

Mitochondrial Encephalomyopathies

Energy failure, mitochondrial genetics and CNS pathology

Mitochondrial genomes • Tissue energy failure • Clinicopathologic syndromes

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Learning objectives

Explain why mitochondrial dysfunction often affects neurons and skeletal muscle

Distinguish mitochondrial from nuclear genetic contributions

Interpret heteroplasmy, tissue lactate and cytochrome oxidase histochemistry

Correlate MELAS, MERRF and Leigh syndrome with characteristic pathology

A family of disorders of energy generation

Primary defect

Impaired mitochondrial
oxidative phosphorylation

CNS consequence

Neurons depend on
mitochondrial ATP
production

Systemic expression

Other energy-dependent
tissues may be involved

Encephalo- and myopathy are linked

Encephalopathy

Neurologic dysfunction may dominate the presentation

Energy-dependent CNS cells are vulnerable

Myopathy

Weakness or characteristic muscle changes may coexist

The same cellular energy system is affected

Neuronal ATP demand explains CNS involvement

Oxidative phosphorylation

Major mechanism
supplying neuronal ATP



Reduced ATP generation

Loss of energy available
for neuronal function



Neurologic disease

Variable clinical and tissue
injury

Mitochondrial ATP synthesis is the shared pathway

Respiratory machinery

Mitochondrial proteins support oxidative phosphorylation



ATP production

Efficient energy generation for active cells



Affected tissues

Neurons and skeletal muscle are prominently vulnerable

Disease mechanisms span two genomes

Mitochondrial DNA

