

Mitochondrial Myopathies

Molecular mechanisms · skeletal-muscle pathology · clinicogenetic syndromes

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Relate impaired mitochondrial ATP production to skeletal-muscle disease.
- Contrast mtDNA and nuclear genetic inheritance.
- Explain heteroplasmy, segregation and the threshold concept.
- Recognize morphology and the named clinicogenetic syndromes.

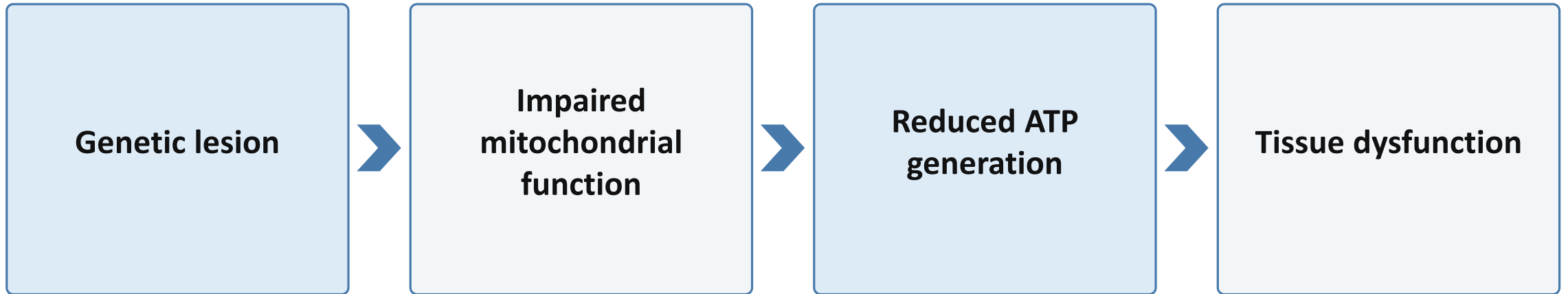
A mitochondrial myopathy is often systemic

- Mitochondrial disease can involve many organs—not skeletal muscle alone.
- Muscle weakness may coexist with neurologic, ocular or cardiac features.
- Systemic manifestations are relevant when interpreting a muscle biopsy.

Clinical / conceptual emphasis

Organ involvement is not restricted to one tissue.

Impaired ATP generation is a central mechanism



Schematic sequence; Arrows denote conceptual progression.

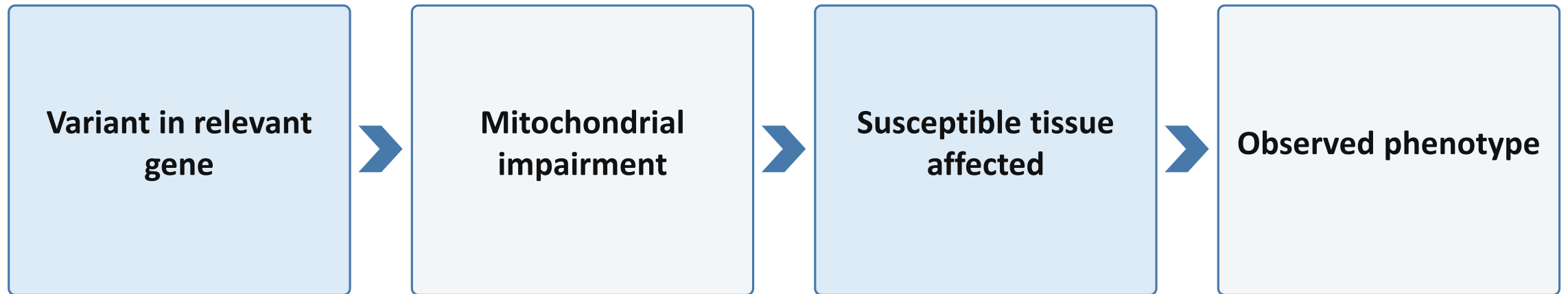
Why skeletal muscle can be affected

- Skeletal-muscle fibers depend on adequate cellular energy supply.
- Mitochondrial defects can therefore produce a primary myopathic phenotype.
- Clinical involvement is variable rather than confined to one muscle group.

Clinical / conceptual emphasis

**Metabolic dysfunction
can become structural
and clinical muscle
disease.**

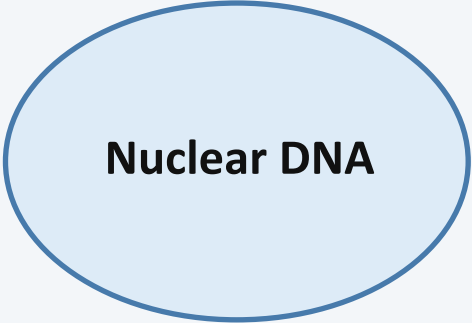
From molecular defect to patient phenotype



Schematic sequence; Arrows denote conceptual progression.

