Mitochondrial diseases affecting nervous system and muscle

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**Respiratory chain** is composed of complexes located at the inner mitochondrial membrane:

- **Complex I**: NADH ubiquinone reductase
- **Complex II**: succinate: ubiquinone oxidoreductase
- **Complex III**: ubiquinol cytochrome c reductase
- **Complex IV**: cytochrome C oxidase
- **Complex V**: ATP synthase

Final goal: production of ATP

Respiratory chain proteins are synthesized from two different genomes: mtDNA and nDNA

- mtDNA encodes 13 respiratory chain polypeptides, 2 rRNAs and 22 tRNAs
- nDNA encodes the majority of respiratory chain polypeptides

Transport of cytosolic proteins and their assembly with mitochondrial-encoded proteins, and proteins needed for mitochondrial transcription and translation, and mitochondrial RNA metabolism are also encoded by nDNA.

Primary mitochondrial diseases (mitochondrial cytopathies, systemic, cerebral, endocrine and muscular, and combinations of all of the them) are the consequence of dysfunctions of both mitochondrial and nuclear genes either separately or in combination. As a result, oxidative phosphorylation (OXPHOS) is defective. Several complexes can be damaged, although the most common deficiencies affect complexes I and IV.
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Molecular genetics of main mitochondrial disorders

mtDNA mutations

large-scale rearrangements
deletions Chronic progressive external ophtalmoplegia (CPEO), Kearns-Sayre syndrome (KSS), Pearson syndrome (marrow-pancreas syndrome)
duplications

point mutations in tRNAs or rRNAs
• MELAS
• MERRF
• Mitochondrial cardiomyopathy and myopathy

point mutations in protein coding genes
• ATP6 mutations: NARP, Leigh syndrome
• Complex I mutations: Leber hereditary optic atrophy (LHON)
• Complex IV (COX) subunit mutations

Nuclear gene mutations
• Autosomal dominant and autosomal recessive progressive external ophtalmoplegia (AdPEO, ArPEO)
• MNGIE: myogastrointestinal encephalopathy: mutations in thymidine phosphorylase gene (22q13)
• Wolfram syndrome (DID-MOAD): mutations in wolframin gene (4p16) associated with large scale mtDNA deletions
• Leigh syndrome caused by nuclear gene mutations affecting complexes I, II or IV
• Infantile hypertrophic cardiomyopathy and encephalomyopathy: mutations in SCO2 gene

Mutations in other mitochondrial protein genes
• Hereditary spastic paraplegia linked to 16q24
• Friedreich ataxia, mutations in the frataxin gene in 9q13
Peripheral aggregates (A) are usually strongly stained with trichrome (B) and show increased SDH immunoreactivity (C) (arrows). This is often accompanied by COX negative, SDH positive fibers (D, short arrow).
Mitochondrial myopathy

Red aggregates (arrows) as seen in mitochondrial myopathy stained with trichrome
Mitochondrial myopathy

Abnormal mitochondria in muscle fibers with altered morphology and crystalline inclusions
Chronic progressive external ophtalmoplegia (CPEO)

Ragged-red fibers as seen following H-E staining (A); mild accumulation of punctate red deposits with modified trichrome (B); SDH enhancement in the periphery of the fibers; and increased COX staining of scattered fibers.
Abnormal mitochondria in muscle fibers with aberrant morphology and crystalline inclusions accompanied by lipofuscin deposits
Mitochondrial myopathy

Mild variation in fiber size (A) accompanied by increased NADH (B) and SDH staining in the periphery of certain fibers (C) and within small fibers (D, E, respectively), and COX negative SDH positive fibers (F)
Abnormal mitochondria in muscle fibers with giant size and altered morphology of the cristae
Mitochondrial myopathy and complex I deficiency

A: Several muscle fibers show sub-sarcolemmal deposits (arrows);
B: two ragged red fibers (asterisks)
Mitochondrial myopathy and complex I deficiency

Large numbers of abnormal mitochondria in muscle fibers. Elongated mitochondria show abnormal cristae and crystalline inclusions.
A, E: H-E, variation in fiber size, sub-sarcolemmal deposits (arrows); B NADH, increased signal in individual fibers (asterisk); C: ATPase pH 4.3, variation in fiber size and one ragged red fiber (short arrow); D: Oil red O showing increased lipid droplets in two fibers; F, SDH, blue-ragged fiber (asterisk); G-I: semi-thin sections stained with toluidine blue, sub-sarcolemmal deposits (arrows): ragged-red fibers.
Increased numbers of mitochondria with abnormal cristae and dense intramitochondrial inclusions
Gel electrophoresis and western blotting to different sub-units of respiratory chain components in control and Kearns-Sayre case processed in parallel.
Expression levels of ATP synthase; cytochrome c reductase; succino dehydrogenase (SDH); cytochrome c oxidase (COX); reduced nicotinamide adenine dinucleotide (NADH) in the pons, cerebral cortex, cerebellum and medulla oblongata of one control and one case of Kearns-Sayre. Reduced expression levels of several subunits are observed in the majority of brain regions in Kearns-Sayre case.
Mitochondrial leucoencephalopathy in infancy with lactic acidosis

