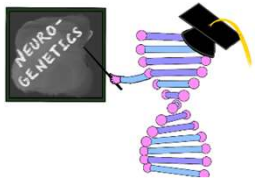
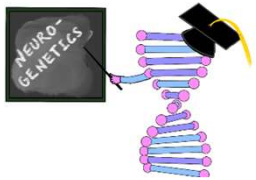
Inborn Errors of Metabolism: Mitochondrial Disease

MODULE 10



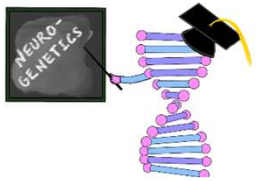
Learning Objectives

- Recognize when to consider mitochondrial disease testing
- Appreciate complexity of testing for mitochondrial diseases
- Understand Modes of Inheritance and associated implications for mitochondrial diseases
- Appropriately utilize counseling for mitochondrial disease evaluation



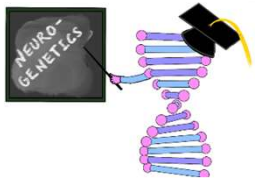
Chief Complaint

- 6 yo F with history of developmental delay and ataxia who develops new-onset seizures in the setting of illness.



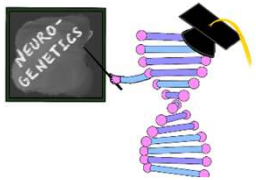
Differential Diagnosis - Interactive

Gene/ Condition	Biochemical Marker	Why?



Differential Diagnosis - Ataxia

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

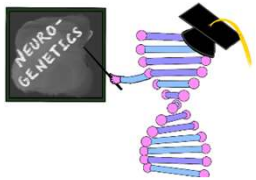


- Primary ataxias
  - Autosomal dominant
    - Repeat expansions
      - SCA1, 2, 3, 6, 7, …
    - Conventional variants
      - SCA29, EA2, …
  - Autosomal recessive
    - Repeat expansions
      - FA
      - CANVAS
    - Conventional variants
      - A-T, AOA1, A0A2, ARSACS, …

Differential Diagnosis (Epilepsy)

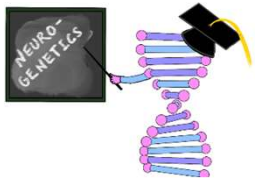
- Channelopathies-many, among the most seen:
  - KCNQ2, KCNQ3, KCNT1, SCN2A

- Cortical malformations
  - Neuronal migrational disorders: *LIS1, ARX, DCX,* tubulinopathies, *RELN,*
  - Peroxisomal biogenesis disorders
  - Walker-Warburg syndrome



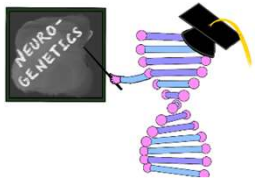
Differential Diagnosis (Epilepsy)

- Disorders of amino acid metabolism and transport
  - MSUD; glycine encephalopathy, disorders of serine synthesis and transport; molybdenum cofactor deficiency, isolate sulfite oxidase deficiency
- Organic acidemias
  - Methylmalonic academia, propionic academia, isovaleric acidemia
- Urea cycle disorders
  - OTC, AS, CPS1, ASL, HHH, NAGS
- Vitamin responsive epilepsy
  - Pyridoxine dependent epilepsy, PNPO deficiency, biotinidase deficiency, holocarboxylase synthetase deficiency
- Disorders of membrane transport
  - Glut1
- Disorders of mineral metabolism
  - Menkes
- Mitochondrial encephalopathy



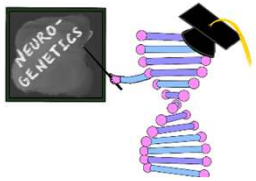
Differential Diagnosis

Gene/ Condition	Biochemical Marker	Why?
Mitochondrial Diseases (too many)	Lactate, GDF15	Decompensation with illness, ataxia, seizures
Pyruvate Dehydrogenase Complex Deficiency (PDCD)	Low Lactate Pyruvate Ratio (Blood)	Seizures, dystonia, abnormal gait, triggered by illness
WWOX (SCAR12)		Cerebellar ataxia and seizures
KCNJ10 (SeSAME)		Ataxia, seizures,
TPP1/PPT1 (NCL)	TPP1/PPT1 enzyme activity (dried bloodspot)	Ataxia, seizures, motor regression (?)



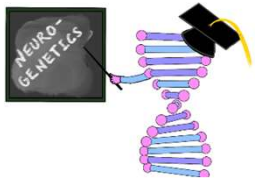
HPI, Exam

- 7-year-old female with GDD and ataxia presenting with new onset seizures in the setting of fever.
- Initially, mom noted patient was sleeping very late. When mom tried to wake her, she was moving back and forth and her arm was shaking.
  - Noted: eyes were rolled back and she was unresponsive for a few minutes - unclear how long this lasted. She had urinary incontinence and was admitted for severely altered mental status.
- Pertinent history: Began walking at 16 months but showed unsteady gait at 2 years and frequently falling on uneven surfaces.
  - First evaluated by neurologist at age 3.
  - Was babbling and ambulatory but with clear deficits. Limited sentences but does seem to understand language fully. Makes good eye contact.
  - No hearing concerns. She began to have significant difficulty during illnesses with increased fatigue, worsening gait, and sometimes needing wheelchair at school. She would return to baseline sometime after illness.



