Mitochondrial diseases for the pediatrician

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Conflict of interest

- Clinical trials: Sanofi Genzyme, Shire, Biomarin
- Advisory board member for Alexion, Horizon, Cycle
- Honoraria: Alexion, Horizon, Cycle , Ultragenyx
- Travel grants: Alexion, Sanofi Genzyme, Horizon

Objectives

- Mitochondrial function
- Genetics of mitochondrial diseases
- Epidemiology of mitochondrial diseases
- Clinical manifestations
- Most common mitochondrial syndromes

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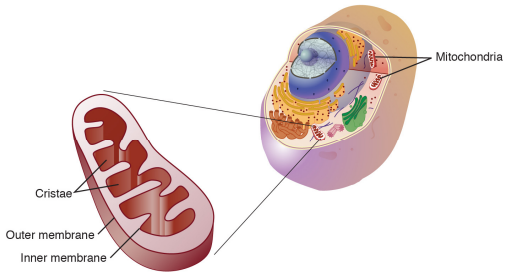
Mitochondria



- Essential organelles
- Present in almost all eukaryotic cells
- Endosymbiotic theory of origin
  - Symbiotic event of free- living bacteria with a host cell

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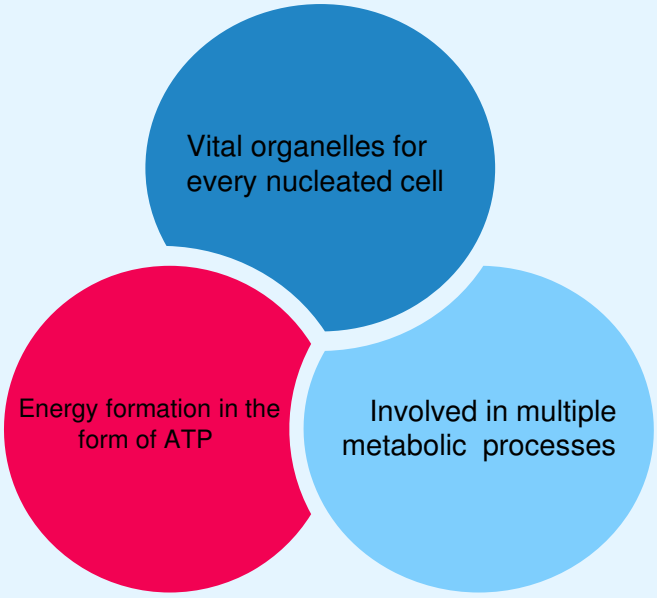
Role of the mitochondria



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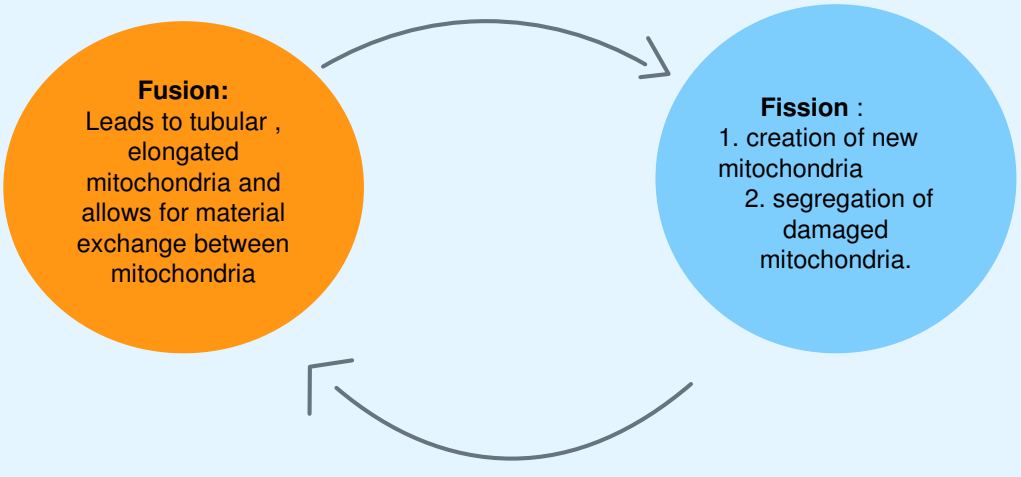
Mitochondrial dynamics



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- Mitochondrial transport: mobility through the cytoskeleton is important for the mitochondrial network quality control
- Mitophagy allows for selective targeting of damaged mitochondria

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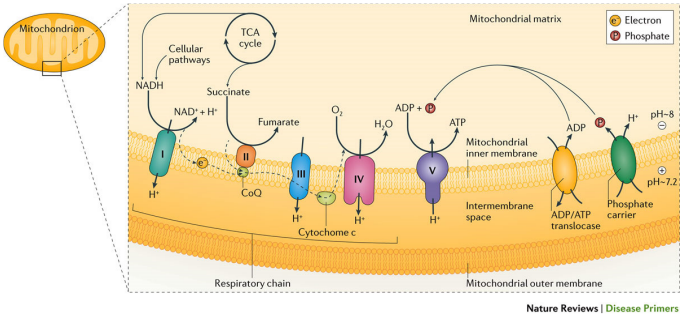
OXPHOS system – energy production