Encodes a small set of proteins and mitochondrial RNAs

Mutations may produce maternal transmission

Nuclear DNA

Encodes most required mitochondrial proteins

Mutations may show Mendelian inheritance

Mitochondrial DNA has a compact coding repertoire

13

Protein-coding genes

22

Transfer RNA genes

2

Ribosomal RNA genes

Most mitochondrial components are nuclear encoded

Nuclear genome

Codes for most proteins needed for mitochondrial structure/function

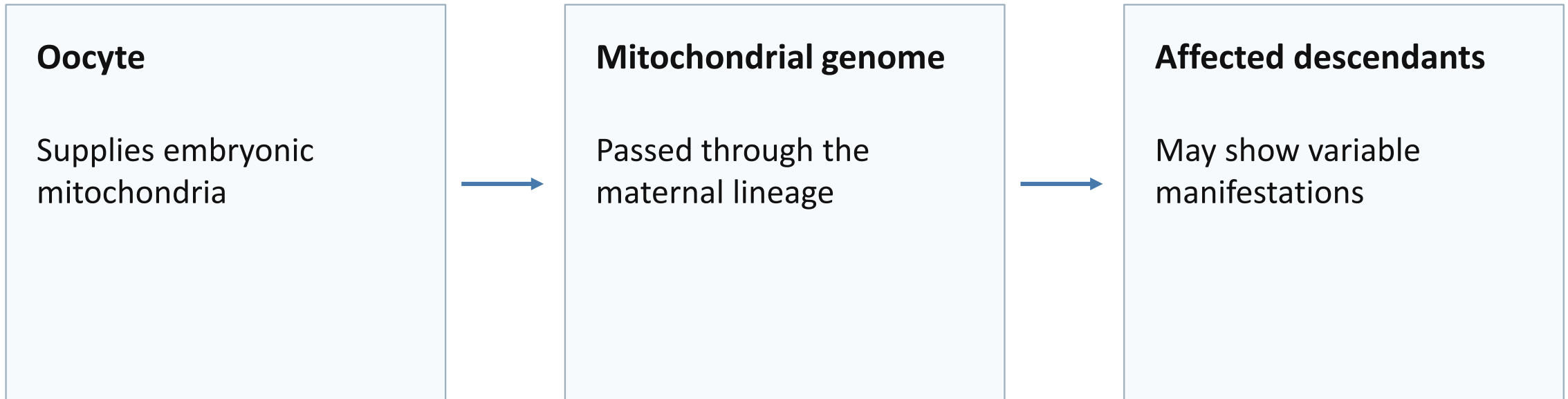
Mitochondrial genome

Codes for 13 proteins and essential RNAs

Clinical consequence

An oxidative phosphorylation disorder need not follow maternal inheritance

Maternal transmission follows organelle origin



Nuclear mutations do not require maternal transmission

MtDNA-associated disease

Maternal transmission can be a clue

Interpret alongside clinical phenotype

Nuclear-gene disease

Mendelian patterns are possible

A negative maternal pattern does not
exclude disease

Pedigree pattern is a clue, not a diagnosis

Maternal clustering can support a mitochondrial-genome mechanism

Nuclear mutations can cause the same broad clinical category

Genetic heterogeneity prevents a single inheritance rule

Pair pedigree interpretation with tissue and molecular evidence

Each cell contains many mitochondrial genomes

Copy number

Cells contain thousands of mitochondrial DNA copies

Distribution

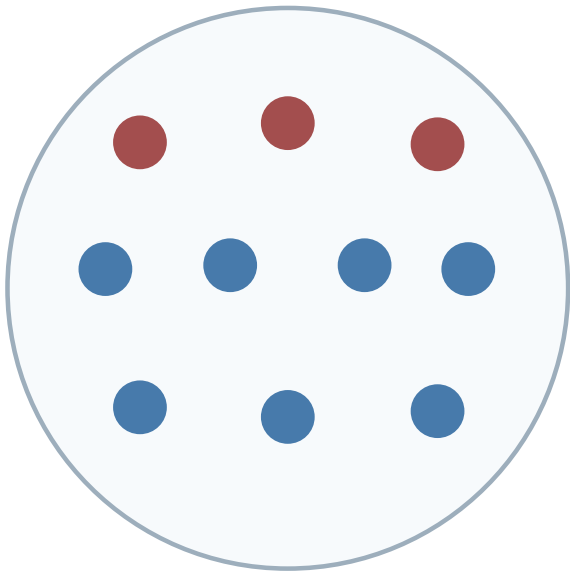
Copies are not partitioned in fixed equal proportions

Consequence

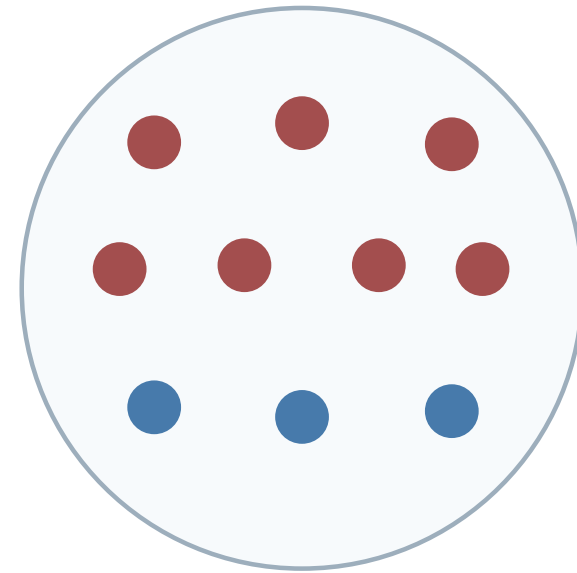
Descendants of a cell may differ genetically

