

- I have no relevant financial or non-financial disclosures for this lecture.

MITOCHONDRION

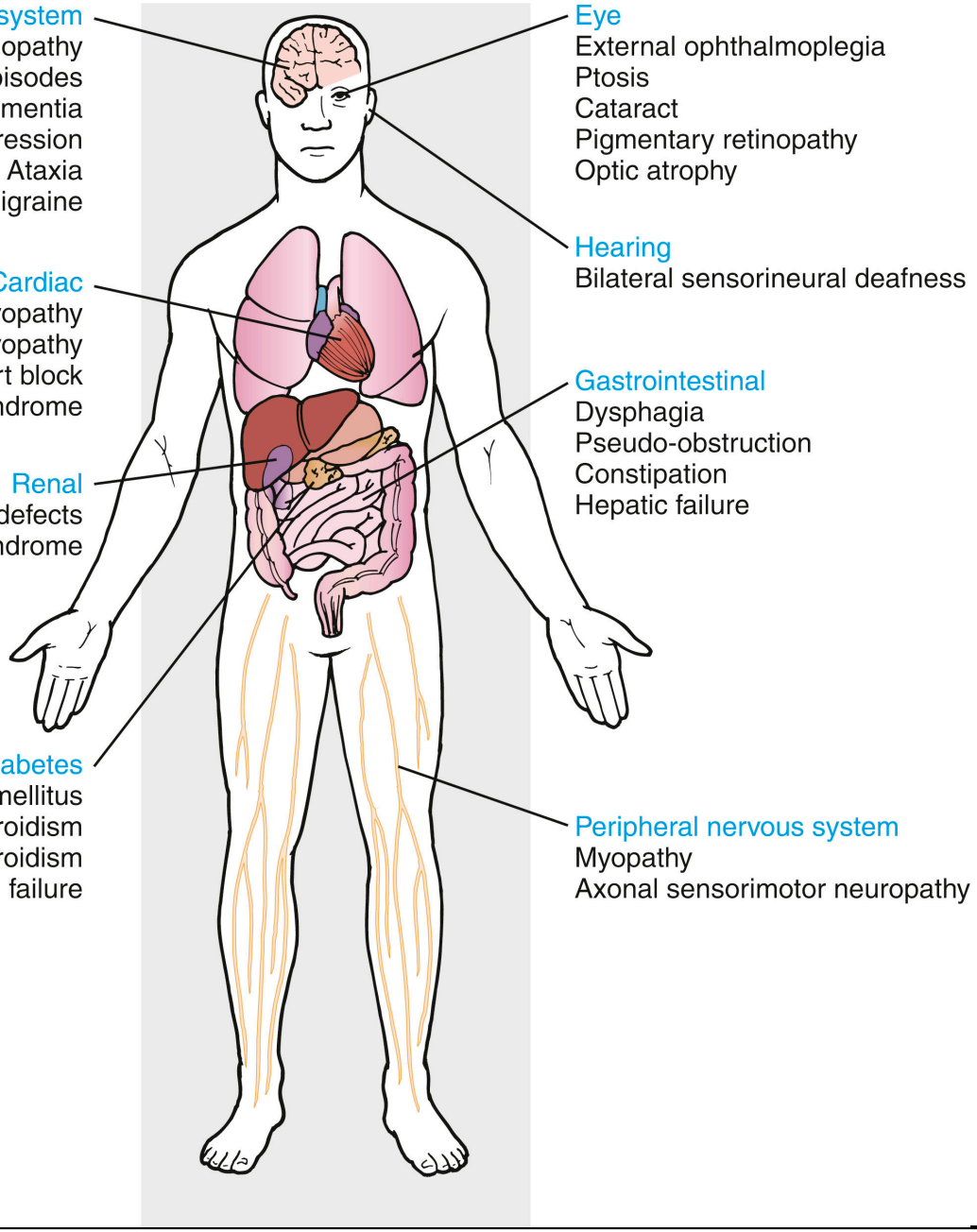
- Membrane-bound cell organelles that generate most of the chemical energy needed to power the cell's biochemical reactions.
- Abundant in places with active processes or those with high energy demands