Atrophy of the cerebral cortex, caudate and putamen, and thalamus, together with reduced cerebral white matter, periventricular demyelination, and enlargement of the lateral ventricles. Demeylination of the cerebellar white matter. Klüver-Barrera staining.
Mitochondrial leucoencephalopathy with lactic acidosis in infancy

A, B and C: variable neuron loss, spongiosis and focal necrosis in the cerebral cortex; D: cystic necrosis in the white matter; E: mineralisation of thalamic neurons; F: neuron loss and marked astrocytic gliosis in the cerebellar cortex; G, H: myelin loss, spongiosis and vascular proliferation in the white matter. H-E staining
Mitochondrial leucoencephalopathy with lactic acidosis in infancy

Myopathy with abnormal mitochondria. Increased numbers of large mitochondria with abnormal cristae in muscle fibers.
Leigh syndrome

A: bilateral necrosis of the putamen; B: cystic necrosis of the basal ganglia; C: demyelination of the cerebellar white matter and pyramidal tracts; D: multiple foci of infarct-like lesions in the pons; E: cystic necrosis of the optic nerves; F: vacuolization of the white matter of the centrum semi-ovale.
Leigh syndrome

A: subthalamus; B: white matter; C: putamenr (PAS stain); D: substantia nigra; E: cerebral white matter; and F: cerebellar white matter (CD68, microglia). Neuron loss, severe white matter involvement, edema, endothelial hyperplasia and microglial activation.
Alpers syndrome

A: marked atrophy of the cerebral cortex, basal ganglia and cerebellum; B: atrophy of the cerebral cortex and caudate; reduced white matter; C: neuronal loss and gliosis of the cerebral cortex; D: neuronal loss and spongiosis in the upper cortical layers; E: marked loss of granule cells and Purkinje cells in the cerebellar cortex.
MELAS

A-C: infarct-like lesions in the cerebral cortex (arrows) and bilateral lucencies in the basal ganglia (asterisks); D: subsarcolemmal slight increase of SDH activity; E: abnormal mitochondria with crystalline inclusions in muscle fibers.
Neuropathy, ataxia, retinitis pigmentaria: NARP

8993 T > G mutation of the mtDNA

A: Atrophy of the cerebral cortex and enlargement of the ventricles, bilateral putaminal hypodensities (arrows). B: Moderate atrophy of the insular region, enlargement of the lateral ventricles, cystic necrosis in the putamen and marked atrophy of the optic pathways
Neuropathy, ataxia, retinitis pigmentaria (NARP)

A: Cerebellar atrophy. B, C: Marked neuronal loss and gliosis in the Purkinje and granular cell layers of the cerebellum, together with focal necrosis in the molecular layer. D: Axonal torpedo in the cerebellum. A-C haematoxylin and eosin; D immunohistochemistry to phosphorylated neurofilaments.
Neuropathy, ataxia, retinitis pigmentaria (NARP)


A: Cystic and submassive necrosis in the putamen. B: Neuron loss and cysts in the caudate. H-E.
Neuropathy, ataxia, retinitis pigmentaria (NARP)

Temporal muscle. A: Variation in fibre size as seen in modified Gomori’s trichrome stained sections. B, C: Increased subsarcolemmal oxidative staining in scattered muscle fibers as seen with SDH (B) and cytochrome c oxidase (C) histochemistry. Cryostat sections.
**MNGIE: myo- and neuro-gastrointestinal leucoencephalopathy**

POLIP: polyneuropathy, ophtalmoplegia, leucoencephalopathy and intestinal pseudo-obstruction; OGIMD: oculo-gastro-intestinal muscular dystrophy; MEPOP: mitochondrial encephalomyopathy, sensorimotor polyneuropathy, ophtalmoplegia and pseudo-obstruction

- White matter hyperlucencies (often asymptomatic)
- Atrophy of the muscular layers of the colon
MNGIE: myo- and neuro-gastrointestinal leucoencephalopathy: POLIP

Combination of denervation atrophy and mitochondriopathy. A. A large group of atrophic fibers; and B. Target fibers consistent with denervation; C and D: Increased SDH reaction in COX negative fibers
**Wolfram syndrome:** diabetes insipidus, insulin-dependent diabetes mellitus, optic neuropathy and deafness

Atrophy of the olfactory bulbs and tracts (white arrows), atrophy of the optic nerves and chiasm (asterisk), atrophy of the cochlear nerve, mild olivopontocerebellar atrophy.

Mutations in wolframin gene (endoplasmic reticulum-related protein) and large-scale mtDNA deletions in some patients.
Wolfram syndrome

A: loss of Purkinje cells, and axonal torpedoe; B: atrophy of the optic nerve; myelin basic protein immunostaining; C: atrophy of the superior colliculus; D: loss of fibers in the cochlear nerve; E: cochlear nucleus; F: moderate neuron loss in the inferior olive