Two genomes contribute to mitochondrial function

NUCLEAR GENOME

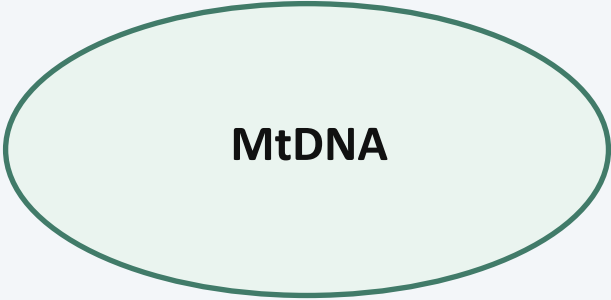


A light blue oval with a dark blue border, representing the nuclear genome, is centered within a larger light blue rectangular box.

Nuclear DNA

Mendelian inheritance

MITOCHONDRIAL GENOME



A light green oval with a dark green border, representing the mitochondrial genome, is centered within a larger light blue rectangular box.

MtDNA

Maternal inheritance

Native vector schematic: Compartments are conceptual, not to anatomical scale.

Mitochondrial proteins and tRNAs

- Disorders need not arise from mutations in protein-coding mtDNA alone.
- Mitochondrial tRNA genes are one source of pathogenic point mutations.
- Altered mitochondrial metabolism is the common biologic theme.

Clinical / conceptual emphasis

Genetic lesion ≠ single obligatory clinical syndrome.

Inheritance depends on the affected genome

Nuclear genome

Mendelian inheritance

Both parental genomes contribute

Multiple possible inheritance patterns

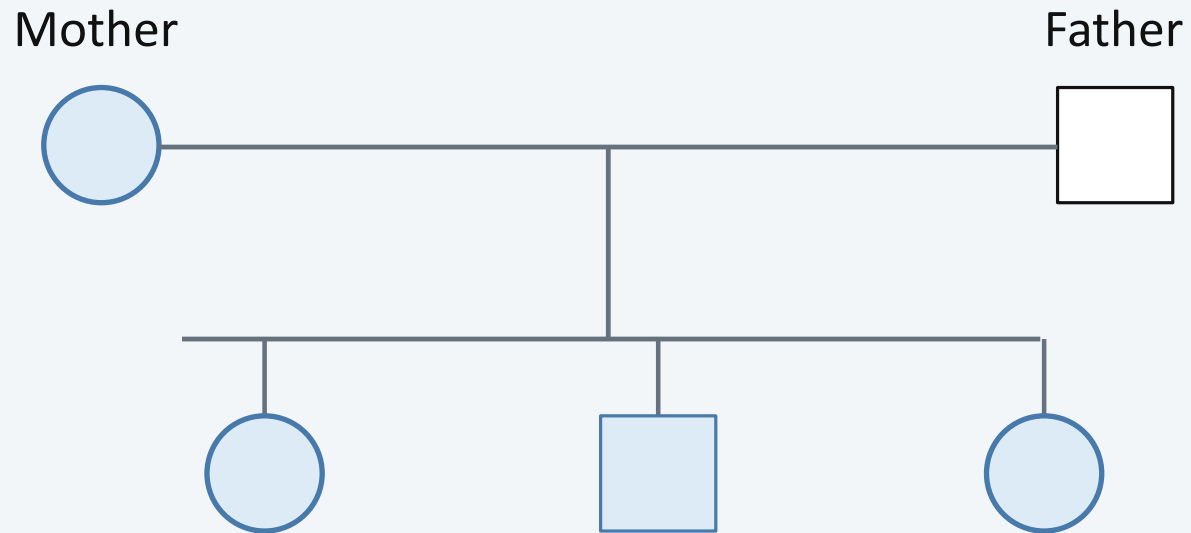
Mitochondrial genome

Maternal inheritance

Oocyte supplies embryonic mitochondria

Heteroplasmy may complicate phenotype

Maternal inheritance of mtDNA



Children receive mitochondria via the oocyte.

Schematic maternal inheritance only; No quantitative risk is represented.

Why paternal mtDNA is not the usual source

- Mitochondrial inheritance to oocyte origin.
- A paternal family pattern should not automatically be classified as mtDNA inheritance.
- Determine whether the causal locus is nuclear or mitochondrial.

Clinical / conceptual emphasis

Identify the gene location before interpreting a pedigree.