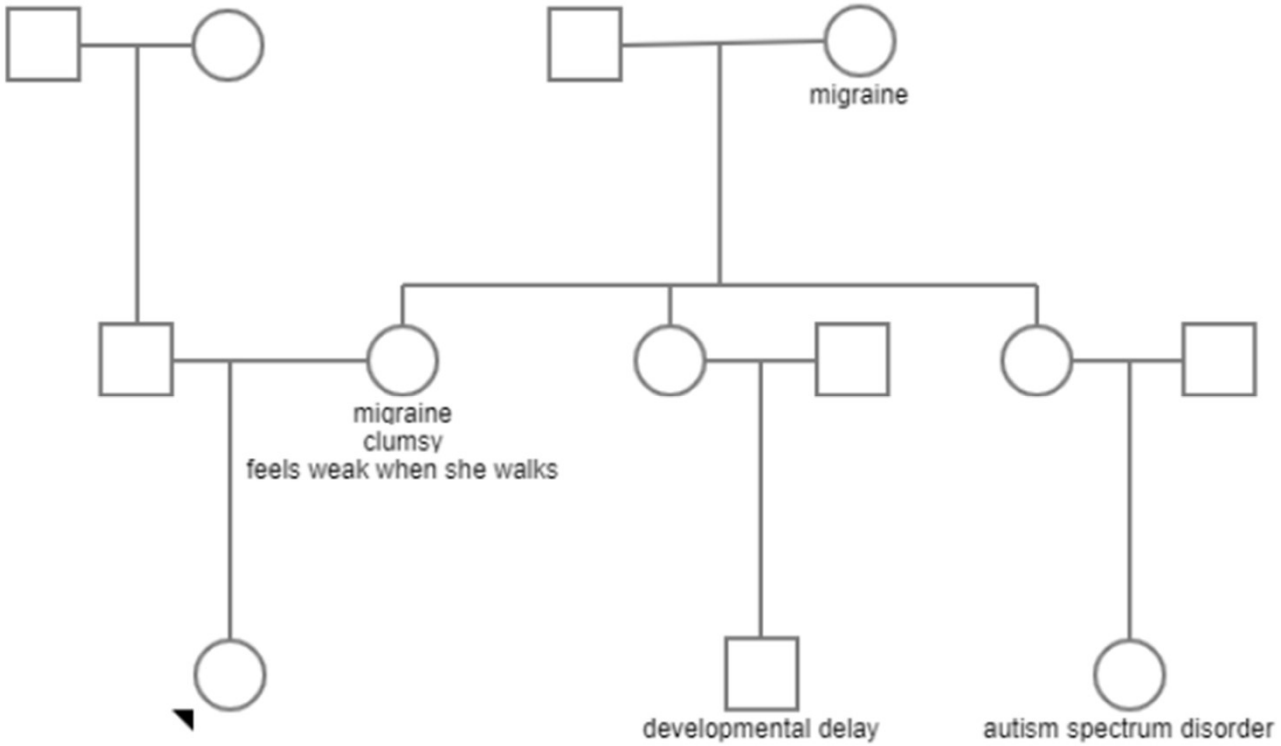
Admission Exam

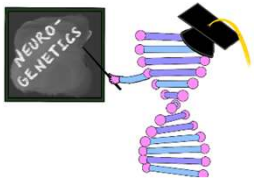
- **Vitals:** temperature was 101F, BP 120/75, Pulse 158, Resp 20 and Sp02 98%.
- **Gen:** Altered, eyes closed, intermittently moaning, unclear if meningismus
- **CV/Lungs:** warm extremities, cap refill ~2-3 seconds; no respiratory distress
- **Skin:** flushed cheeks, no rash appreciated
- **Abdomen:** No organomegaly
- **Neuro:**
  - **MS:** Stuporous, eyes closed: eyes do not open to pain, intermittently moans in response to sternal rub but does not open eyes, flexion to pain: ***GCS 6-7***
  - **CN:** pupils ~3mm and sluggish bilaterally. Negative Dolls eyes. Face symmetric. Tongue midline. Patient not gagged during exam.
  - **Motor:** Minimal spontaneous movement of extremities. Noted: anti-gravity movements of bilateral UE and LE during PIV placement. Hypertonic LE>UE with knees flexed bilaterally. Tight heel cords. No clonus. Upgoing toes bilaterally.
  - **Sensory:** groans unreliably in response to noxious stimuli but does withdraw
  - **DTR:** Arm boards in place bilaterally so unable to elicit biceps reflex, +3 patellar bilaterally and +2 ankle. Tight heel cords. No clonus. Toes upgoing bilaterally.
  - **Coord/Gait:** unable to assess.



Family History

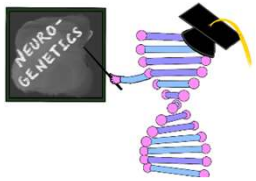
What are clues of a maternally inherited mtDNA disorder?





Investigations (Non-Genetic)

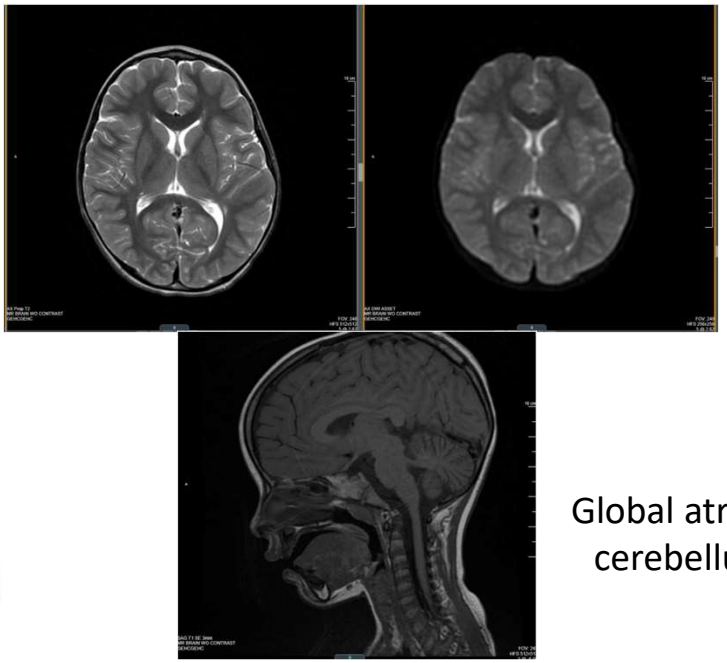
- <u>During admission (7 yo):</u>
  - CMP, Ca, Mg, P all normal
  - CBC with elevated WBC, ANC
  - CSF: 10 WBC, <1 RBC, Glu 61, Protein 36
  - Post-admission MRI (not completed inpatient):
    - 1. Mild, diffuse cerebellar volume loss is not significantly changed from previous
    - 2. Punctate focus of T2 hyperintensity in the left periatrial white matter, likely nonspecific gliosis, also unchanged.
- <u>Labs completed during prior workup before admission (3-4 yo)</u>:
  - CBC, CMP, CK and AFP were all normal
  - MRI Brain and Spine at time of initial evaluation:
    - 1. Mild diffuse cerebellar volume loss, particularly involving the vermis. Questionable mild volume loss of the medulla. The findings are non-specific, and differentials would include prior/in utero insult as well as metabolic and hereditary disorders.
    - 2. Small focus of gliosis in the left periatrial white matter.
    - 3. Unremarkable rest of the non-contrast brain and spine MRI.