- Complexes I to IV are multi-subunit enzymes that create electrochemical gradient across the mitochondrial membrane
- Complex V (ATP synthase) uses the gradient in forming ATP
- Fluid system model
- Solid state model - super complexes



Schematic representation of oxidative phosphorylation
Gorman et al, 2016

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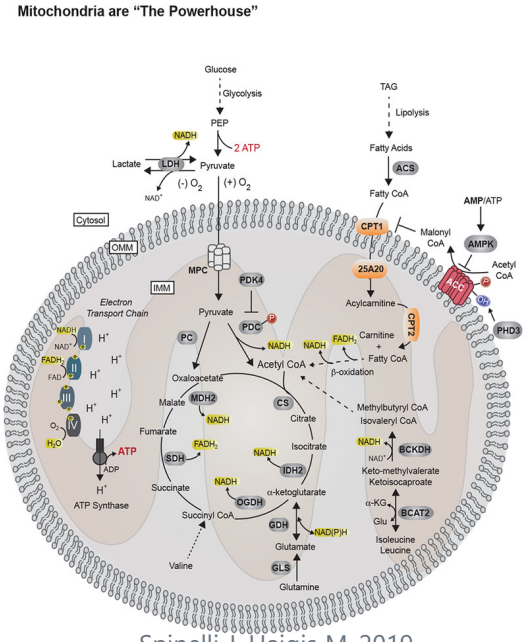
Metabolic functions

- Catabolize nutrients for energy,
- Generate biosynthetic precursors for macromolecules,
- Compartmentalize metabolites for the maintenance of redox homeostasis
- Function as hubs for metabolic waste management

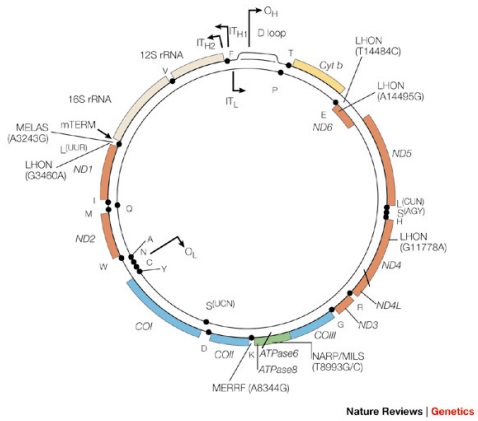


Spinelli J, Haigis M.,2019

Mitochondrial genetics

Dual genetic control

- Nuclear genes
- Mitochondrial genes
- Mitochondrial diseases can be inherited as :
  - autosomal dominant
  - autosomal recessive
  - X-linked
  - Maternal



Smeitink et al, 2001

Mitochondrial DNA is a *multicopy genome*

mtDNA genomes can be either:

- *homoplasmic*
or
- *heteroplasmic*

Mitochondrial DNA is *compact*

has only one non coding sequences

Inheritance of mtDNA is *strictly maternal*

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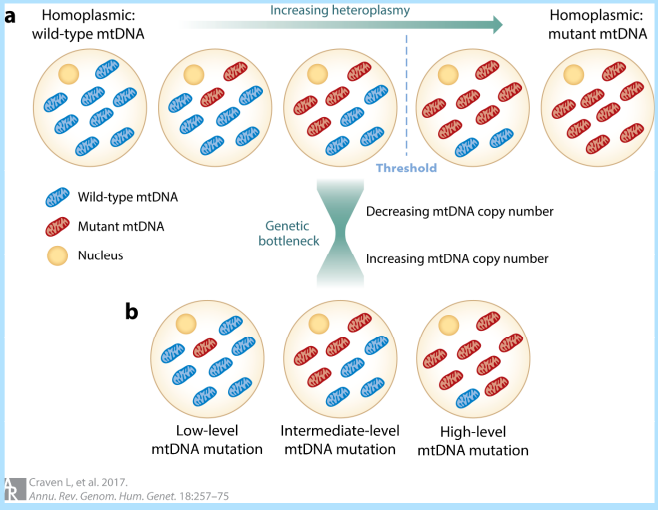
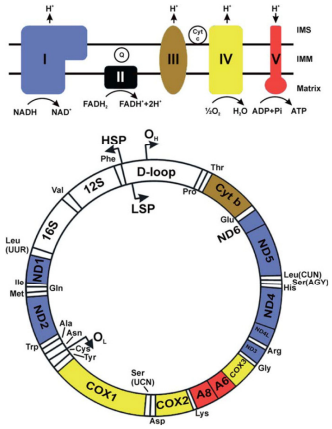


Annual Reviews

Mitochondrial DNA

- mtDNA point mutations
  - estimated prevalence of 1in 200
  - Variable phenotype
- mtDNA rearrangements
- Single, large-scale mtDNA deletions
  - population frequency of 1.5/100,000
  - three main associated phenotypes: chronic progressive external ophthalmoplegia , Kearns–Sayre syndrome and Pearson syndrome



Ylikallio E, Suomalainen A, 2012

Nuclear DNA

- >1500 different nuclear genes encode mitochondrial proteins
- Mutations in nuclear genes can cause defects in :
  - mtDNA maintenance
  - mtDNA translation
  - Mitochondrial homeostasis