Nuclear mutations require a separate framework

Nuclear disease gene

Typically two nuclear copies per somatic cell

Mendelian pedigree interpretation

Mitochondrial protein may still be affected

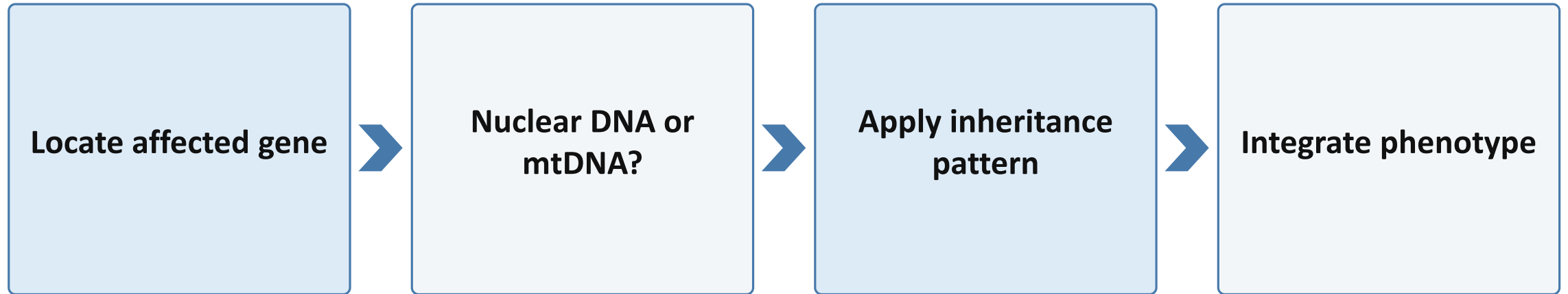
MtDNA variant

Many mitochondrial DNA copies per cell

Maternal inheritance

Heteroplasmy and cell-to-cell variance

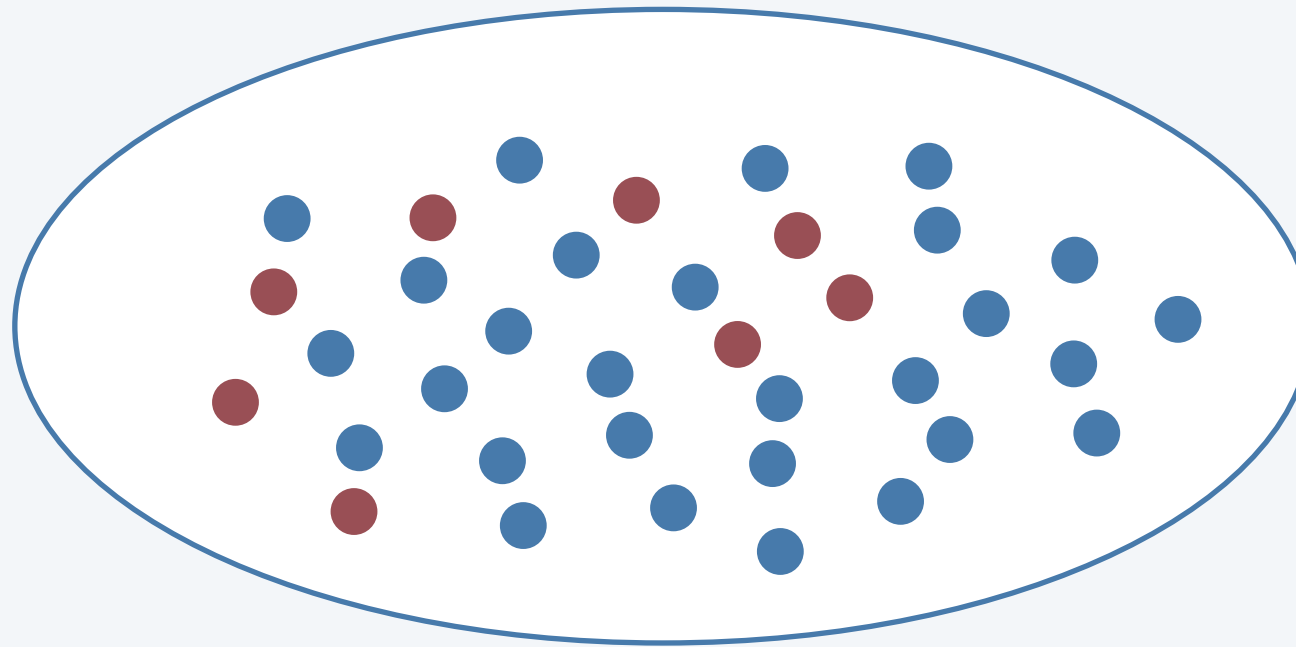
Inheritance pattern: A teaching decision



Schematic sequence; Arrows denote conceptual progression.