MRI Findings: Non-Diagnostic

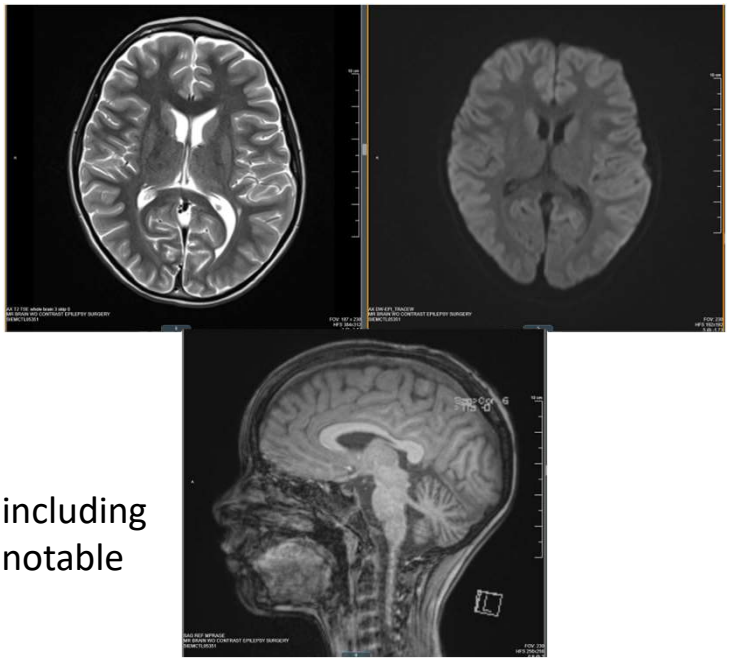
At age 3 – nonspecific findings

T2 DWI

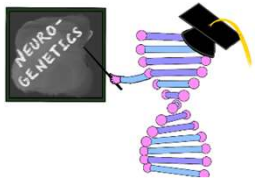


At age 7 – mostly unchanged

T2 DWI

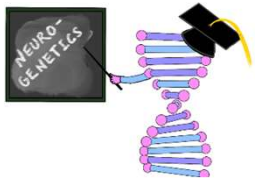


Global atrophy including cerebellum is notable



Investigations (Metabolic)

- Amino acids: non-diagnostic (normal alanine)
- Ammonia: normal on multiple occasions
- Acylcarnitine profile: normal
- Carnitine: normal
- B12/Folate: normal
- NCL enzymes: normal
- Lactate: normal x4, once abnormal to 3.6 during a hospitalization.

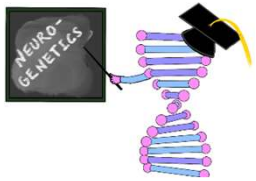


Investigations (Genomic)

- Genome Microarray: Normal
- Prader-Willi/Angelman Syndrome Methylation:
  - No deletions or duplications were detected. Methylation pattern of targeted imprinted genes is normal. Both the maternally and paternally derived copies of the PWS/AS critical region are present.
- ES + Mito:
  - No variants identified in nuclear genes.
  - Mito:

POSITIVE

Gene	mtDNA	Variant	Heteroplasmy(%)	Classification
MT-ATP6	m.9185 T>C	p.Leu220Pro (L220P)	Approximately 93%	Pathogenic Variant



Subsequent testing of this individual's mother (GeneDx# 1848544) by Sanger sequencing found that she harbors the m.9185 T>C variant in the MT-ATP6 gene at a much lower level of heteroplasmy. Specifically, the mother's heteroplasmy is estimated to be approximately 30%.

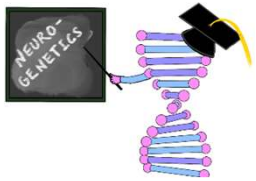
Exercise Involving Genetic Testing

- The gene result given was:

POSITIVE

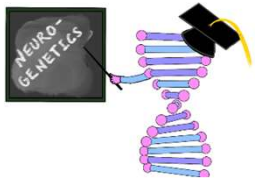
Gene	mtDNA	Variant	Heteroplasmy(%)	Classification
MT-ATP6	m.9185 T>C	p.Leu220Pro (L220P)	Approximately 93%	Pathogenic Variant

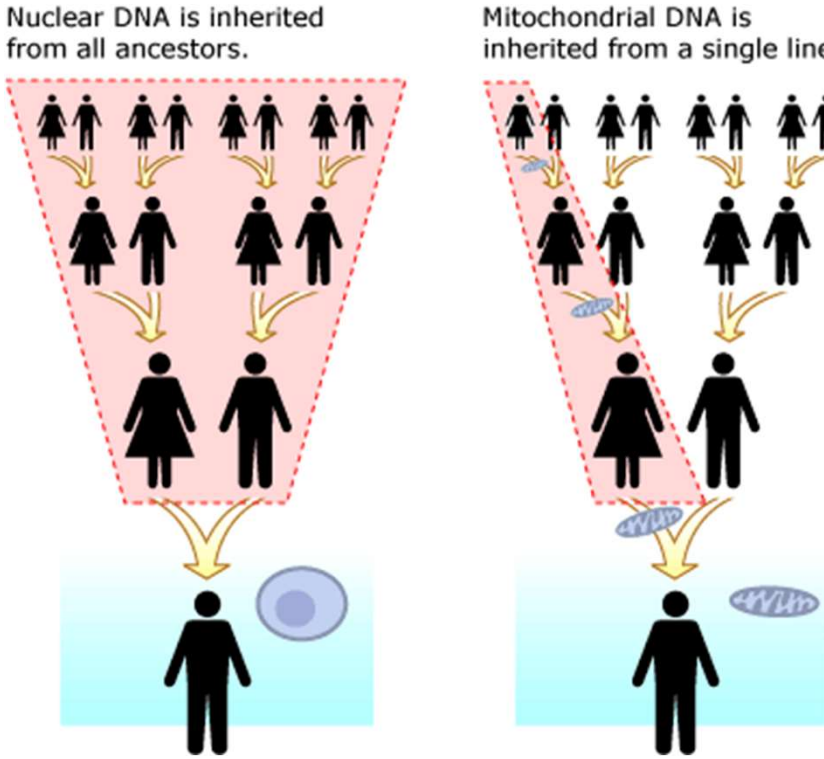
- Based on this finding, please break into groups to address the following questions:
  - Team A: What is the general understanding of how mtDNA disorders cause disease?
  - Team B: What are they canonical diseases caused my mtDNA disorders?
  - Team C: What is the mode of inheritance of mtDNA disorders and who should be screened?
  - Team D: Do you think this gene is the cause of your patient's symptoms? How will you decide?
  - Team E: What biomarkers are used for mitochondrial diseases? How did they apply in this case?



