MRC Mitochondrial Biology Unit

UNIVERSITY OF CAMBRIDGE

Mitochondrial disease: cause

- Many mitochondrial disorders, resulting from mutations in both nuclear and mitochondrial DNA, have been characterised
- Here, we focus on some of the diseases caused by mutations to mitochondrial DNA

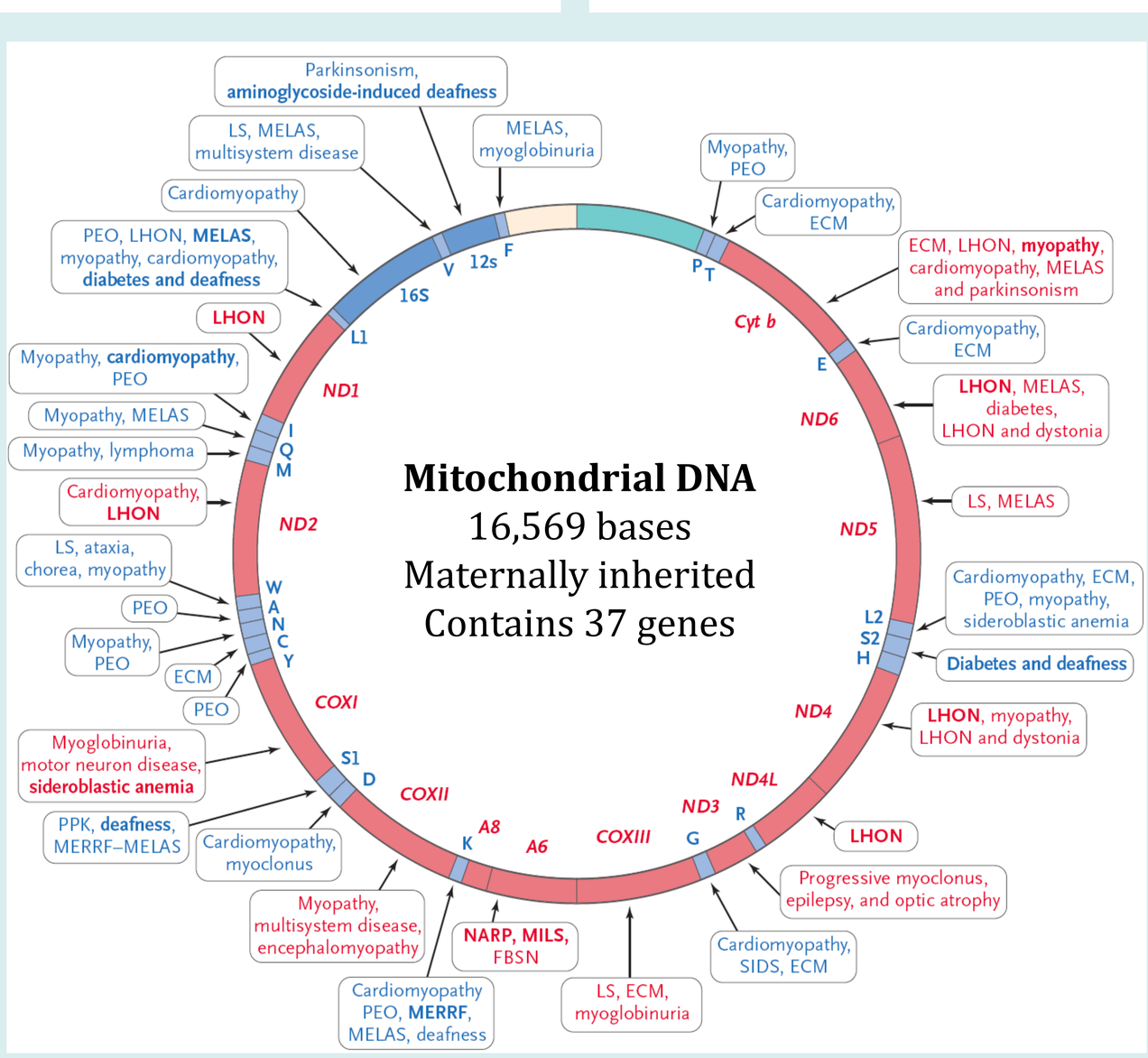
LHON (Leber's hereditary optic neuropathy)

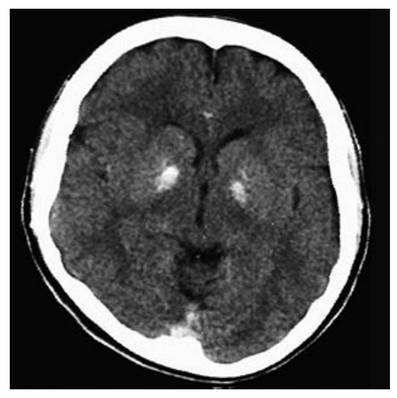
- Mutations: 3460G>A (complex I: ND1)
  11778G>A (complex I: ND4)
  14484T>C (complex I: ND6)
- Affects: Rentinal ganglion cells
- Symptoms: Sudden, painless loss of central vision, initially in one eye; second eye affected after 2 – 3 months

MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

- Mutations: 3243A>G (transfer RNA: leu)
  3271T>C (transfer RNA: leu)
- Affects: Brain and nervous system
- Symptoms: Stroke-like episodes in the brain, migraines, vomiting, seizures; muscle weakness, exercise intolerance

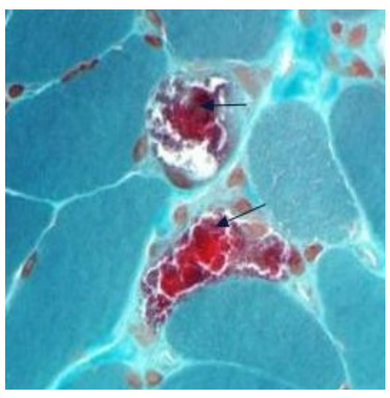
Typical sight impairment of a LHON sufferer



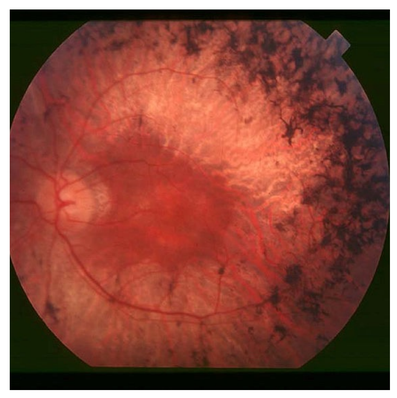


A CT scan of a MELAS sufferer

Clumps of diseased mitochondria appear as "ragged red fibers" in muscle



Retinal atrophy of a NARP sufferer



MERFF (Myoclonic Epilepsy with Ragged Red Fibers)

- Mutations: 8344A>G (transfer RNA: lys)
  8356T>C (transfer RNA: lys)
- Affects: Muscles and nervous system
- Symptoms: Myoclonus (muscle jerks), seizures, ataxia and muscle weakness; deafness and short stature

NARP (Neuropathy, ataxia, and retinitis pigmentosa)

- Mutation: 8993T>G (ATP synthase: ATP6)
- Affects: Nervous system
- Symptoms: NARP causes retinitis pigmentosa (blindness), neuropathy and ataxia

- Other mitochondrial diseases involve large deletions of the mitochondrial genome:
  - Kearns-Sayre syndrome: myopathy, ophthalmoplegia, cardiomyopathy
  - CPEO: paralysis of eye movement