A cell contains many mtDNA copies

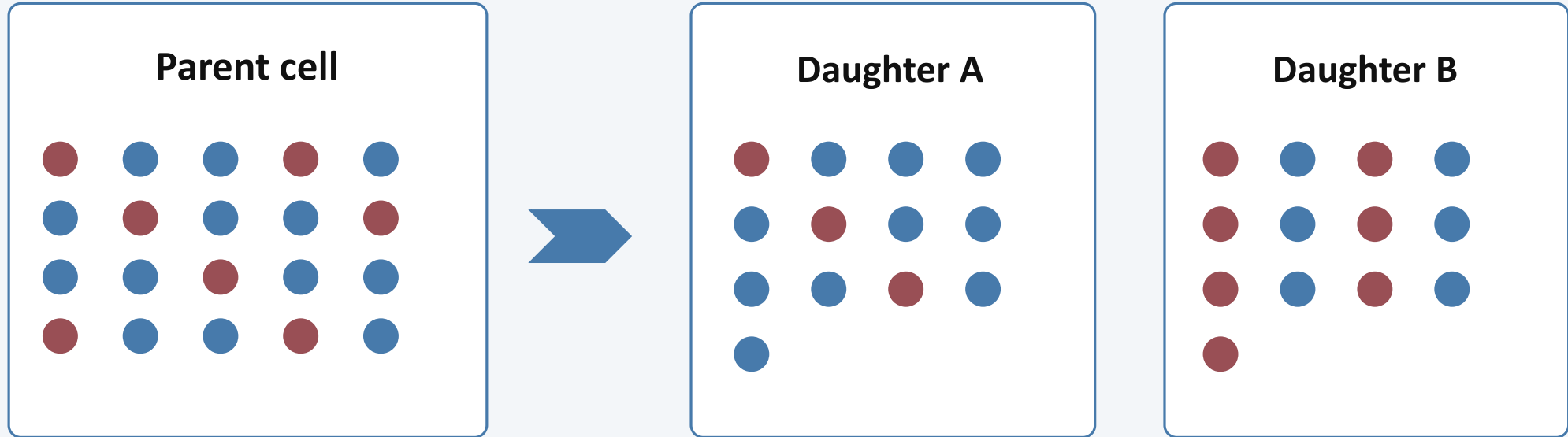
Schematic: MtDNA copies within one cell



Many genome copies

Illustrative distribution; Marker counts do not represent measured mtDNA fractions.

MtDNA copies partition during cell division



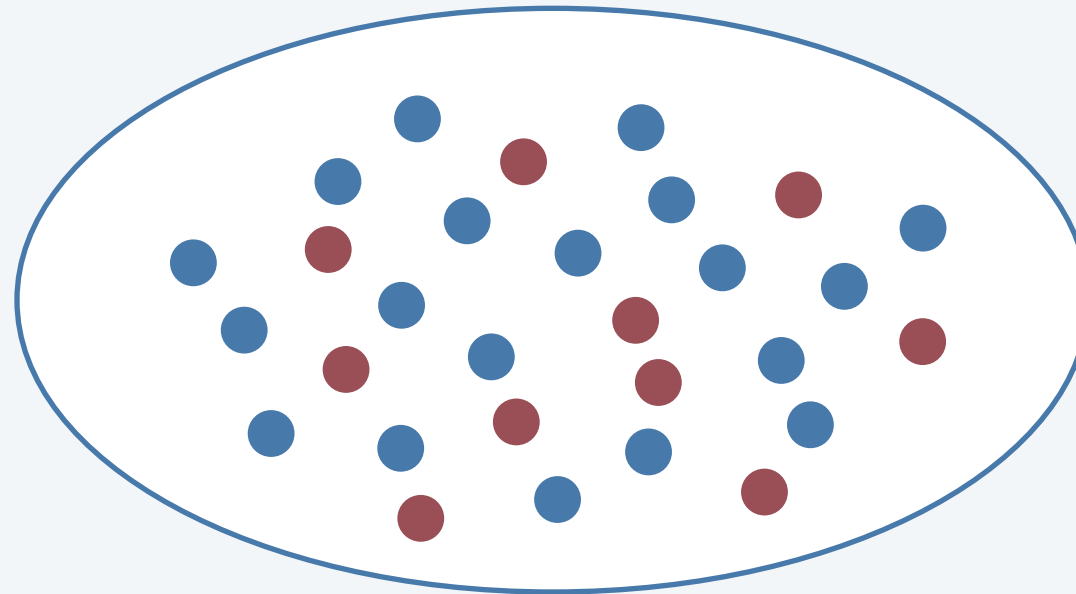
Random segregation can change the relative proportions.