https://doi.org/10.1038/s41556-018-0124-1

MITOCHONDRIAL DISORDERS

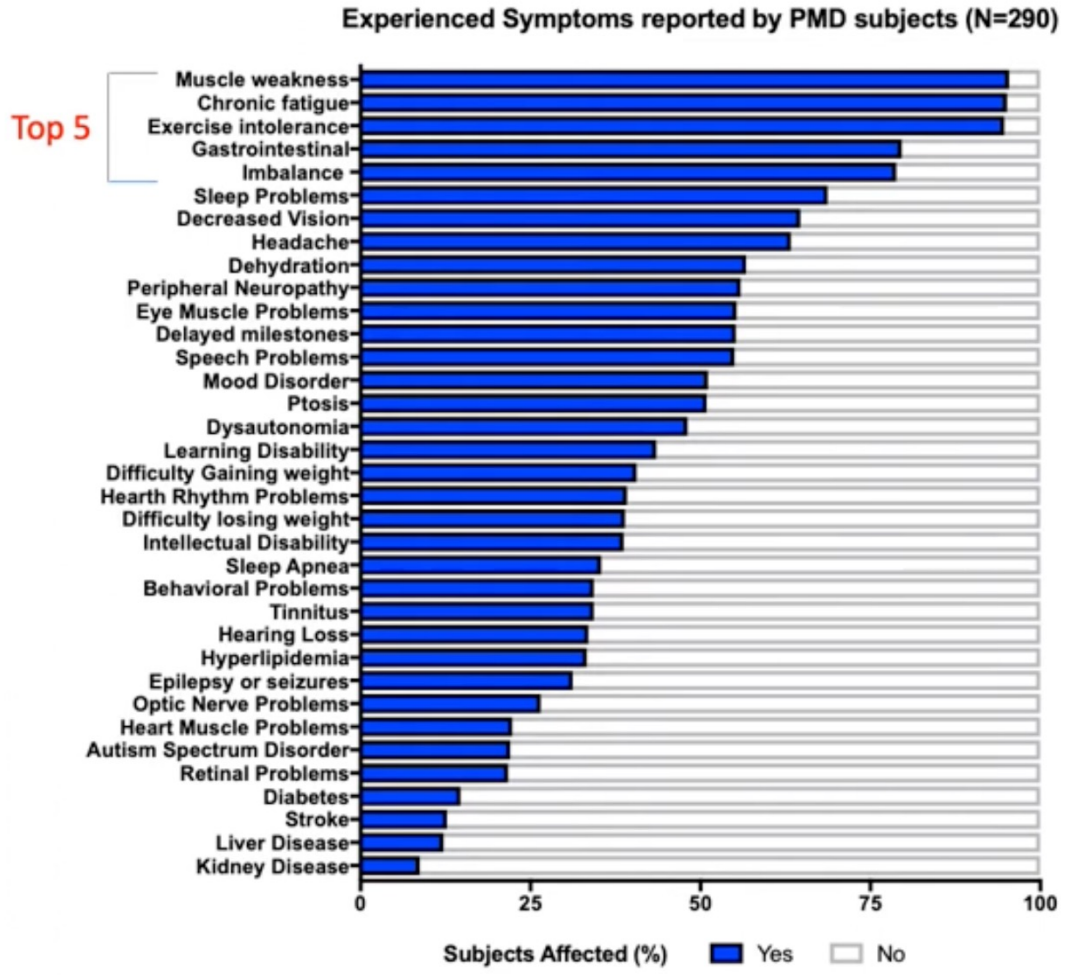
- The mitochondrial respiratory chain is the final common pathway for aerobic metabolism
- Tissues and organs that are highly dependent on aerobic metabolism are preferentially involved in mitochondrial disorders
- "Primary mitochondrial disorders" are known or presumed genetic disorders caused by pathogenic variants in genes coding for the mitochondrial respiratory chain and related proteins.
- Mitochondrial disorders can result from mutations in either mtDNA or nuclear DNA.