1: 5,000

Overall incidence of mitochondrial diseases

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5 to 15 cases per 100,000 individuals

Estimated prevalence of all forms of childhood onset mitochondrial diseases

2.5 cases per 100,000 births

Estimated prevalence of Leigh syndrome

Prevalence of mitochondrial diseases in the pediatric population

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9.6 cases per 100,000

Prevalence in adult individuals due to mutations in mtDNA

2.9 cases per 100,000

Prevalence in adult individuals due to nDNA mutations

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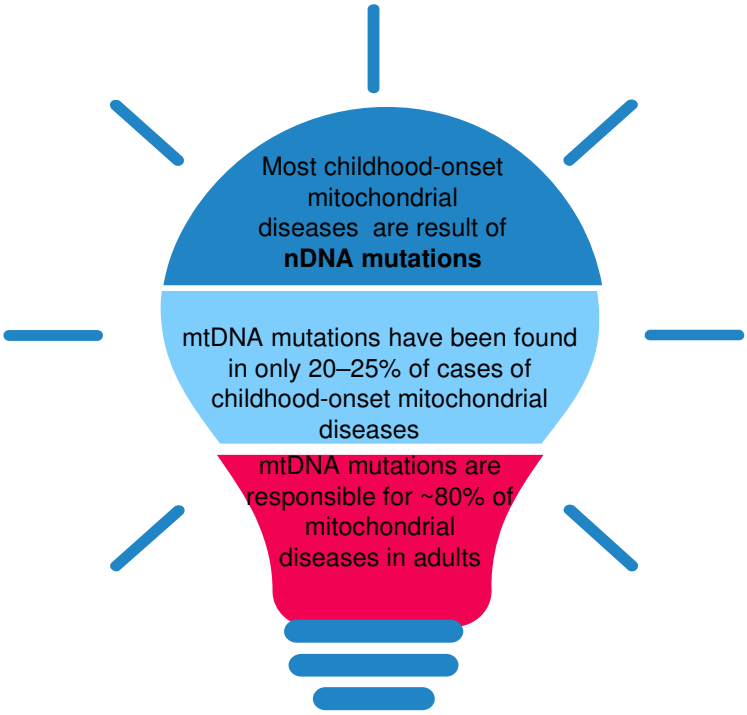

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> ***mitochondrial diseases manifest at any age and in any tissue system'***

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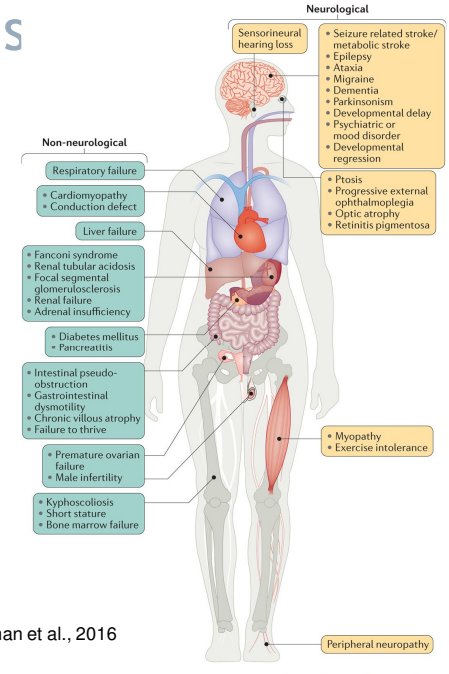
Clinical manifestations

- Diverse phenotype affecting almost every organ and system
- Bimodal onset with peak in:
  - first 3 years of life
  - teenage years to adulthood



Gorman et al., 2016

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CNS manifestations

- CNS manifestations can be :
  - Clinical
  - Clinical with abnormalities on imaging studies
  - Permanent or transient

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Developmental delay

- Variety of developmental disabilities can be seen in isolation or in various combinations, including :
  - ID, autism, CP, or isolated learning disabilities,
  - Attention deficit disorder with or without hyperactivity
  - concomitant or isolated language or motor disability can also be present.
- Mitochondrial diseases can all present with isolated or global developmental delay and/or ID
- Many mitochondrial diseases can also cause "neuro-regression" or "psychomotor regression."

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Epilepsy

- Presenting or late feature in mitochondrial diseases
- 35–60% of infants, children, and adolescents with mitochondrial diseases
- Focal and generalized seizures, epilepsia partialis continua, myoclonus, and infantile spasms have all been noted.
- Patients may also have progressive myoclonic epilepsy or recurrent status epilepticus.

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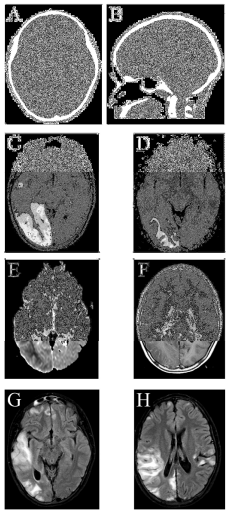
Stroke-like episodes

- Typical finding in MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes)
- Also reported in other metabolic syndromes
- Clinical manifestations:
  - Cortical blindness, psychiatric disorders, headache, hemiparesis, epilepsy, aphasia, visual and auditory agnosia



El-Hatabb et al., 2015

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Headache

- Headaches are seen more frequently in several mitochondrial diseases
  - Migraine, cluster, tension headache
  - Up to 58 % of patients with m.3243 A>G mutations have headache
- Severe headaches in MELAS patients have been associated with stroke-like episodes and seizures.