Schematic only: No real copy numbers or quantitative segregation rates are implied.

Heteroplasmy: Mixed mitochondrial genotypes

One cell can contain normal and altered mtDNA

●
One mtDNA
population



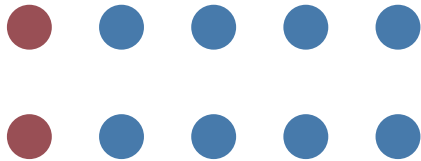
●
Different mtDNA
population

Schematic heteroplasmy; Number of symbols is not measured mutation burden.

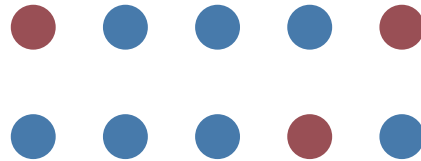
Random segregation creates tissue variability

Descendant cell groups may differ

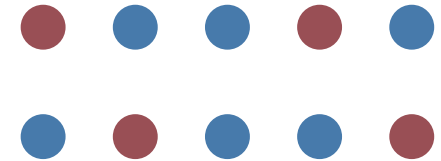
Cell population A



Cell population B



Cell population C



Illustrative clonal variation after random segregation; No quantitative rates asserted.

A threshold governs disease expression

Conceptual mutation burden

Below a functional threshold

Function may be preserved

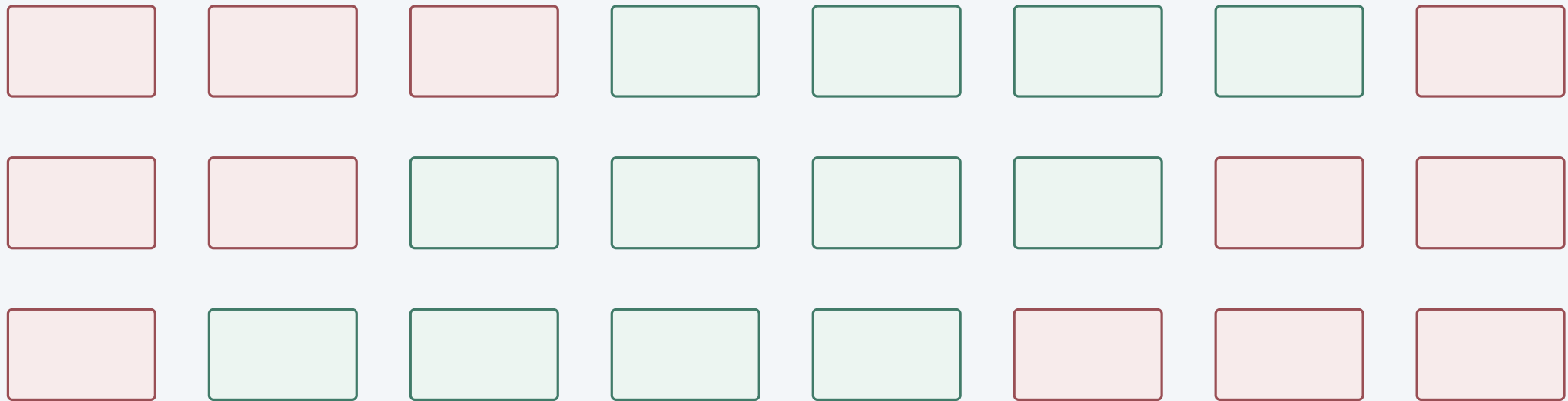
Exceeds a functional threshold

Susceptible cells may show disease

No numerical threshold is asserted. This is a qualitative disease model.

A tissue-level threshold matters

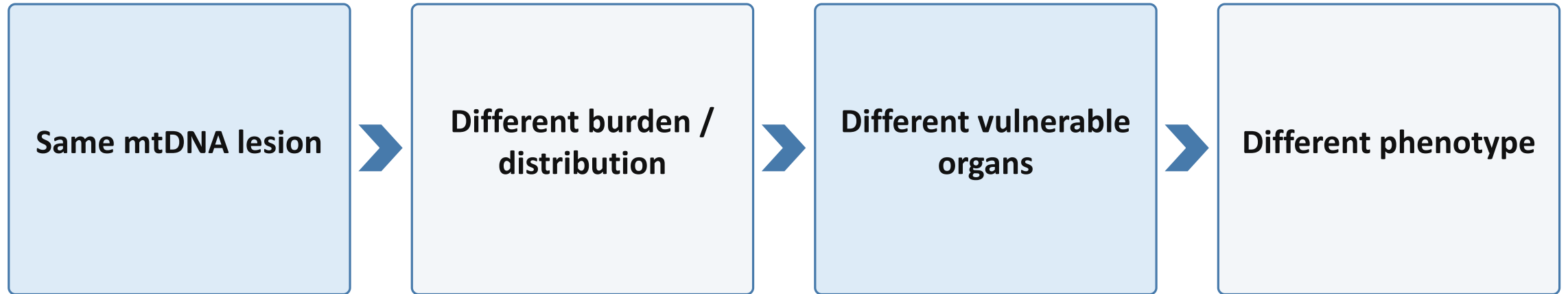
At-risk muscle tissue: A mixture of cells