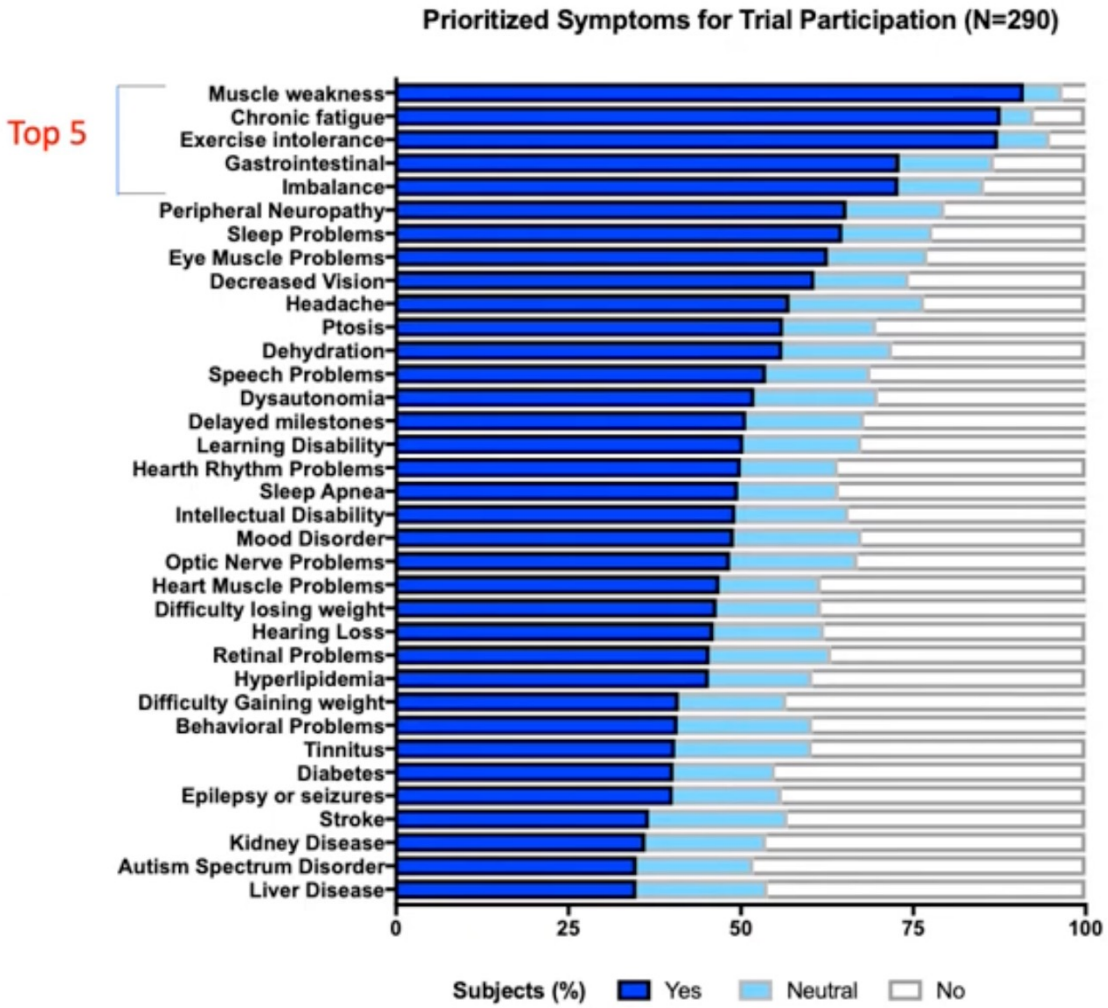


~16 symptoms

Thompson and Thompson Genetics and Genomics in Medicine

Mitochondrial disease patient motivations and barriers to participate in clinical trials





2018 paper by Zolkipli-Cunningham Z, et al.

WHAT IS NARP?

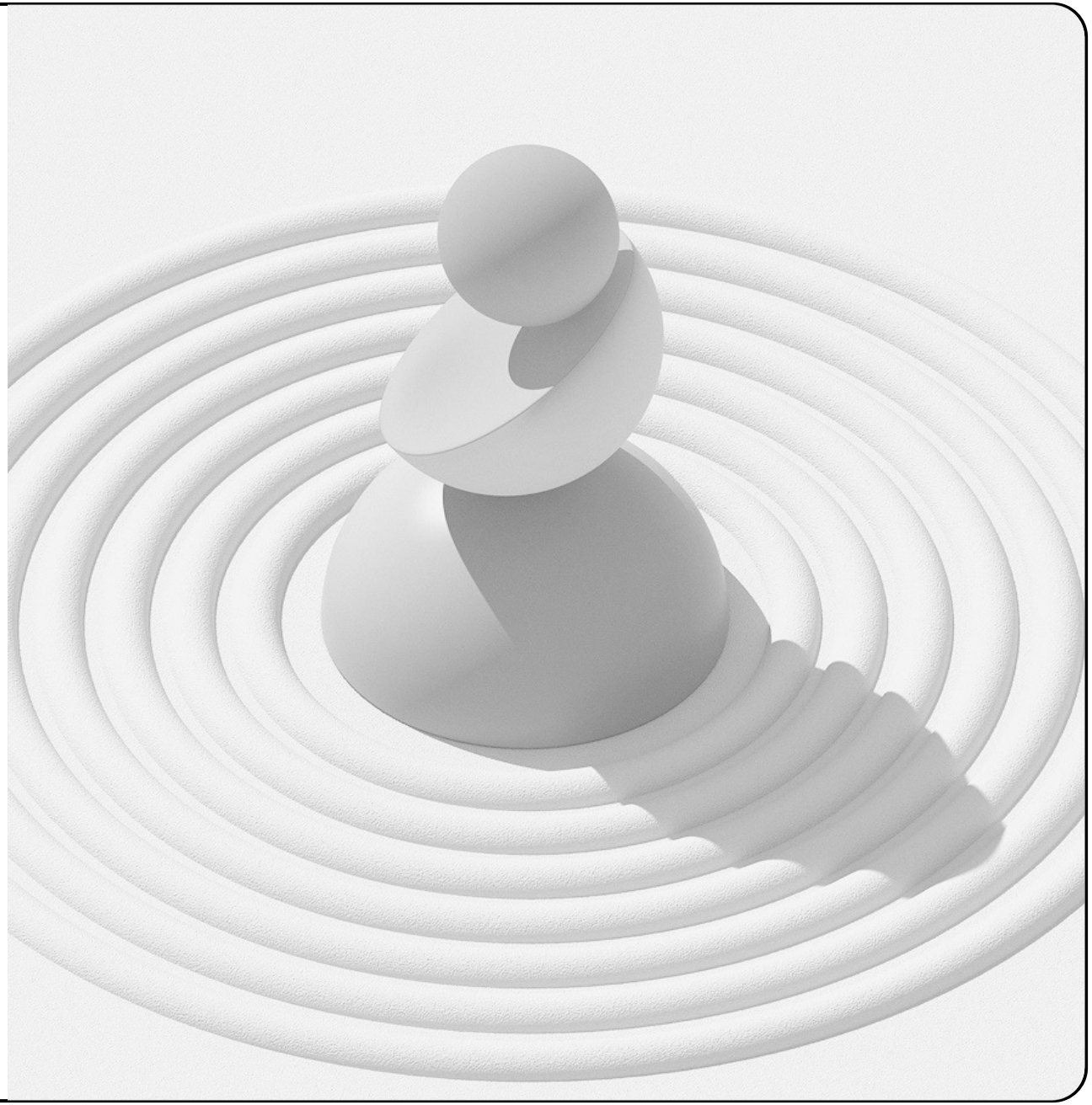
- Neuropathy ataxia and retinitis pigmentosa (NARP) is a rare, maternally-inherited condition caused by mutations in mitochondrial DNA
- The condition typically begins in childhood or early adulthood and presents with a wide range of symptoms.
- These may include learning difficulties, muscle weakness (particularly around the eyes), uncoordinated movements (ataxia), and sensory changes in the hands and feet.
- It is estimated that NARP affects about 1 to 9 people per 100,000.