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Movement disorders and altered tone

- Patients with primary mitochondrial disease are at risk of movement disorders
- Result of injury to the basal ganglia, cerebellum, cortex, or corticospinal tracts.
- Mixed movement and tone disorder:
  - hyper- and hypokinetic or cerebellar types of movements,
  - hypotonia, spasticity, rigidity, and dystonia.
  - myoclonus, ataxia, gait disturbance, Parkinsonism, and rigidity have also been noted.

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Myopathy

- Common manifestation
- Early onset myopathy may present with profound hypotonia in infancy.
- Patients are at risk of associated dysphagia, respiratory insufficiency, cardiomyopathy, exercise intolerance, myalgia, fatigue, and infrequently rhabdomyolysis.
- Mitochondrial myopathies do not typically lead to marked baseline elevations in CK levels

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Neuropathy

- Mitochondrial diseases can lead to primary neuropathy
- Neuropathy can also occur secondarily as a complication of mitochondrial diabetes, renal insufficiency, or side effects from treatments

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Cardiac involvement

- >30% of mitochondrial patients have cardiac involvement
- Cardiac involvement can be :
  - structural or functional,
  - primary or secondary
- Myocardium is most frequently affected

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Cardiac manifestations

Cardiac conduction defects

reported in > 10% of patients

arrhythmias can be cause of death especially in KSS syndrome and patients with m.3243A>G mutation

Cardiomyopathy

- 20-40% of patients have CMP

-hypertrophic CMP is more prevalent

-dilated CMP, restrictive LV noncompaction and histiocytoid CMP have been reported

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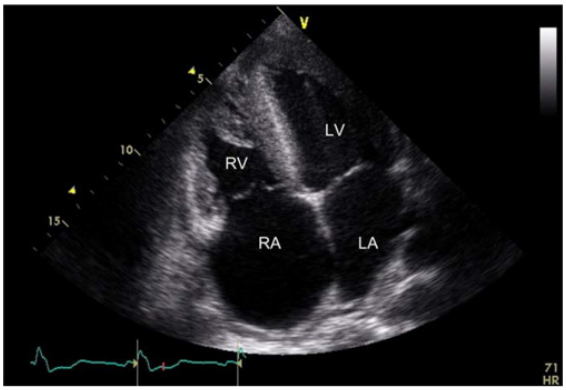

Gerber et al. 2010 BMJ C

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Pulmonary manifestations

- Lungs are indirectly affected due to neuromuscular and CNS involvement
- Symptoms : noisy breathing, hoarseness, stridor, congestion, cough, sleep disturbances, daytime hypersomnolence, exercise intolerance, hypoventilation, pulmonary hypertension.
- Pulmonary edema as a result of heart failure
- Anesthesia may worsen respiratory symptoms and precipitate respiratory failure

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Gastrointestinal involvement

- GI dysmotility is relatively common
- Dysmotility manifest as
  - Satiety, weight loss, nausea, constipation, overflow diarrhea
- Constipation is result of underlying myopathy, neuropathy , dietary changes, decreased fluid intake and decreased mobility

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Gastrointestinal involvement

- Chronic intestinal pseudo-obstruction(CIPO):
  - More than 6 months of severe symptoms of intestinal obstruction, including abdominal pain, nausea, vomiting, with radiological findings of dilated bowels in absence of mechanical obstruction
- Increased burden of strokes in MELAS patients following episode of CIPO

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Gastrointestinal involvement

- Oropharyngeal weakness or dyscoordination: risk of aspiration pneumonia
- Exocrine pancreatic insufficiency is seen in Pearson, KSS , patients with m3243A>G mutation
- Liver dysfunction and failure : in mtDNA depletion or deletion (*POLG, DGUOK MPV17*)
- Obesity is a less common feature

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Renal manifestations

- Kidneys contain high density of mitochondria
- Renal tubular dysfunction is more frequently seen in childhood onset mitochondrial diseases
  - Mild tubular dysfunction is seen in particular in patients with mtDNA deletions
- Glomerular dysfunction – can progress to focal glomerular sclerosis
- Chronic tubulointerstitial nephritis
- Renal failure requiring transplant

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Endocrine manifestations

- Reported in large number of nuclear encoded defects
- Underling disease mechanisms :
  - failure to synthesize /secrete hormones due to lack of ATP or oxidative stress
  - Impaired cellular signaling
  - Calcium handling