Cells need not share the same functional state.

Schematic tissue heterogeneity; Colors are illustrative, not measured proportions.

Why the same mutation can yield different disease



Schematic sequence; Arrows denote conceptual progression.

Integrated mitochondrial disease model

Genetic architecture

Two genomes and
heterogeneous inheritance

Cellular energy deficit

Reduced mitochondrial ATP
generation

Multisystem expression

Muscle and other organs can
be affected

Conceptual summary; Categories are not quantitative or exhaustive.

The clinical entry point may be weakness

- Skeletal-muscle weakness is one possible presentation.
- Robbins does not assign a single obligatory distribution of weakness.
- The clinical pattern must be interpreted alongside extra-muscular findings.

Clinical / conceptual emphasis

Weakness is compatible with mitochondrial disease, but is not specific.

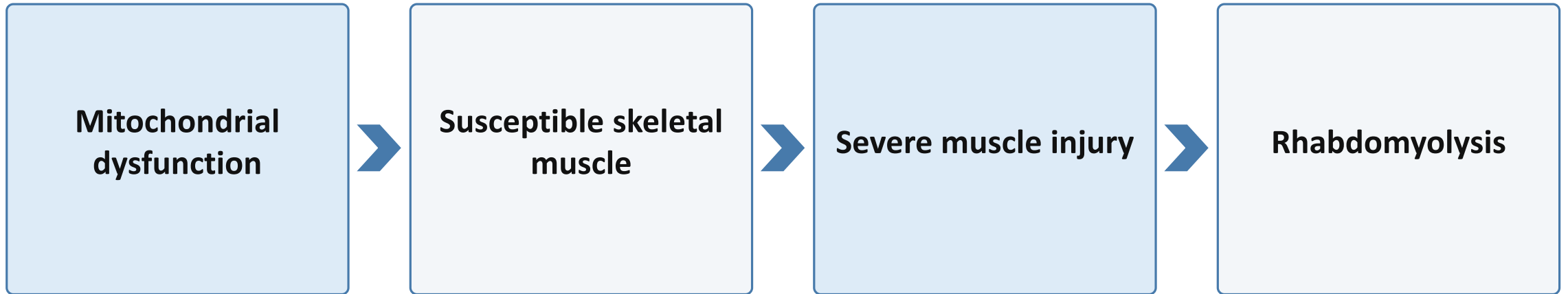
Serum creatine kinase may be elevated

- Elevation of serum creatine kinase is one recognized manifestation.
- An elevated CK indicates muscle injury rather than a unique mitochondrial cause.
- The textbook does not provide a diagnostic CK cutoff for this category.

Clinical / conceptual emphasis

Laboratory findings support a phenotype; They do not determine its gene.

Rhabdomyolysis is a possible presentation



Schematic sequence; Arrows denote conceptual progression.