HISTORY

-NARP was first described in 1990 by Holt and colleagues in a single four-generation family

-Characterized as a variable combination of:

- Developmental delay/regression
- Retinitis pigmentosa
- Dementia
- Seizures
- Ataxia
- Proximal muscle weakness
- Sensory neuropathy



HISTORY

One of the earliest examples of a specific point mutation in mitochondrial DNA being linked to a defined neurological syndrome.

Phenotype has broadened considerably to include cardiomyopathy, renal involvement, and maternally inherited Leigh syndrome (MILS) on the same disease continuum.

Over 300 patients with MT-ATP6 variants have now been reported.

HISTORY OF DIAGNOSIS

Then vs. Now

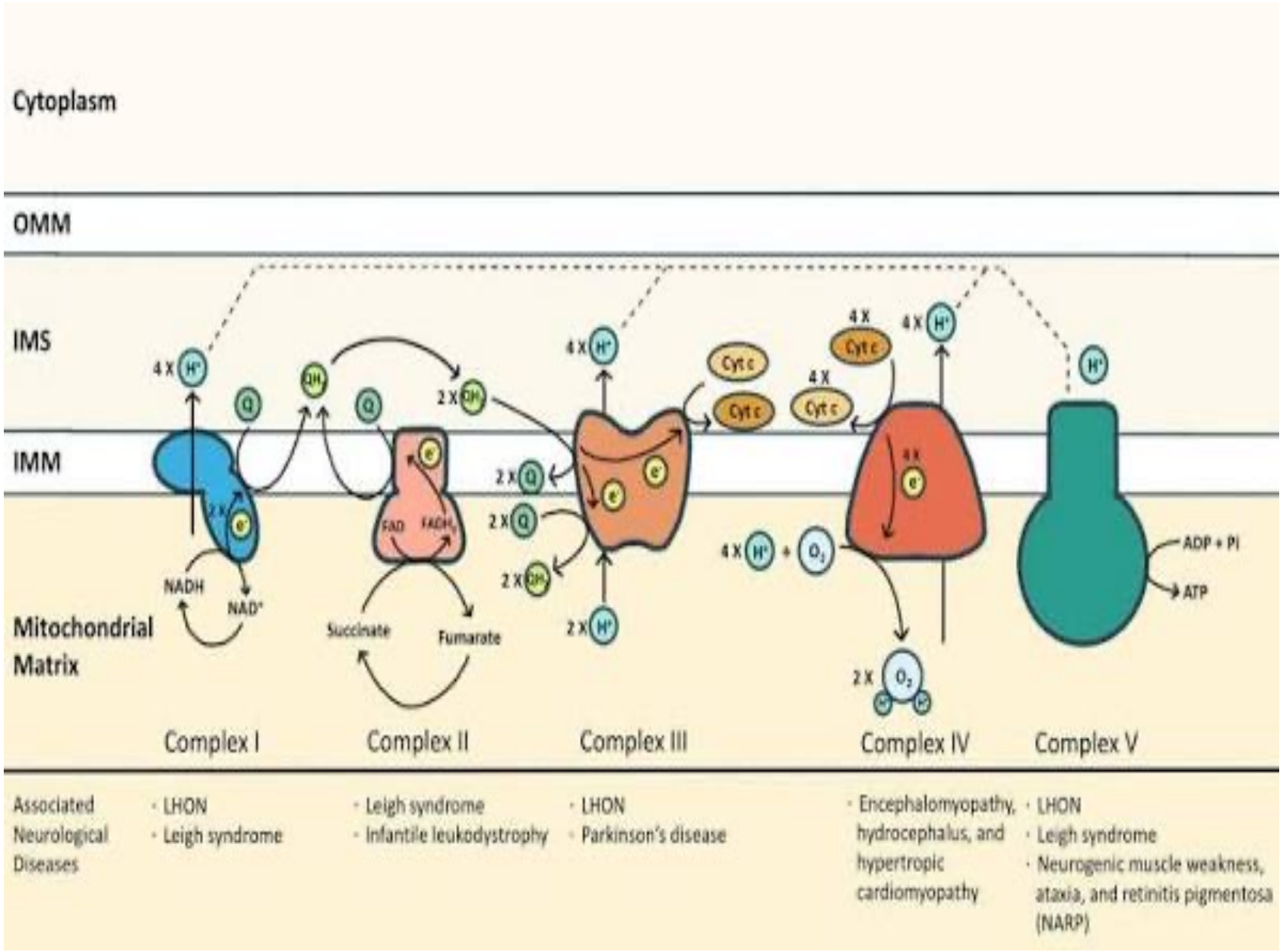
- Originally, a clinical diagnosis was made by recognizing the clinical triad in a maternally inherited family history
- P**lasma lactate is frequently normal and muscle biopsy usually lacks the hallmark findings** (typically does **not** show ragged red fibers)
- This made NARP notoriously difficult to confirm on biochemical grounds.
- Fundoscopy- typically a dilated eye exam confirms retinitis pigmentosa
- MRI brain may show cerebellar/brainstem changes

HISTORY OF DIAGNOSIS

- **Today**, diagnosis is molecular
  - **Mitochondrial DNA analysis by next-generation sequencing**
    - identifies the causative variant and quantifies heteroplasmy across tissues (blood, muscle, skin biopsy)
    - Targeted point-mutation assays or broader mtDNA/nuclear panels are standard.