Mitochondrial Disease: Genetic Causes

- Disease can be caused through <u>Mendelian inheritance</u>
  - Autosomal recessive diseases are most common (e.g. Leigh Syndrome, MNGIE, etc.)
  - Autosomal dominant disease (e.g. POLG progressive external ophthalmoplegia, MFN2 Charco-Marie-Tooth, etc.)
  - And x-linked (e.g. PDHA Pyruvate dehydrogenase deficiency, etc.)
- Disease can be caused through Mitochondrial DNA inheritance (maternal)
  - Mother transmits mtDNA through fertilized egg.
  - mtDNA in sperm is destroyed on entry to egg

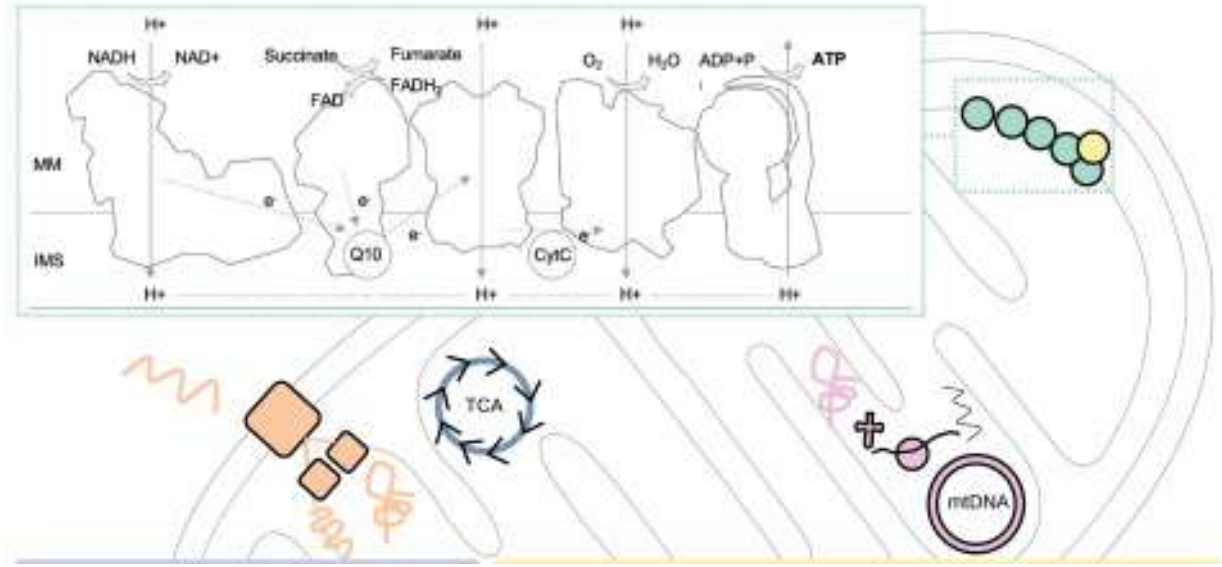


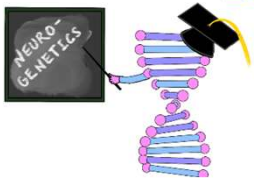


File:Mitochondrial DNA versus Nuclear DNA.gif - Wikimedia Commons

Mitochondria – The Powerhouse of the Cell!

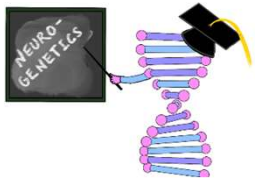
- Most disease is caused by **deficiency** of electron transport chain
- Disease is also caused by **impairment** of mtDNA maintenance, metabolism of substrates, and mitochondrial dynamics





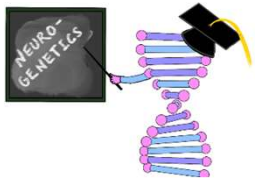
Limitations of Testing

- For this patient, an exome study + mitochondrial genome was included.
  - This kind of test is considered comprehensive but pushes the limit of what we know clinically.
- Mitochondrial DNA variants may have a “heteroplasmy level” which can be confounding for VUS. Usually having mother tested is helpful (see next few slides).
- Exome limitations apply the same as for other Mendelian disorders.
  - Deep intronic DNA is not tested on the ES for this patient
  - Undiscovered rare genes may not be reported
  - Nuclear genes causing mitochondrial disease may have a broad phenotype and may not be reported on first analysis