Muscle involvement is anatomically variable

What may vary

Distribution of muscle weakness

Presence or absence of rhabdomyolysis

Degree of CK elevation

A useful clinical clue

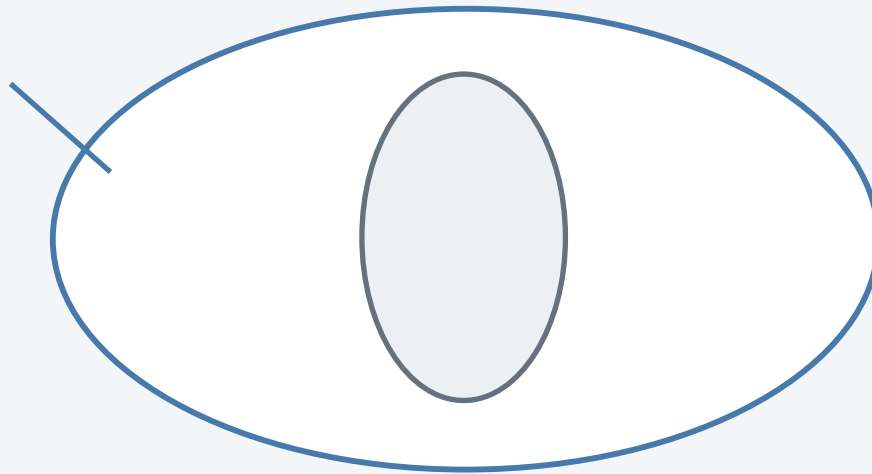
Extraocular muscle involvement

Chronic progressive ophthalmoplegia

Associated systemic manifestations

Extraocular muscle involvement is conspicuous

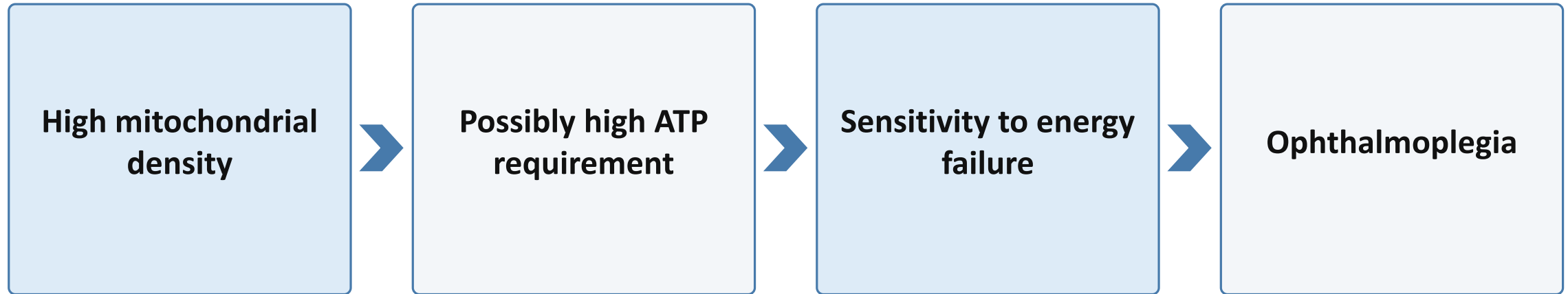
Extraocular muscles



CPEO may be isolated or syndromic.

Symbolic eye diagram; Not an anatomical drawing or clinical photograph.

The extraocular ATP hypothesis is uncertain



Proposed mechanism, not proven explanation

Chronic progressive external ophthalmoplegia

- Chronic progressive external ophthalmoplegia (CPEO) is common in mitochondrial disease.
- CPEO can occur alone or as part of a multisystem syndrome.
- The ocular phenotype by itself does not define a unique mtDNA variant.

Clinical / conceptual emphasis

CPEO describes a clinical phenotype, not one molecular diagnosis.