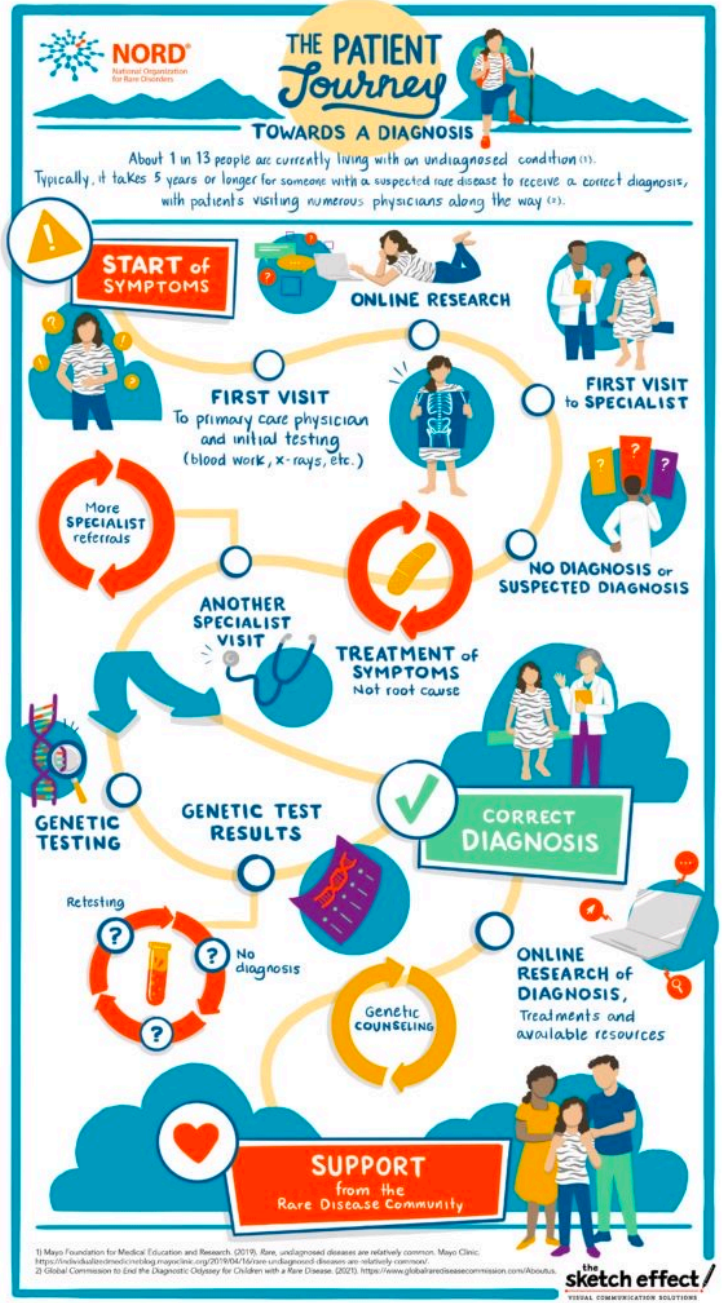
GENES ASSOCIATED WITH NARP

- **MT-ATP6 is the single causative gene**, located in mitochondrial DNA, encoding subunit 6 of ATP synthase: the enzyme responsible for the final step of ATP (energy) production.
- **m.8993T→G** is the most common mutation
- **m.8993T→C** produces a generally milder phenotype but a higher frequency of ataxia.
- The related gene **MT-ATP8** causes a related phenotype with cardiomyopathy, diabetes, encephalopathy, neuropathy, and ophthalmoplegia.



https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2021.797833/full

WHY DO GENETIC TESTING?



WHAT ARE THE BENEFITS OF GENETIC TESTING?

Ends the diagnostic odyssey, avoiding unnecessary invasive testing

Provides prognostic information via heteroplasmy quantification — heteroplasmy of ~70–90% typically produces NARP, whereas >90% tends to cause the far more severe maternally inherited Leigh syndrome.

Enables genetic counseling and reproductive planning given maternal inheritance

Facilitates anticipatory, organ-specific surveillance and access to trials/therapies by defining the precise genotype.

SYMPTOMS OF NARP

Primary features:

1. Late-childhood or adult-onset peripheral neuropathy
2. Ataxia
3. Pigmentary retinopathy

The clinical triad of neuropathy, ataxia, and retinitis pigmentosa can occur without being NARP.

NARP is a specific molecular diagnosis (MT-ATP6), and the phenotype overlaps with several other disorders

VISION ABNORMALITIES

Vision may get worse over time.

This might include:

- Tiny dark and light spots in the retina ("salt and pepper" appearance)
- Retinitis pigmentosa – vision loss that starts with night or side vision
- Uncontrolled eye movements (nystagmus)
- Weak or stiff eye muscles (ophthalmoplegia)
- Trouble seeing in the dark (night blindness)
- Blind spots or tunnel vision.