Heteroplasmy: Mixed normal and mutant mtDNA

Lower mutant fraction



Higher mutant fraction

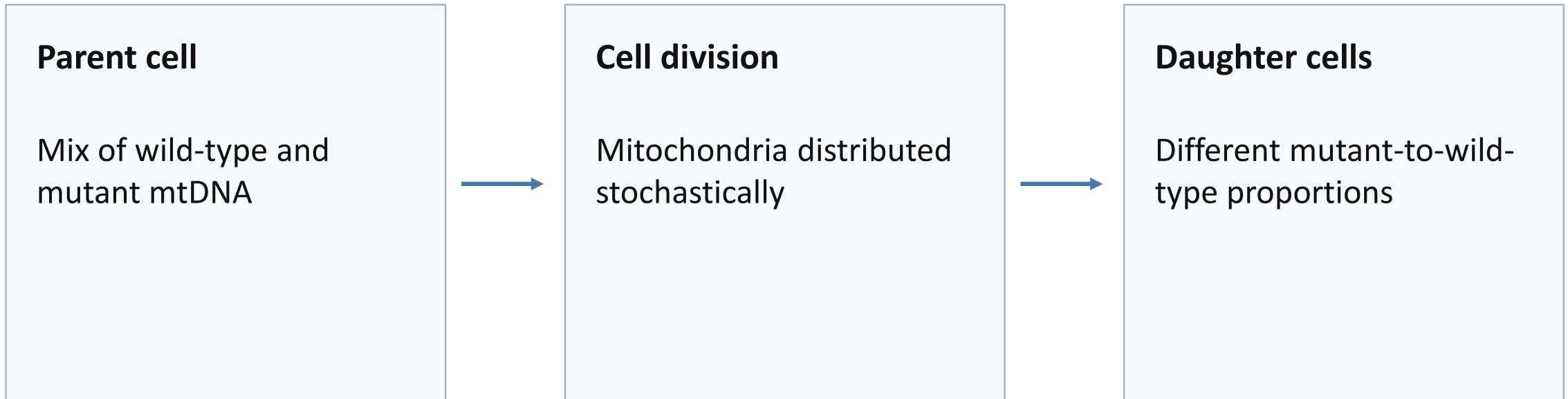


● Wild-type mtDNA

● Mutant mtDNA

Schematic mtDNA proportions (not measured)