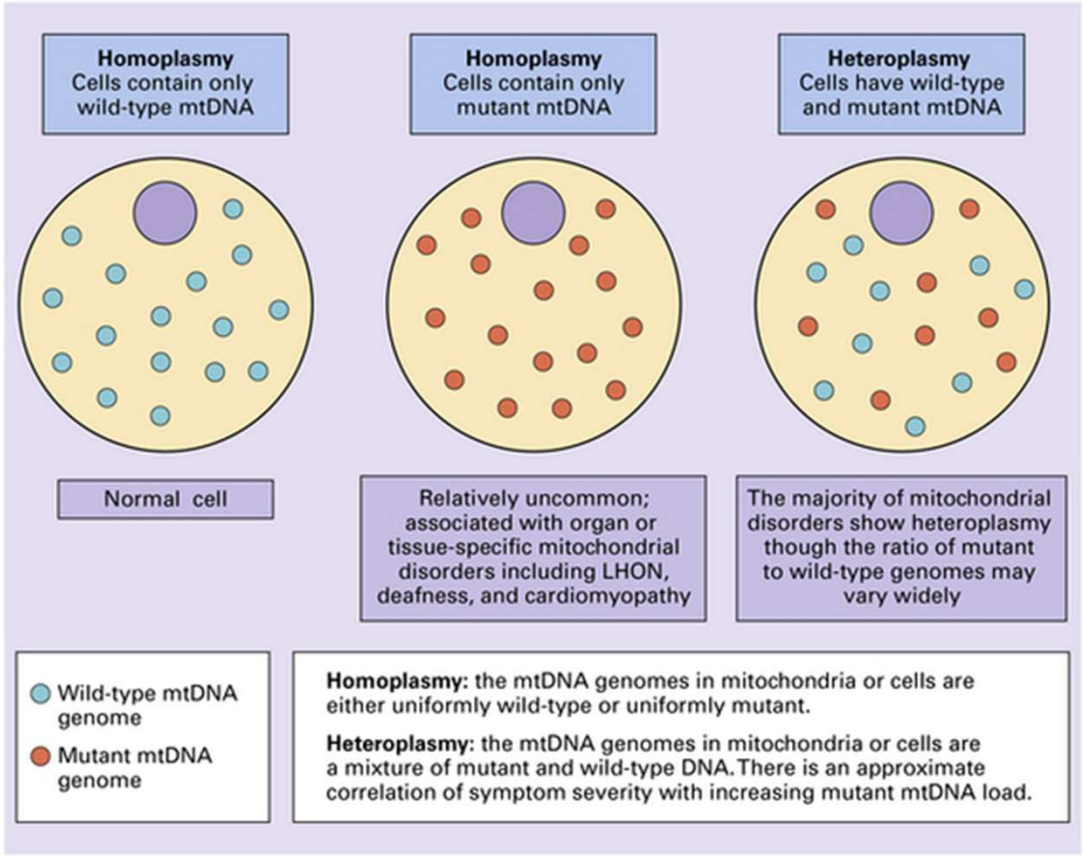


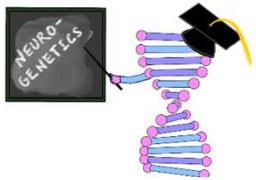
Principles Only Applicable to mtDNA Variants

- Heteroplasmy
  - The mixture of variant mtDNA and “normal” mtDNA in a patient, usually reported by tissue time (e.g. blood, urine, muscle).
- Bottleneck effect
  - Refers to segregation of mtDNA during Oogenesis
- Threshold effect
  - Refers to level of heteroplasmy at which a disease phenotype occurs