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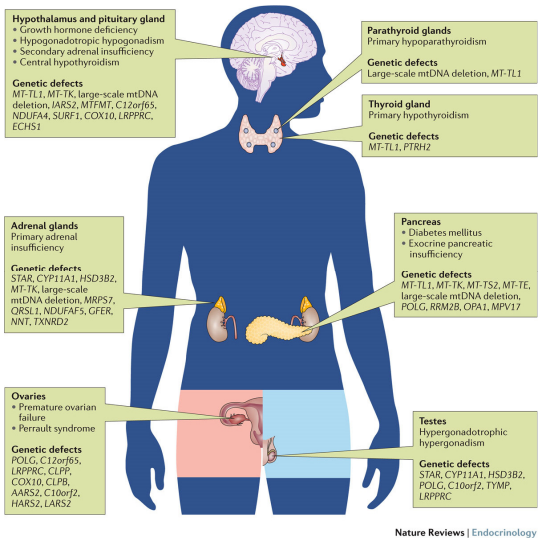
Figure 2 Endocrine dysfunction in mitochondrial disease and their associated gene defects



Chow, J. *et al.* (2016) Mitochondrial disease and endocrine dysfunction
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2016.151

Endocrine manifestations

Diabetes mellitus:

- Well described in mitochondrial diseases
- Mitochondrial dysfunction can lead to type I and II DM
- Average age of onset is 38 years for the common mutation
- point mutation m.3243A>G in *MT-TL1* cause of 0.5-2.9% of all cases of DM
- Present with non-insulin dependent diabetes but progress to insulin dependent DM

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Endocrine manifestations

- Short stature is a common feature
- Up to 48% of patients with MELAS and in up to 90% in patients with Leigh syndrome
- Growth hormone deficiency
  - Seen both in patients with nDNA and mtDNA mutations
  - Treatment with GH should be used with caution

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Endocrine manifestations

- Thyroid involvement :
  - hypothyroidism and hyperthyroidism(less frequently)
- Hypoparathyroidism
  - reported in some subtypes of mitochondrial diseases, most frequently in KSS.

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Endocrine manifestations

- Adrenal insufficiency
  - Most cases have been associated with Pearson or KSS, MELAS, and *POLG*-related disease.
  - Adrenal insufficiency with hyperpigmentation and hyponatreima can be the first presenting symptoms
- Ovarian premature failure –can be presenting feature
- Male infertility

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Hematological findings

- Not a common occurrence, apart form mild anemia
- Sideroblastic anemia : Pearson syndrome

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Immune system

- In vitro studies show that mitochondria are crucial for the normal function of the cellular and humoral immune system
- Patients seem to be at higher risk of infections, sepsis

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Ophthalmologic manifestations

- 35 to 81% of patients have ophthalmological findings
- Dominant features :
  - Ophthalmoplegia, ptosis
- Nonspecific features :
  - cataract, retinal disease, nystagmus, strabismus

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Orthopedic manifestations

- Result of variety of causes : myopathy, abnormal tone, strokes, basal ganglia, cerebellar disease
- Include: spasticity, scoliosis, hip dislocation, limb deformities

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Psychiatric disorders

- Psychiatric disorders appear to have higher prevalence in patients with mitochondrial
- Manifestations:
  - Mood disorders, major depression, anxiety

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Mitochondrial diseases classification

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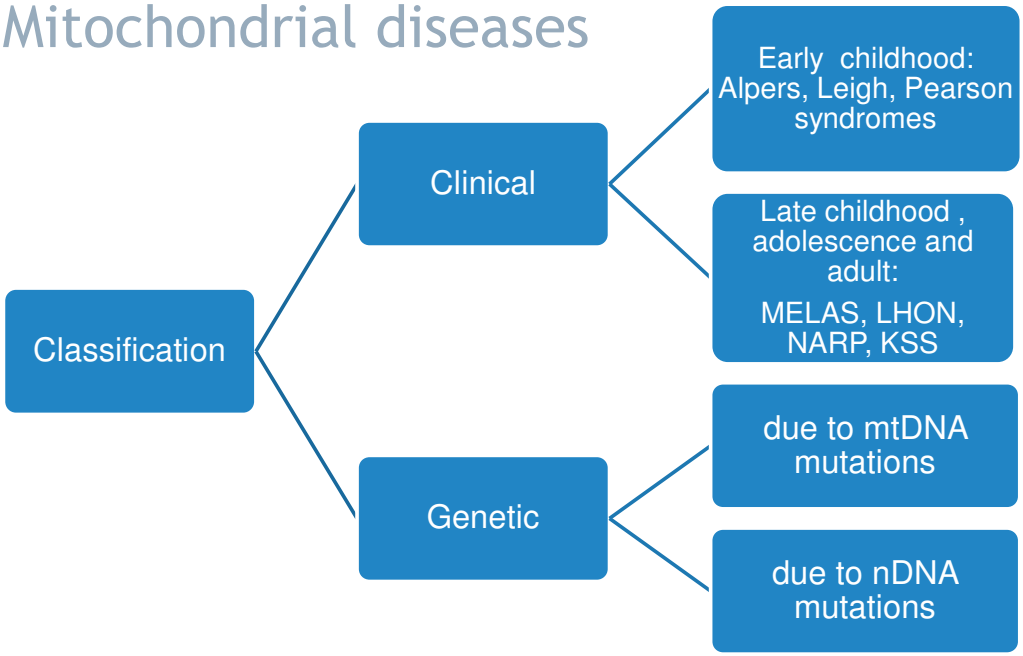
Mitochondrial diseases