Random mitochondrial segregation changes mutant load



Heteroplasmy produces tissue-level mosaicism

Cell A

Lower proportion of
mutant mtDNA

Cell B

Higher proportion of
mutant mtDNA

Clinical result

Variable functional
impairment within tissues

A tissue threshold helps explain clinical onset

Variable mutant load

Heteroplasmy differs by cell and tissue



Functional threshold

Sufficiently high burden impairs ATP production



Symptomatic tissue

Vulnerability depends on tissue energy demand

One mutation can produce different clinical phenotypes

One genetic variant

Mitochondrial leucine tRNA variant

Different manifestations

**Isolated external ophthalmoplegia or
severe MELAS**

A similar phenotype can result from different variants

Shared phenotype

Leigh syndrome

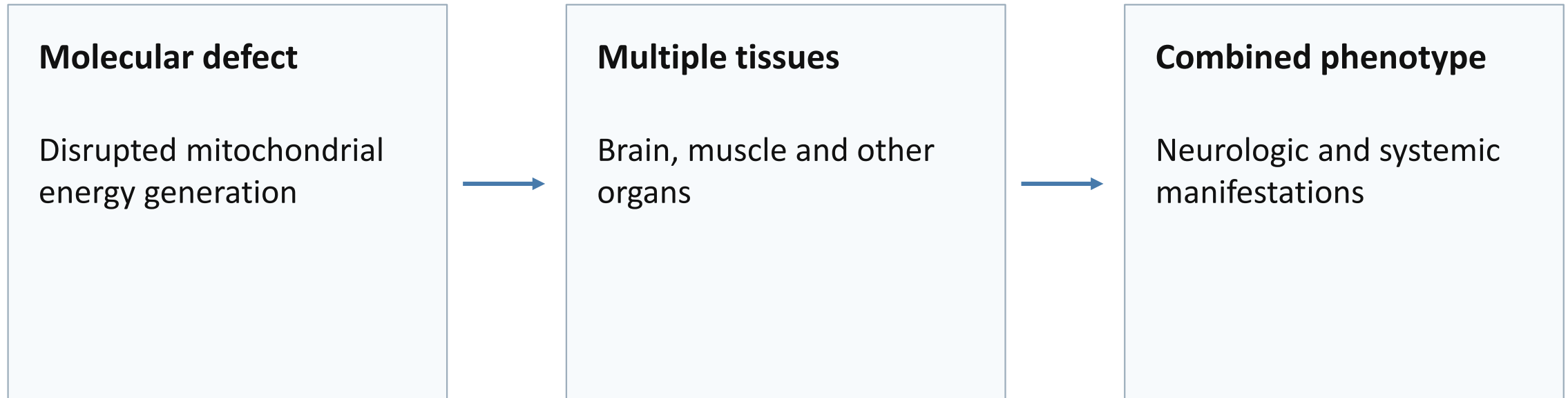
Multiple causes

Mutations in mtDNA or
nuclear genes

Unifying dysfunction

Essential mitochondrial
metabolic pathways

Pleiotropy links neurologic and non-neurologic signs



Skeletal muscle can reveal systemic mitochondrial disease

Variable weakness may accompany CNS dysfunction

Serum creatine kinase can be elevated

Rhabdomyolysis is possible in some mitochondrial myopathies

Extraocular muscle involvement is a useful clinical clue

External ophthalmoplegia signals an energy-sensitive muscle

Clinical sign

Chronic progressive
external ophthalmoplegia

Muscle physiology

Extraocular muscles have
very high mitochondrial
content

Interpretation

Can be isolated or part of a
multisystem syndrome

Mitochondrial myopathy has characteristic structural changes

Light microscopy

Subsarcolemmal
mitochondrial aggregates

Electron microscopy

Morphologically abnormal
mitochondria

Histochemistry

Reduced activity of
specific mitochondrial
enzymes

Ragged red fibers reflect mitochondrial accumulation

Abnormal mitochondria

Accumulation beneath the sarcolemma



Gomori trichrome

Reddish granular fiber periphery

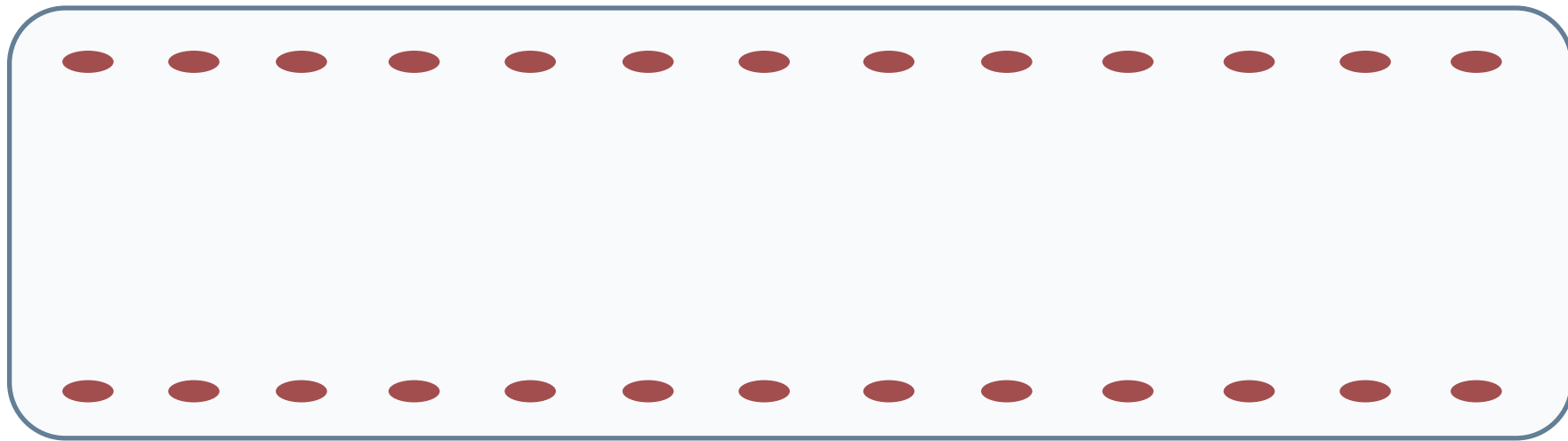


Ragged red fiber

A structural clue to mitochondrial myopathy

Ragged red fiber: What the stain indicates

Schematic muscle fiber (not a photomicrograph)