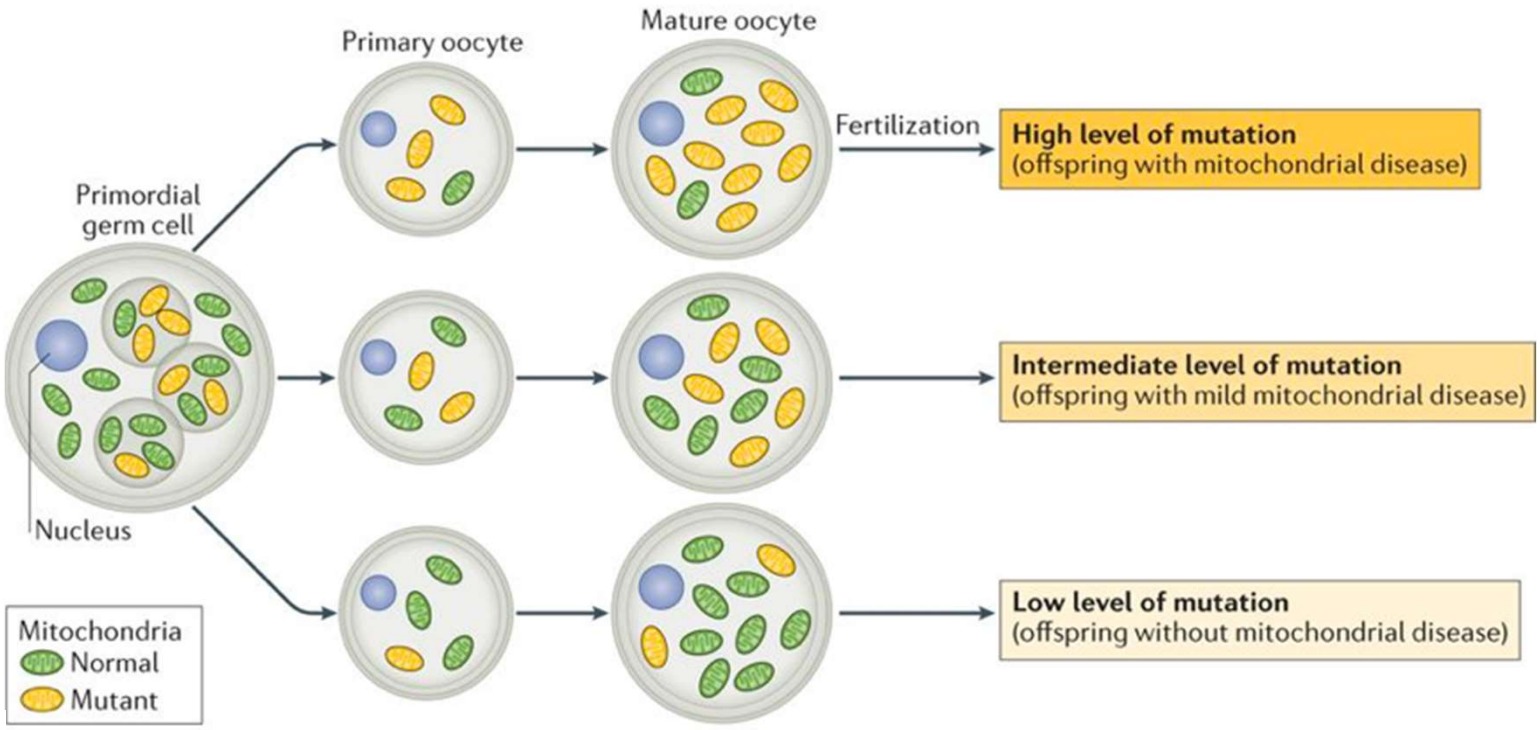
Homoplasmy v. Heteroplasmy

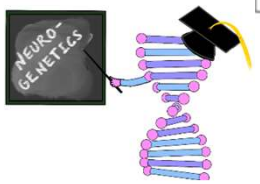




https://clinicalgate.com/mitochondrial-encephalopathies/

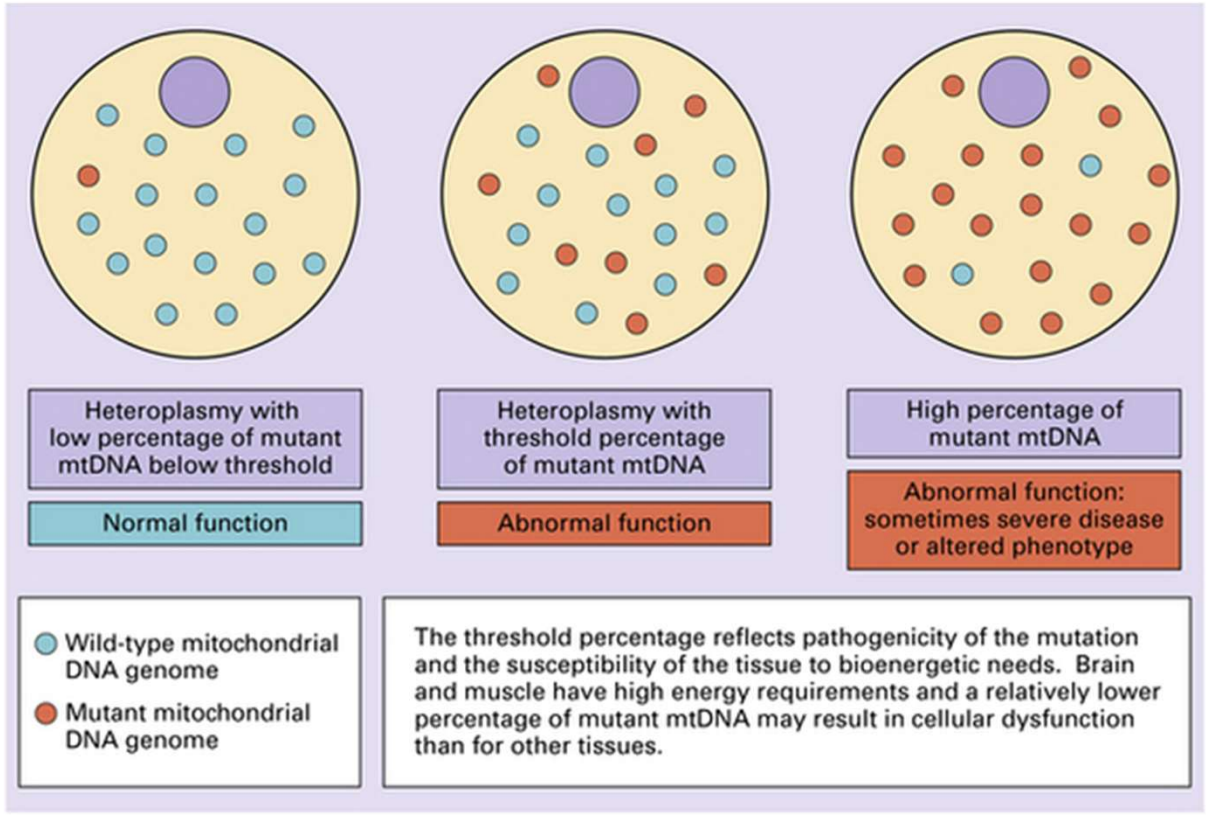
Heteroplasmy: Bottleneck Effect

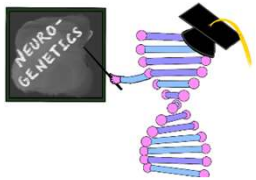




Gorman et al. *Nat Commun Rev Dis Primer, (2016).*

Degrees of Heteroplasmy





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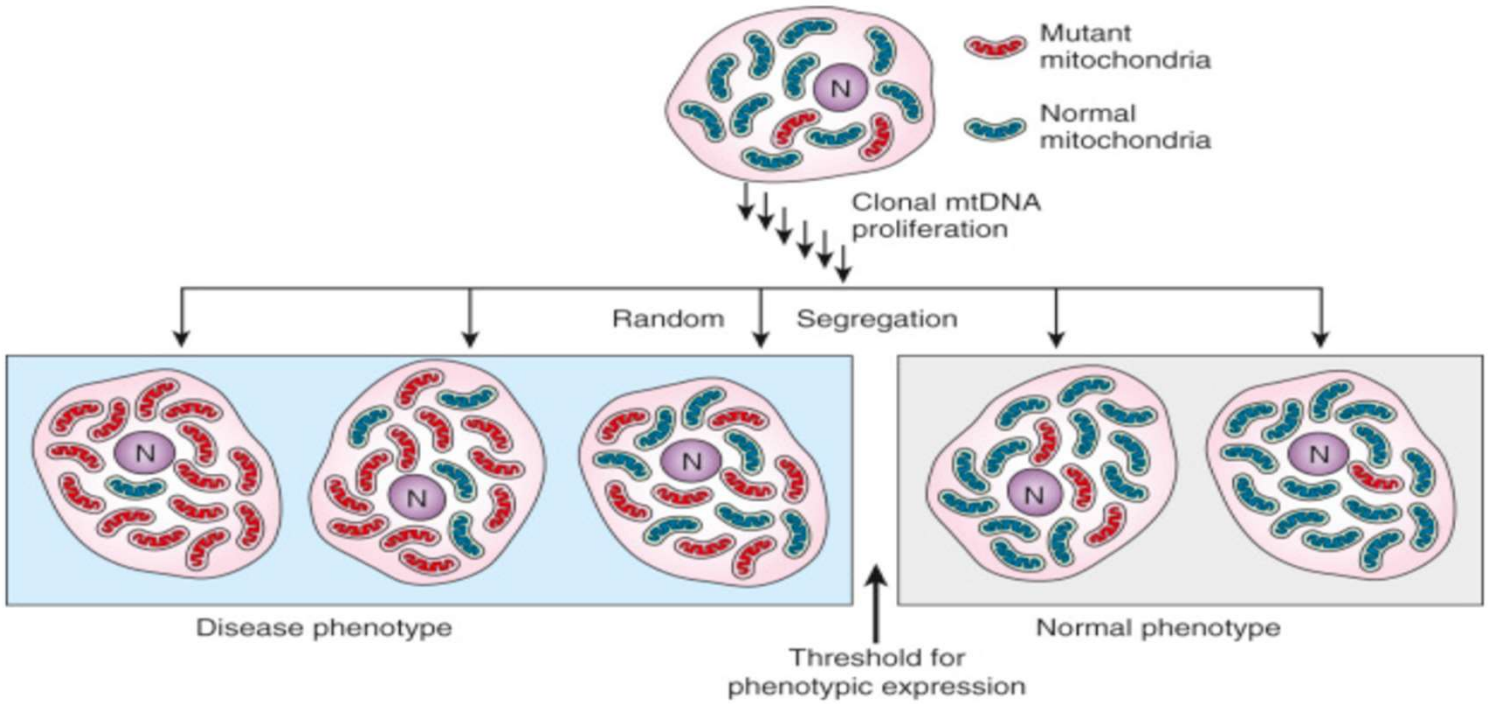
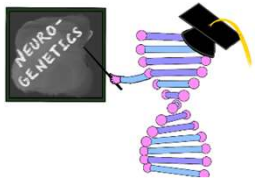
Heteroplasmy: Threshold Effect

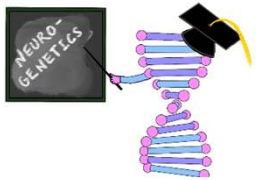




Thompson & Thompson Genetics in Medicine

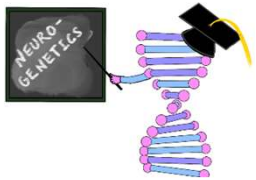
Brief Review of mtDNA-Related Diseases

- MT-ATP6 is one of many mtDNA related diseases.
- Most common mtDNA condition is MT-TL1 related Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS)