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Mitochondrial diseases – Clinical syndromes

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Leigh syndrome

- onset at 3 – 12 months of age
- Caused by more than 80 different nuclear genes
- Decompensation during viral illness
- Psychomotor retardation or regression
- Hypotonia, spasticity, movement disorders, ataxia
- Hypertrophic cardiomyopathy
- Elevated lactate

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Leigh syndrome

- The most common syndrome associated with childhood-onset mitochondrial diseases
- Leigh syndrome spectrum encompasses:
  - Leigh syndrome (subacute necrotising encephalomyelopathy)
  - Leigh –like syndrome : term used when not all criteria for Leigh syndrome are present

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Leigh clinical manifestations

- Neurological manifestations: spasticity, hypotonia, movement disorder, cerebellar ataxia, peripheral neuropathy, ptosis, muscle weakness
- Extra neurological :
  - Hypertrophic cardiomyopathy
  - Hypertrychosis,
  - Anemia
  - Renal tubulopathy
  - Liver involvement

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Leigh syndrome

- Diagnostic criteria:
  - Characteristic clinical presentation
  - Brain MRI findings of characteristic bilateral symmetric T2 weighted hyperintensities in the basal ganglia
  - Evidence of abnormal energy metabolism:
    - elevated lactate in blood and/ or CSF
    - Disturbed oxidative phosphorylation or PDH activity
  - Pathogenic variants

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Leigh syndrome

- Diagnosis:
  - Blood and CSF lactate
  - Brain MRI
  - Enzyme activity
  - Muscle biopsy
  - Molecular testing

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Leigh syndrome treatment

Specific treatment for treatable nuclear encoded Leigh like syndromes:

- Biotin and thiamine for biotin-thiamine responsive basal ganglia disease
- Biotin for biotinidase deficiency
- Coenzyme Q10 for coenzyme Q10 biosynthesis deficiency

- Supportive treatment
- Prevention of secondary complications:
  - Careful consideration of anesthesia

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Alpers-Huttenlocher syndrome

1:51,000
Early childhood onset

Majority due to mutations in POLG gene

Intractable seizures
Psychomotor regression
Liver failure

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Alpers-Huttenlocher syndrome

- Seizures are first sign in ~ 50% of patients
  - most common early types are partial or secondary generalized tonic-clonic seizures
  - Status epilepticus or epilepsia partialis continua may be the first presentation
  - Seizures evolve in complex epileptic disorder
  - Valproic acid should be avoided

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Alpers-Huttenlocher syndrome

- Headaches: common first presenting symptoms, associated with visual auras
- Stroke like episodes
- Movement disorders :primarily myoclonus and choreoathetosis
- Neuropathy
- Ataxia
- Episodic psychomotor regression
- Loss of cognitive functions

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Alpers-Huttenlocher syndrome

- Liver involvement can progress rapidly to end stage liver failure
  - Treatment with Valproic acid and phenytoin is associated with rapid onset liver failure
- Disease progression is variable
- Life expectancy from 3 month to 12 years since onset of symptoms

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PEARSON Syndrome

mtDNA deletion syndrome

Bone marrow failure and transfusions dependent Sideroblastic anemia

Exocrine pancreatic insufficiency

May be fatal in infancy

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PEARSON syndrome

- Progressive condition
- Anemia manifests in 1st year of life, associated with pancytopenia,
- Multisystemic involvement :
  - Failure to thrive
  - Renal Fanconi
  - Endocrinopathies
  - Impaired cardiac function
  - Refractory diarrhea, malabsorption, steathorrea
- Treatment : transfusions, replacement of pancreatic enzymes, Coenzyme q10, antioxidants

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Sanger syndrome

AGK gene

Congenital cataracts
Proximal myopathy
Hypertrophic cardiomyopathy

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MELAS

65% to 76% affected individuals are <20 years
Multisystemic progressive disorder

80% due to m.3243 A>T mutation in MT-TL1 gene

Mitochondrial myopathy
Encephalopathy
Lactic Acidosis
Stroke-like episodes

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Neurological manifestations

Stroke like episodes	• aphasia, cortical vision loss, motor weakness, headaches, seizures
Epilepsy	• 71-96% of patients • focal and generalized seizures
Dementia	• 40-90% of patients • affecting language, perceptions, memory, attention,
Headaches	• 54-91% of patients • Migraine headaches
Myopathy	• Exercise intolerance • Weakness • Delay in motor skills

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Cardiac	• dilated and hypertrophic CMP, • cardiac conduction abnormalities
Endocrine	• short stature • diabetes
Gastrointestinal	• Cyclical vomiting, gastric dysmotility, , pseudo-obstruction, constipation, diarrhea, • Recurring pancreatitis
Renal	• Fanconi proximal tubulopathy, proteinuria,
Dermatology	• Vitiligo, hypertrichosis

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MELAS diagnostic criteria

- If the following criteria are met (Hirano et al.,):
  - Stroke-like episode before age of 40
  - Encephalopathy characterized with seizures and dementia
  - Mitochondrial myopathy
- And at least 2 of:
  - Normal early development
  - Recurrent headaches
  - Recurrent vomiting