Peripheral mitochondrial aggregates

Reddish granular subsarcolemmal pattern on Gomori trichrome

Electron microscopy can show abnormal mitochondria

Ultrastructural examination may disclose mitochondrial abnormalities

Concentric membranous rings are described figure

Rhomboid paracrystalline inclusions may occur

These observations are morphologic, not a stand-alone genotype

Cytochrome c oxidase activity is a functional marker

Mitochondrial dysfunction

Loss of enzyme activity in some disorders



Nonfixed tissue

Histochemical assessment of cytochrome oxidase



Interpretation

Functional evidence complementing morphology

An unremarkable biopsy does not exclude disease

Some patients

Show ragged red fibers or enzyme loss

Histochemical abnormality is supportive

Other patients

Lack conspicuous muscle morphologic changes

Enzyme assays or genetic analysis may be required

Impaired oxidative metabolism is reflected in lactate

Reduced oxidative ATP generation

Metabolic energetic impairment



Tissue lactate

Often elevated in CNS mitochondrial disease



Diagnostic evidence

Supports—but does not alone define—the disorder

MR spectroscopy can demonstrate elevated tissue lactate

Biochemical signal

Increased lactate
associated with energy
failure

Imaging method

Spectroscopic imaging of
involved tissues

Interpretation

A physiologic clue in the
appropriate clinical setting

Diagnostic assessment must integrate evidence

Phenotype and pedigree

Neurologic, muscle and family features



Metabolic and tissue studies

Lactate, histochemistry, morphology



Molecular evaluation

Variants in mitochondrial or nuclear DNA

Three recognizable clinical patterns

MELAS

Stroke-like episodes, lactic acidosis and encephalomyopathy

MERRF

Myoclonus and ragged red fibers, often with ataxia

Leigh syndrome

Infantile psychomotor arrest and symmetric destructive CNS lesions

MELAS: Clinical meaning of the acronym

M

Mitochondrial

E

Encephalomyopathy

LA

Lactic acidosis

S

Stroke-like episodes

MELAS causes recurrent acute neurologic episodes

Recurrent episodes of acute neurologic dysfunction are characteristic

Cognitive changes may develop

The presentation occurs in the context of systemic mitochondrial dysfunction

Clinical episodes should be interpreted together with metabolic findings

Lactic acidosis and weakness anchor MELAS systemically

CNS

**Acute neurologic dysfunction and
cognitive disturbance**

Muscle / metabolism

Weakness and lactic acidosis

MELAS can produce infarct-like tissue destruction

Neuropathology

Infarcts may be found

Associated findings

Vascular proliferation can accompany lesions

Additional change

Focal calcification may be present

Vascular proliferation and calcification in MELAS

Disease context

Mitochondrial
encephalomyopathy

Parenchymal observation

Infarcts may occur

Associated morphology

Vascular proliferation ±
focal calcification

MELAS is often associated with a leucine tRNA gene

Frequent association

Mutation in the
mitochondrial leucine
tRNA gene

Textbook designation

MTTL1 in the supplied
Robbins text

Interpretation

A common association,
not a universal genotype

MELAS illustrates variable expressivity

Same variant

Mitochondrial leucine tRNA change

Phenotypic range

Isolated ophthalmoplegia or MELAS

MELAS: A clinicopathologic synthesis

Recurrent neurologic attacks