  - MELAS can be caused by other mtDNA
    - Controversial if nuclear-encoded genes cause MELAS
- Disease from mtDNA variants is (usually) caused by deficiency in providing essential subunits to enzyme complexes of the electron transport chain.



How to counsel MT-ATP 6?

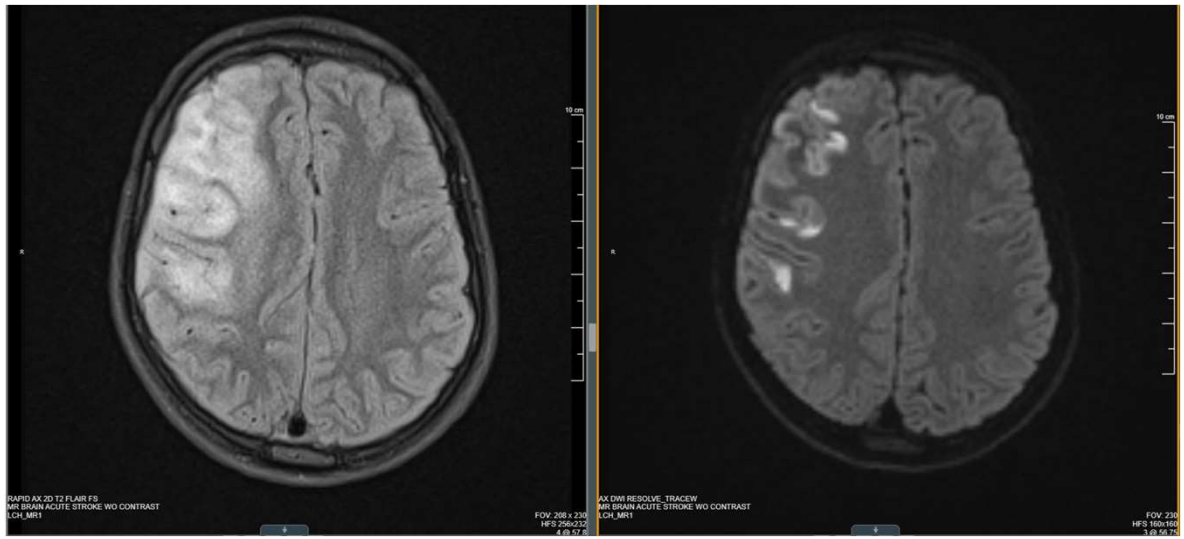
- Range of MT-ATP6 disease is wide.
- Most common phenotypes are Leigh syndrome, NARP (Neuropathy, Ataxia and Retinitis Pigmentosa), non-syndromic sensorimotor neuropathy.
- Our patient had an ataxia/epilepsy/developmental delay phenotype but evolved to MELAS over time.
- Given the complexity of disease/prognosis/screening implications it is critical to have genetic counseling involved.
- Connect family with United Mitochondrial Disease Foundation (UMDF), which is the single largest patient advocacy group for Mitochondrial Diseases.