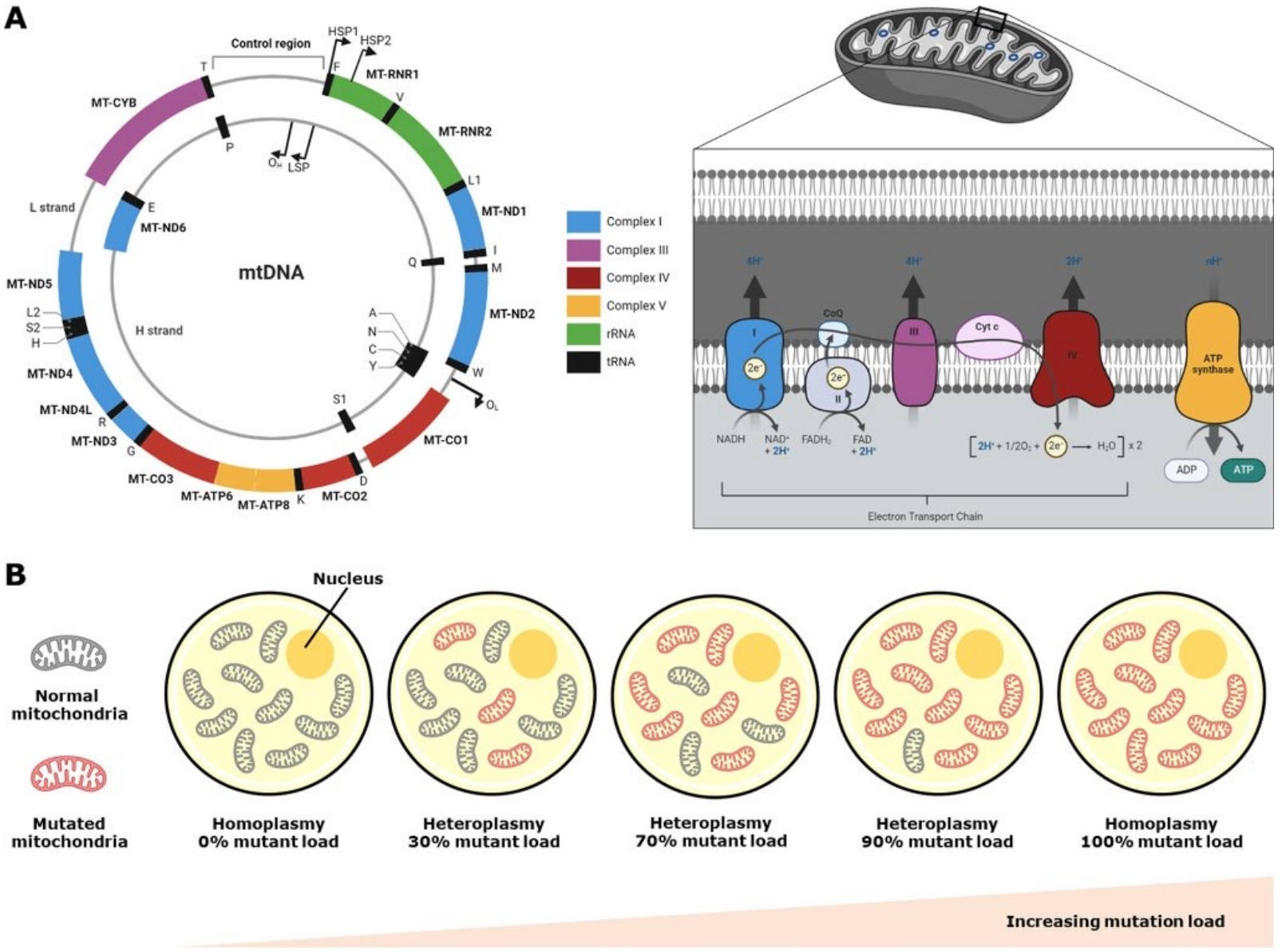
VARIABILITY AMONG PATIENTS

- Variability is a defining feature, driven largely by **heteroplasmy (mutant mtDNA load) and its distribution across tissues**, plus the specific variant.
- **Severity spectrum**: higher heteroplasmy (>90%) shifts the phenotype toward severe infantile maternally inherited Leigh syndrome; ~70–90% typically produces NARP.
- **Age of onset ranges from birth to late adulthood** (average ~8 years, but as late as the 50s), and onset subgroups (infantile, pediatric, late) carry different courses.

VARIABILITY AMONG PATIENTS

- Which organs are affected and the severity varies significantly— even within the same family
- **Variant matters**: m.8993T→C tends to be milder but more ataxia-predominant; some variants present as near-pure neuropathy.