With cognitive alteration



Muscle and metabolism

Weakness and lactic acidosis



Neuropathology

Infarcts $\pm$ vascular proliferation/calcification

MERRF: A neuromuscular–epileptic phenotype

M

Myoclonic

E

Epilepsy

RRF

Ragged red fibers

**Mat
erna
l**

Maternally transmitted
syndrome

MERRF combines myoclonus with mitochondrial myopathy

Neurologic

Myoclonus, a seizure manifestation

Muscle

Myopathy with ragged red fibers

Ataxia in MERRF correlates with cerebellar neuron loss

Cerebellar neuronal loss

Recognized pathology in
MERRF



Disrupted coordination

Functional consequence



Ataxia

A common clinical feature

MERRF may damage spinal white matter tracts

Affected tissue

White matter tracts in spinal cord

Morphologic change

Degeneration

Clinical context

Additional neurological dysfunction with ataxia

Most MERRF cases involve mitochondrial tRNA genes

Genetic substrate

Pathogenic variants in
mitochondrial tRNA genes

Transmission

Commonly maternal

Phenotype

Myoclonus, myopathy,
ataxia

Ragged red fibers support MERRF but are not exclusive

MERRF

Uses ragged red fibers in its syndrome name

Other disorders

Mitochondrial myopathies can also show mitochondrial aggregates

MERRF links muscle and CNS pathology

Mitochondrial tRNA defect

Disrupted mitochondrial function



Muscle involvement

Ragged red myofibers



Neural involvement

Myoclonus, cerebellar loss, tract degeneration

Leigh syndrome: A severe early-life disorder

Typical onset

Infancy

Early course

Psychomotor development
arrests

Systemic metabolism

Lactic acidemia commonly
occurs

Leigh syndrome has a broad neurologic presentation

Feeding difficulties can be prominent

Seizures may develop

Extraocular muscle palsies may occur

Weakness with hypotonia is characteristic

Leigh syndrome preferentially affects deep CNS structures

Brainstem nuclei

Typically involved

Thalamus

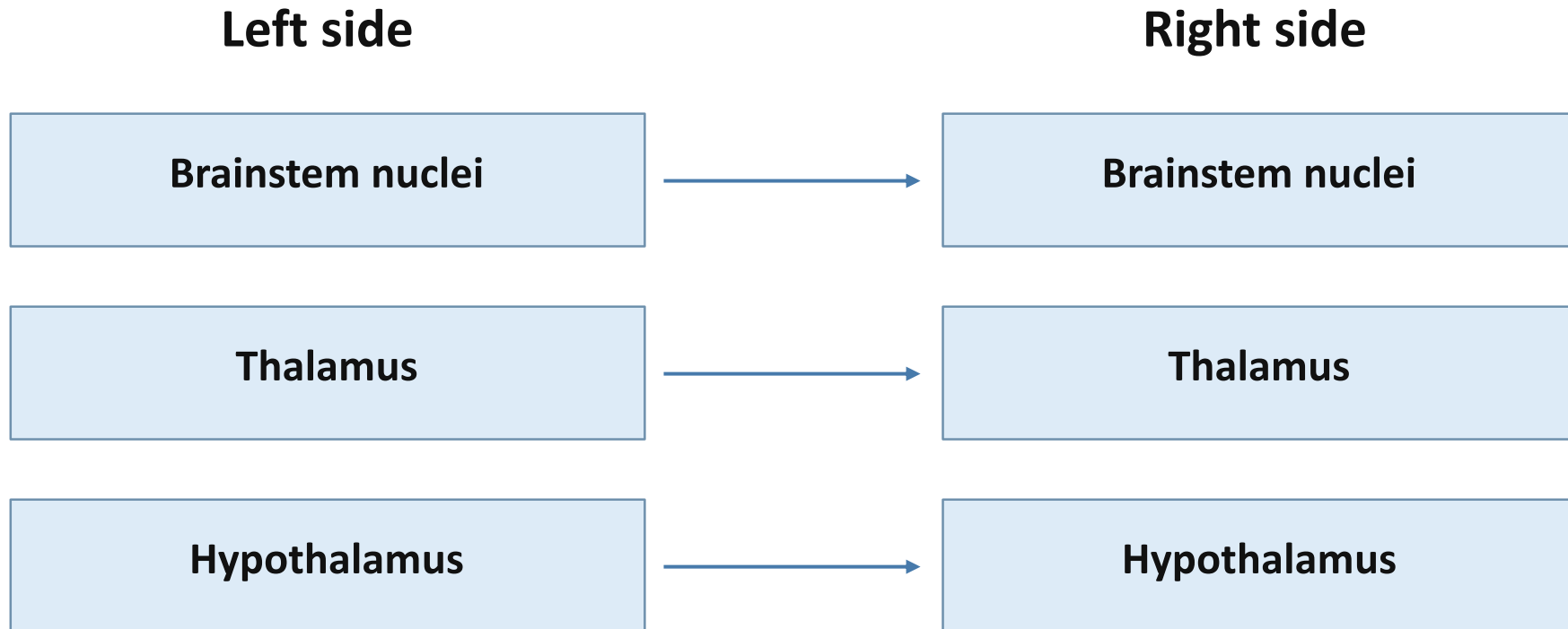
Typically involved

Hypothalamus

Typically involved

Leigh lesions are often bilaterally symmetric

Schematic paired distribution: Not an anatomical section



Usually symmetric lesions involving characteristic deep structures

Leigh histology shows destructive spongiform lesions

Parenchyma

Multifocal areas of tissue destruction

Background

Spongiform appearance

Vessels

Associated vascular proliferation

Leigh has marked nuclear and mtDNA heterogeneity

Mitochondrial DNA

**Some disease-causing mutations
reside in mtDNA**

Nuclear DNA

**Many mutations affecting
mitochondrial metabolism are also
implicated**

Classic infantile Leigh disease is often rapidly progressive

Textbook description emphasizes the severe infantile presentation

Psychomotor arrest accompanies multiple brainstem / deep gray manifestations

Death usually within 1–2 years in this classic presentation

The statement should not be generalized to every molecularly defined phenotype

Leigh: Pathology explains its clinical localization

**Symmetric brainstem /
deep nuclei**

Multifocal spongiform
destructive injury



**Ocular, feeding, motor
functions**

Neural pathways and
nuclei affected



**Infantile neurologic
syndrome**

Palsies, feeding problems,
hypotonia, seizures

Compare hallmark manifestations across syndromes

Feature	MELAS	MERRF	Leigh
Dominant presentation	Stroke-like episodes	Myoclonus / myopathy	Infantile psychomotor arrest