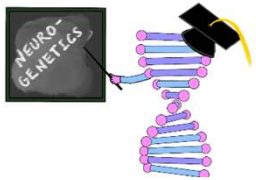


Metabolic Stroke

- About 3 years after her initial diagnosis, she presented with focal seizure involving the left face and arm, which did not resolve despite maximal therapy. She was found to have a metabolic stroke:

T2 DWI





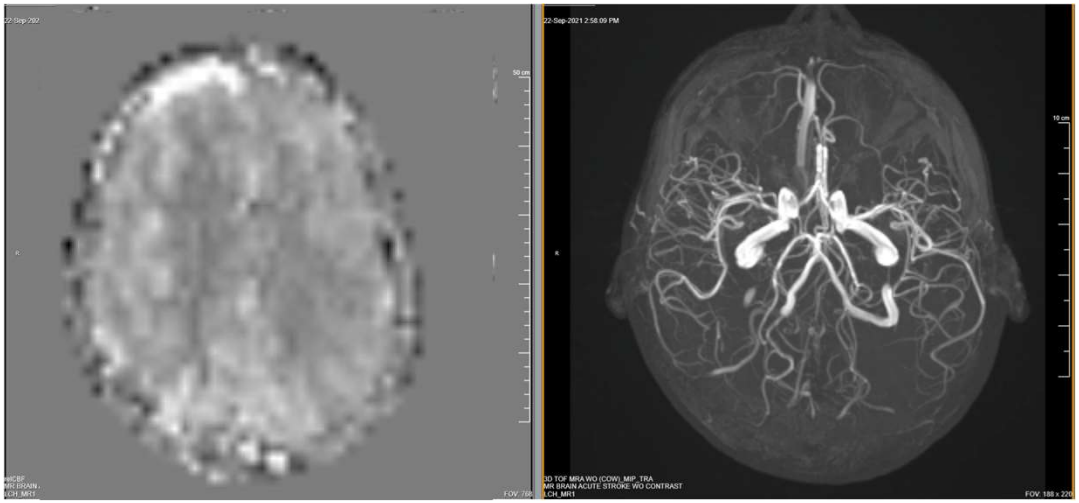
Teaching point:

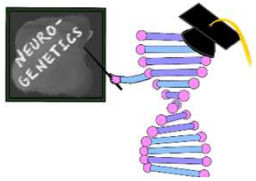
Diffusion restriction is not in a defined vascular pattern. This does not look like an ischemic stroke of vascular etiology.

Metabolic Stroke – Advanced Imaging

- Metabolic stroke-like episode may be caused by abnormally increased blood flow (RelCBF) in otherwise normal vasculature (MRA). In this patient, the right frontal area has increased RelCBF but normal MRA:

RelCBF MRA





Teaching point:

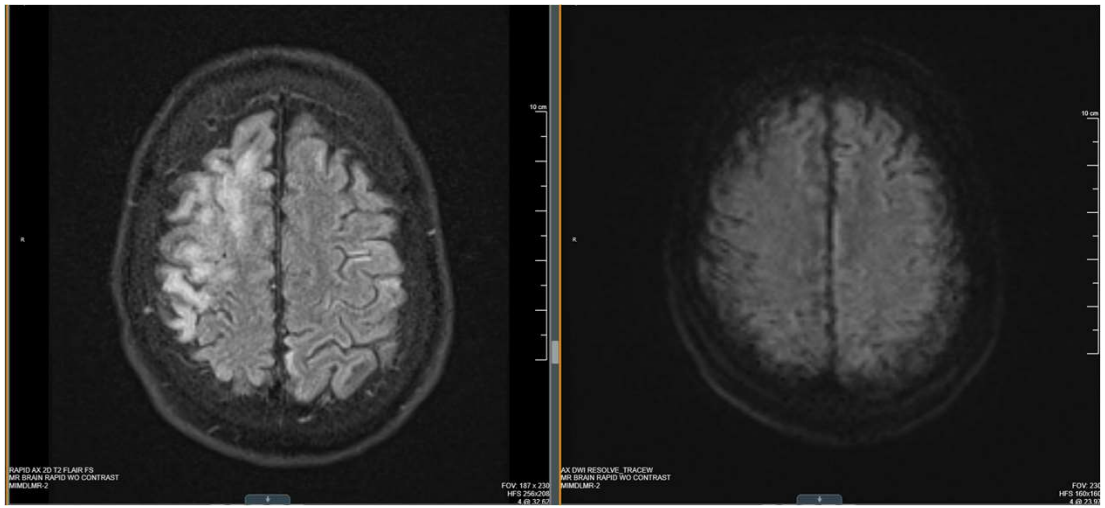
Some patients (particularly MELAS MT-TL1 A3243G patients) have an arginine deficiency. This is thought to cause a relative Nitric Oxide deficiency resulting in abnormal vasoconstriction.

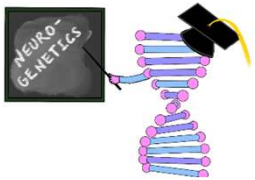
Can treat with Arginine to increase NO production.

Metabolic Stroke - Recovery

- About 2 years after her initial stroke-like episodes, during which time she had more, she had persistent gliosis and volume loss, but no diffusion restriction in those areas.

T2 DWI



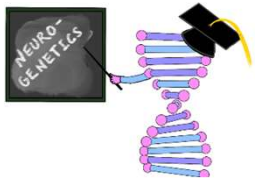


Teaching point:

Although initial imaging can look quite devastating at first, sometimes only mild gliosis without encephalomalacia or even complete resolution of lesions occurs.

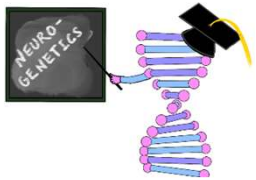
Take Home Points

- Patient with static encephalopathy presenting with decompensation or crisis in the setting of illness can be suggestive of mitochondrial disorder.
- There are both maternally inherited and nuclear genes associated with mitochondrial diseases.
- Threshold and bottleneck effect are unique effects seen in maternally inherited mitochondrial diseases.
- MRI can have classic findings, such as stroke-like episodes or Leigh syndrome (bilateral basal ganglia lesions), but sometimes may be non-specific.



Suggested Reading

- Parikh, S., Goldstein, A., Koenig, M. *et al.* Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med* **17**, 689–701 (2015).
- Ganetzky RD, Stendel C, McCormick EM, Zolkipli-Cunningham Z, Goldstein AC, Klopstock T, Falk MJ. MT-ATP6 mitochondrial disease variants: Phenotypic and biochemical features analysis in 218 published cases and cohort of 14 new cases. Hum Mutat. 2019 May;40(5):499-515. PMID: 30763462; PMCID: PMC6506718.
- Taylor, R., Turnbull, D. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* **6**, 389–402 (2005).
- Parikh, S., Goldstein, A., Karaa, A. *et al.* Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med* **19**, 1380 (2017).



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