At lest two category A and 2 category B criteria are met (Yatsuga et al,):

- Category A: headaches with vomiting, seizures, hemiplegia, cortical blindness, acute focal lesions on MRI
- Category B: high plasma or CSF lactate, abnormal mitochondria on muscle biopsy, pathogenic variant

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MELAS

Diagnosis:

- Based on diagnostic criteria
- Laboratory : lactate, plasma amino acids
- Molecular testing
- Muscle biopsy

Prognosis

- Progressive course
- episodic deterioration in relation to stroke like episodes
- Estimated median survival 16.9 years from onset of neurological features

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Treatment

- Acute management:
  - Arginine during acute event : 0.5 gr/kg IV bolus, followed by same dose 0.5 gr/kg/day continuous infusions for 2-3 days
- Chronic management :
  - Supportive
  - Arginine 150-300 mg/kg/day PO
  - Coenzyme q10 10-30 mg/kg/day PO
  - Creatine 100 mg/kg/day PO
- Avoid Valproic acid

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NARP

Prevalence not established
Pathogenic variants in MT-ATP6

Presents in childhood,
but may be quiescent or stable into adult life

Neurogenic muscle weakness
Ataxia
Retinitis pigmentosa

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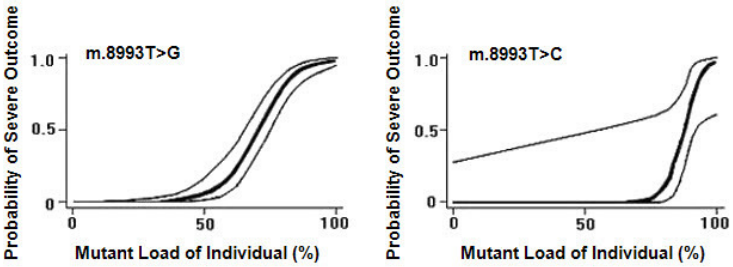
NARP

- Strong phenotype genotype correlation
- m.8993T>G phenotype depends on heteroplasmy
  - <70% are asymptomatic
  - 70-90% manifest NARP
  - >90% manifest clinically as Leigh
- m.8893T>C manifest at heteroplasmy >90%



Thornburn et al, 2017 Gene reviews

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NARP

- Clinical features:
  - Neurogenic muscle weakness, ataxia, pigmentary retinopathy
  - Seizures, learning difficulties, dementia
  - SNHL
  - Cardiac conduction defects
  - Anxiety disorder
  - MRI brain may show cerebral and cerebellar atrophic changes
- Treatment symptomatic
- Can be stable for years,
- Episodic deterioration with viral illness

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Leber Hereditary Optic Neuropathy

Common pathogenic variants account for 95% of patients

MT-ND1 MT-ND4 MT-ND6

Maternally inherited

Peak age 2nd or 3rd decade

Variable expression

Males x 4-5 times higher risk than females

Positive prognostic factors: early presentation and subacute course

Bilateral painless subacute visual failure

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Leber Hereditary Optic Neuropathy

Ophthalmological:

- Acute phase:
  - blurring of central vision, enlarged central scotoma
- Atrophic phase
  - Optic atrophy
  - Visual impairment

- Neurological
  - Tremor
  - Peripheral neuropathy
  - Movement disorder
  - Multiple sclerosis like illness
- Cardiac arrhythmias

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Leber Hereditary Optic Neuropathy

- NO preventative treatment
- Idebenone for symptomatic patients
- Supportive

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Kearns-Sayre Syndrome

Progressive cardioencephalomyopathy

single large-scale deletions in mtDNA

Retinitis pigmentosa
Ophthalmoplegia
Onset <20 y of age
Plus at least one of :
-Cardiac conduction defects
-Cerebellar ataxia
-Elevated CSF protein

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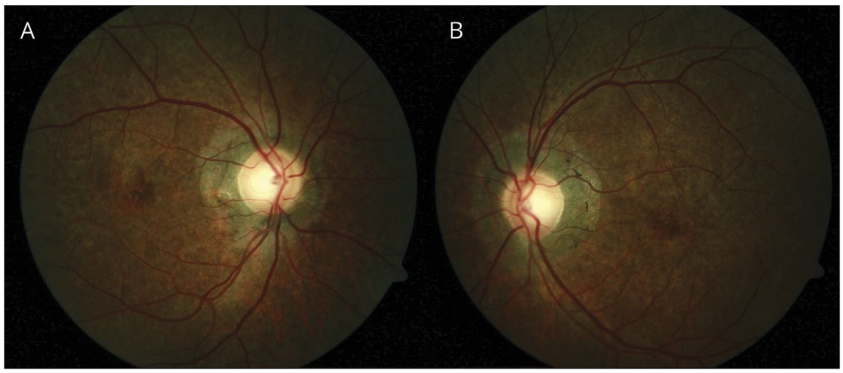
Figure 2 Pigmentary retinopathy