Metabolic feature	Lactic acidosis	Oxidative dysfunction	Lactic acidemia
Structural clue	Infarcts, vascular change	Ragged red fibers	Symmetric spongiform lesions

Anatomical pattern helps separate phenotypes

Syndrome	Typical anatomic clue	Underlying tissue change
MELAS	Brain parenchyma	Infarcts $\pm$ vascular proliferation
MERRF	Cerebellum and spinal tracts	Neuronal loss; tract degeneration
Leigh	Brainstem / thalamus / hypothalamus	Symmetric destructive spongiform lesions

Genetic patterns differ even with one mechanism

Pattern	Relevant example	Diagnostic implication
Maternal mtDNA	MERRF; common MELAS variant	Maternal history may help
Nuclear-gene variants	Some Leigh cases	Nonmaternal pedigrees possible
Heteroplasmy	Across mtDNA disorders	Variation within families and tissues

Different kinds of evidence answer different questions

Phenotype

Which organs and functions are involved?

Morphology / biochemistry

Is mitochondrial dysfunction plausible?

Molecular testing

Which genome and variant are implicated?

Three common diagnostic over-interpretations

“Always maternal”

Incorrect: Nuclear genes also cause mitochondrial disease

“Normal biopsy excludes”

Incorrect: Some disorders lack overt muscle morphology

“One mutation = one syndrome”

Incorrect: Genotype–phenotype mapping is complex

Teaching case: Episodic neurologic dysfunction

A patient has recurrent acute neurologic episodes and cognitive changes

Muscle weakness accompanies elevated lactate

Neuropathology documents infarct-like changes with vascular proliferation

Which of the three syndromes is most strongly suggested?

Case resolution: MELAS

MELAS

Recurrent stroke-like neurologic dysfunction is the discriminating clue

Lactic acidosis and muscle involvement strengthen the pattern

The infarct-type pathology and vascular changes match the Robbins description

Teaching case: Myoclonus with abnormal muscle stain

Myoclonic epilepsy develops with a myopathy

Muscle biopsy shows subsarcolemmal red granularity on Gomori trichrome

Ataxia and cerebellar neuronal loss are documented

Identify the clinicopathologic syndrome.

Case resolution: MERRF

MERRF

Myoclonus plus ragged red fibers identifies the classic syndrome

Ataxia corresponds to cerebellar neuronal loss

Mitochondrial tRNA mutations are associated with most cases

Teaching case: Infantile regression with symmetric lesions

An infant develops feeding difficulty, hypotonia and psychomotor arrest

Lactic acidemia is present

Symmetric brainstem and thalamic spongiform destructive lesions are identified

Which syndrome best explains this combination?

Case resolution: Leigh syndrome

Leigh syndrome

Infantile neurologic deterioration and lactic acidemia fit the syndrome

Symmetric deep gray and brainstem involvement is highly characteristic

Both nuclear and mitochondrial gene defects are possible

Principles to retain

Defective oxidative phosphorylation links neurologic and muscle disease

Both nuclear and mitochondrial genomes can be causal

Heteroplasmy helps explain variable tissue expression

MELAS, MERRF and Leigh have distinguishing clinicopathologic patterns

Primary reading

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026).

Chapter 28: The Central Nervous System — Mitochondrial Encephalomyopathies, pp. 1174–1175.

Chapter 27: Peripheral Nerves and Skeletal Muscles — Mitochondrial Myopathies, pp. 1123–1125.