Heteroplasmy



https://www.nature.com/articles/s41433-023-02523-x

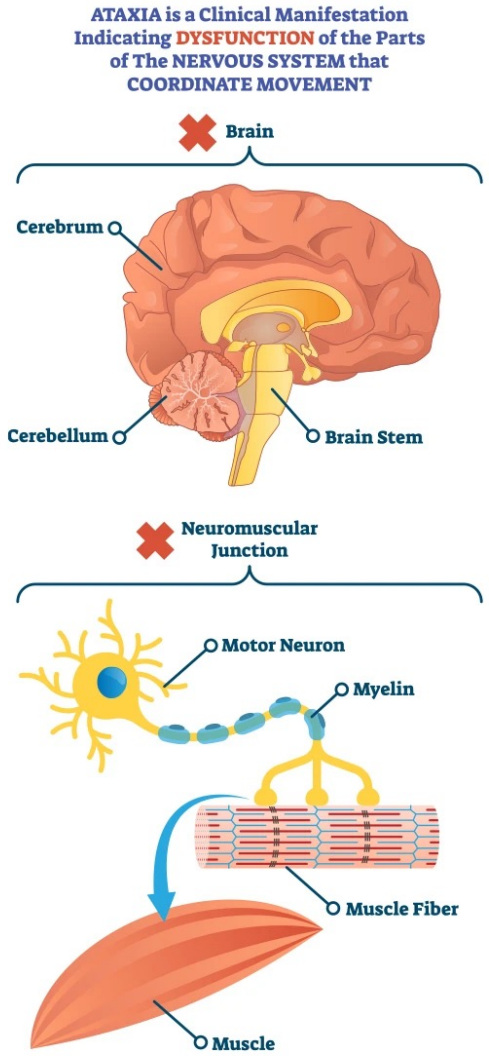
WHAT ABOUT COGNITIVE FUNCTION?

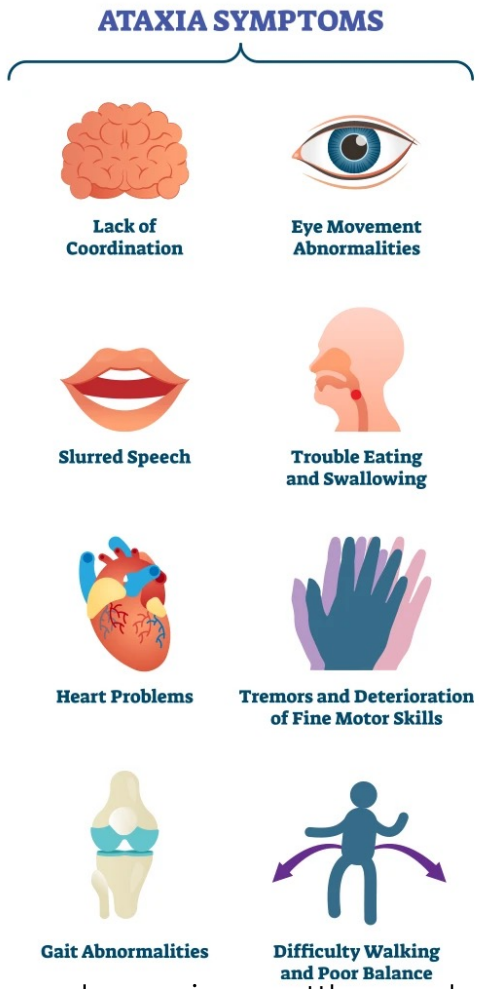
- Cognitive impairment and developmental delay are common in children, and older individuals may experience loss of intellectual function (dementia).
- On imaging, MT-ATP6 disease commonly shows cerebellar atrophy, along with Leigh-like basal ganglia, cortical atrophy, and white matter changes
- In the largest natural-history cohort, 91% of patients imaged had brain MRI abnormalities.

ATAXIA

- Ataxia is a neurological disorder that affects coordination, balance, and speech.
- The term “ataxia” comes from the Greek words “a-” meaning “without” and “taxia” meaning “order.”
- This condition indicates a disruption in the body’s ability to coordinate voluntary movements.
- Ataxia is a symptom rather than a specific disease and can result from various underlying conditions affecting the cerebellum or other parts of the nervous system.

ATAXIA

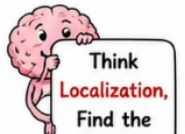




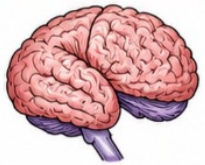
https://www.visionexercisephysiology.com.au/cerebellar-ataxia-and-exercise-matthew-osborn-aep/

MedicoNotes

7 Causes of ATAXIA



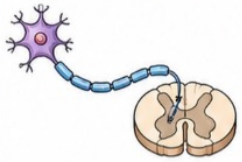
1 CEREBELLAR ATAXIA



- Lesion in cerebellum or its pathways
- Cerebellitis, stroke, tumor, degenerations

Pearl: Dysmetria, intention tremor, nystagmus, scanning speech

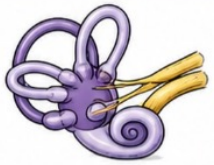
2 SENSORY ATAXIA



- Loss of proprioception, vibration, position sense
- B12 deficiency, tabes dorsalis, neuropathy

Pearl: Positive Romberg (sign), worse in dark, stamping gait

3 VESTIBULAR ATAXIA



- Lesion in vestibular system (peripheral)
- Labyrinthitis, vestibular neuritis, Meniere's

Pearl: Vertigo, nausea, nystagmus, imbalance worse with head movement

4 ALCOHOL ATAXIA

- Chronic alcohol toxicity → cerebellar degeneration
- Thiamine deficiency common

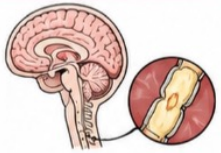
Pearl: History of chronic alcohol use, nutritional deficiency, wide-based gait