Michael T.B. Nguyen et al. Neurology 2019;92:e519-e520

AMERICAN ACADEMY OF NEUROLOGY

Kearns-Sayre Syndrome

- CNS: cerebellar ataxia, intellectual disability, dementia, SNHL
  - Epilepsy and metabolic stroke are rare occurrence
  - Secondary cerebral folate deficiency described
- Muscle involvement: ptosis, progressive external ophthalmoplegia, oropharyngeal , esophageal dysfunction, fatigue, proximal limb weakness
- Heart : conduction block, CMP
- Endocrinopathies: diabetes, exocrine pancreatic dysfunction, short stature
- Renal tubular acidosis

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Kearns-Sayre Syndrome

Diagnosis:

- CSF protein elevation
- Molecular testing
- Muscle biopsy showing ragged-red fibers
- Decreased activities of complexes encoded by mtDNA (I. III, IV)

Management

- Symptomatic
- Folate supplementation

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Chronic Progressive Ophthalmoplegia

- Adult onset
- Result of mtDNA deletions
- Ptosis
  Ophthalmoplegia
  Proximal limb weakness

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Genetic classification

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POLG gene

Nuclear gene that encodes the catalytic subunit of DNA polymerase γ, enzyme responsible for replicating the mitochondrial DNA

- Frequency of recessive POLG disease estimated to be ~1 in 10,000
- *POLG* mutations can lead to mtDNA depletion and/or accumulation of multiple mtDNA deletions.

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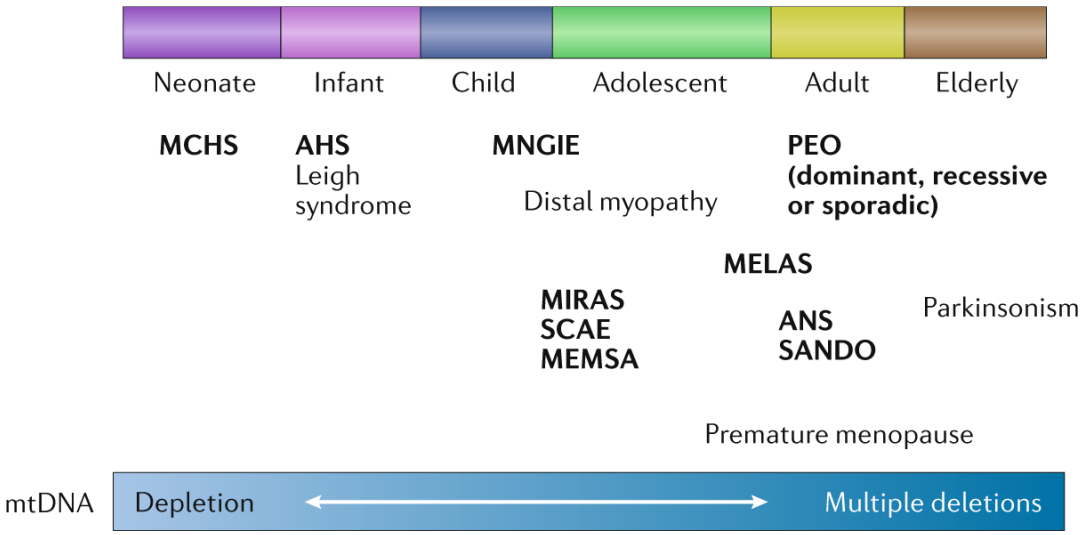

Rahman S, Copeland W , 2019

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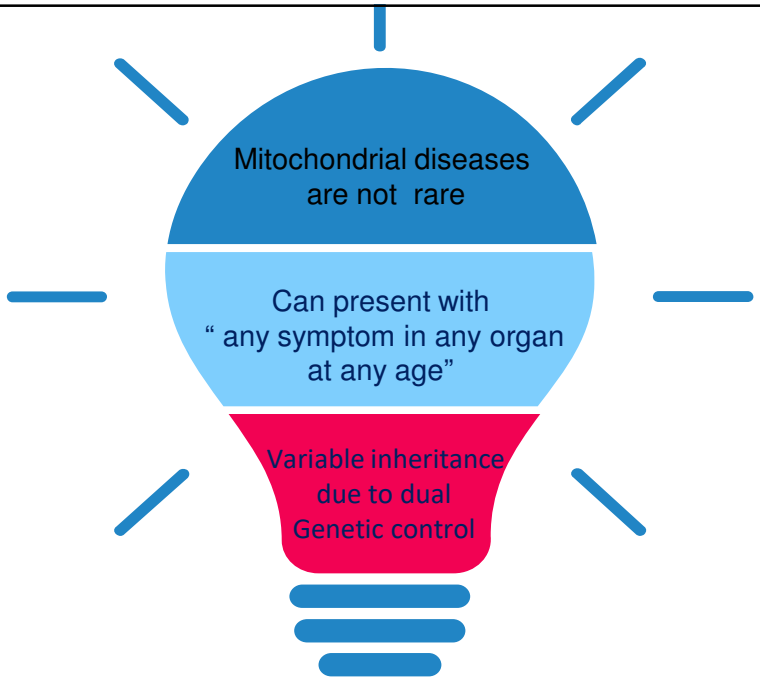

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Thank you !

Slides Carnival

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