5 VITAMIN B12 DEFICIENCY ATAXIA

- Subacute combined degeneration of spinal cord
- Demyelination of dorsal columns & corticospinal tracts

Pearl: Anemia, paresthesia, loss of vibration sense, positive Romberg

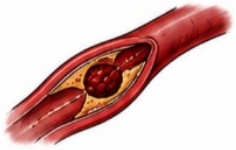
6 MULTIPLE SCLEROSIS ATAXIA



- Demyelinating plaques in cerebellum or pathways
- Young adults, relapsing neurological deficits

Pearl: Other neuro signs present – optic neuritis, spasticity, diplopia

7 CEREBROVASCULAR (STROKE)



- Infarct/hemorrhage in cerebellum or brainstem
- Sudden onset ataxia with other focal signs

Pearl: Acute onset, headache, vomiting, cranial nerve signs

CLINICAL APPROACH TO ATAXIA

1. **HISTORY** — Onset, duration, substance use, vitamin deficiency, family history
2. **EXAMINATION** — Gait, coordination, Romberg test, nystagmus, tone, sensory system
3. **LOCALIZATION** — Cerebellar? Sensory? Vestibular? Mixed?
4. **INVESTIGATIONS** — B12 levels, MRI brain, vestibular tests, others as indicated

PEARL

ATAXIA is a SIGN, not a disease.
Localize the lesion, look for associated signs, and then find the cause!

ATAXIA MNEMONIC

A	T	A	X	I	A
Alcohol	Trauma/ Toxin	Autoimmune (MS)	eXtra-cerebellar (stroke)	Infection	Atrophic/ B12 deficiency

IMPORTANT THINGS TO CONSIDER

Features to consider in Ataxia: Age of onset, tempo, and family history

- Onset before ~25 years or affected siblings suggests recessive disease
- An affected parent suggests dominant disease
- Maternal inheritance raises mitochondrial or X-linked causes

DIAGNOSTIC APPROACH

- Evaluation proceeds by first excluding acquired and treatable causes
- Imaging: MRI
- Biochemical markers (vitamin E, lactate)
- Family history to focus genetic testing

WHAT ATAXIA LOOKS LIKE IN NARP

Ataxia in NARP has both **cerebellar (central) and sensory (peripheral) components:**

Because the cerebellum coordinates movement throughout the body, ataxia can affect:

- **Gait and balance** — unsteady wide-based walking, truncal swaying, frequent falls.
- **Limbs** — dysmetria (over/undershooting), incoordination of fine hand movements, tremor.
- **Eyes** — nystagmus and abnormal eye movements.
- **Speech** — ataxic dysarthria (slow, imprecise, scanning speech).
- **Swallowing**

WHAT HELPS ATAXIA IN NARP?

No treatment reverses the underlying ataxia, so management is supportive and symptom-directed:

- **Physical therapy and balance/gait rehabilitation**, and **occupational therapy**, with assistive devices as needed.
- **Speech-language therapy** for ataxic dysarthria and for swallowing assessment/strategies; behavioral swallowing interventions are used for ataxic dysphagia.
- **Exercise/resistance training**, which has increased muscle strength in some mtDNA myopathies and is generally encouraged for its broad health benefits with little evidence of harm.

TREATMENT FOR NARP

- **No established disease-modifying cure**; care is largely supportive.
- **Supplements/cofactors** are commonly offered despite limited evidence:
  - antioxidants (**coenzyme Q10, idebenone, vitamin C, vitamin E**)
  - respiratory-chain cofactors (**thiamine, riboflavin, carnitine, creatine**).
  - It is common practice to offer coenzyme Q10, often combined with thiamine, riboflavin, and vitamin C, to patients with a confirmed mitochondrial disorder
  - No established efficacy, and no trial evidence supports routine supplementation in adults.

TREATMENT FOR NARP

- **Peripheral neuropathy** management focuses on neuropathic pain control and rehabilitation.
  - Avoid **dichloroacetate**, which has causes peripheral nerve toxicity in related mtDNA disorders.
- **Symptom- and organ-directed therapy**:
  - antiepileptics for seizures
  - hearing aids/cochlear implants for hearing loss
  - pacemaker for conduction defects
  - treatment of diabetes
  - low-vision aids for retinopathy
  - nutritional/respiratory support.

TREATMENT- REQUIRES MULTIDISCIPLINARY CARE

As NARP affect multiple systems, optimal care requires coordinated **multidisciplinary team** with regular surveillance

- **Neurology** (ideally with knowledge of mitochondrial disease) — core coordination, ataxia, neuropathy, epilepsy, brainstem risk.
- **Ophthalmology** — retinopathy monitoring and low-vision rehabilitation (every ~1–2 years)
- **Cardiology** — ECG and echocardiography for conduction defects/cardiomyopathy (annually or more often depending on findings).
- Geneticist – typically as the primary care coordinator
- Therapists as deemed necessary

CLINICAL TRIALS

- There are no active treatment trials
- North American Mitochondrial Disease Consortium (NAMDC) Patient Registry and Biorepository (NCT01694940) — a recruiting registry and biorepository that is a central hub for genetically confirmed mitochondrial disease patients in North America, supporting natural-history data collection and future trial recruitment.
- Enrolling is beneficial to learn the natural history and to learn about upcoming clinical trials

QUESTIONS?

Thank you!