Isolated versus syndromic ophthalmoplegia

Isolated CPEO

Ophthalmoplegia as predominant finding

Can reflect mtDNA point mutation or deletion

A phenotype, not a standalone genotype

Syndromic CPEO

Ophthalmoplegia with other organ involvement

Consider features of MELAS or Kearns–Sayre

Search for a coherent multisystem pattern

Case 1: Progressive ocular muscle disease

Clinical reasoning prompt

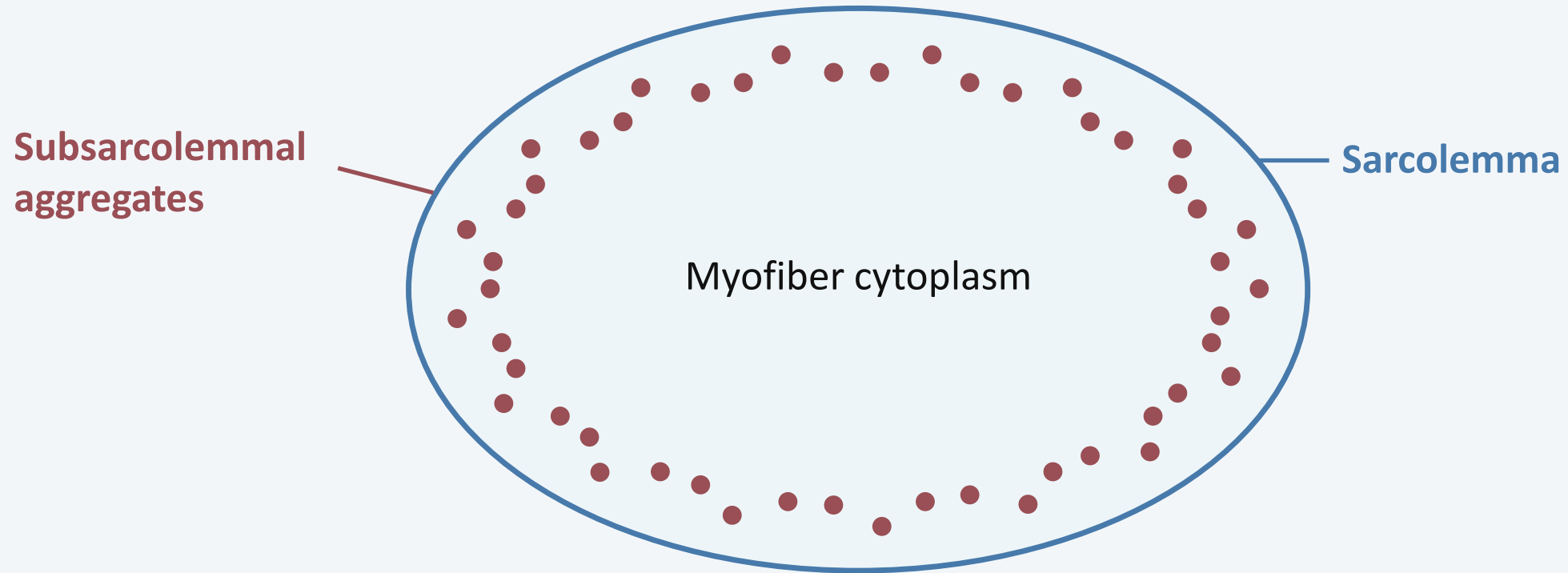
- A patient has gradually progressive extraocular muscle weakness.
- A mitochondrial myopathy enters the differential diagnosis.
- Question: Is ophthalmoplegia alone sufficient to name a specific mutation?

Case 1: Interpret the phenotype correctly

Interpretation

- No: Chronic progressive ophthalmoplegia is not mutation-specific.
- The same genetic lesion can produce distinct clinical syndromes.
- Assess the broader clinical pattern and select appropriate confirmatory studies.

Muscle biopsy: The principal morphologic lesion



Schematic illustration — not a clinical specimen or microscopic image.

What “ragged red” signifies

Mitochondrial aggregates



Peripheral fiber distribution

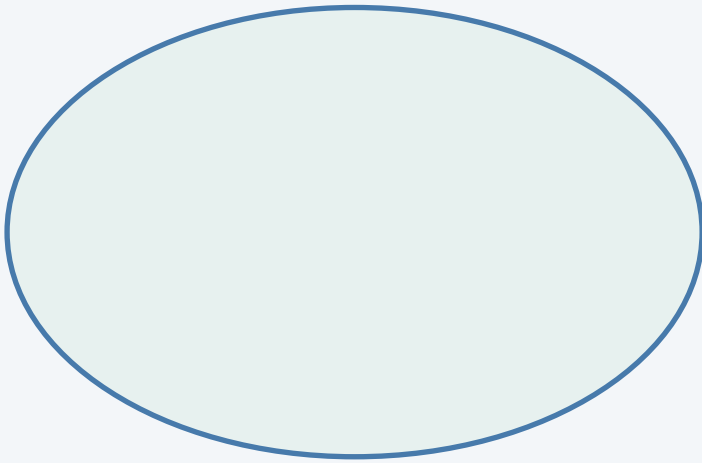


Reddish granules on Gomori stain

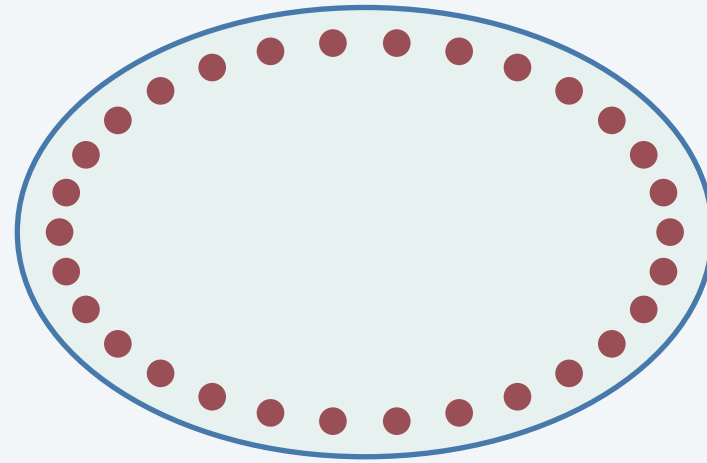
Schematic sequence; Arrows denote conceptual progression.

Gomori trichrome is a morphology stain

No conspicuous aggregate

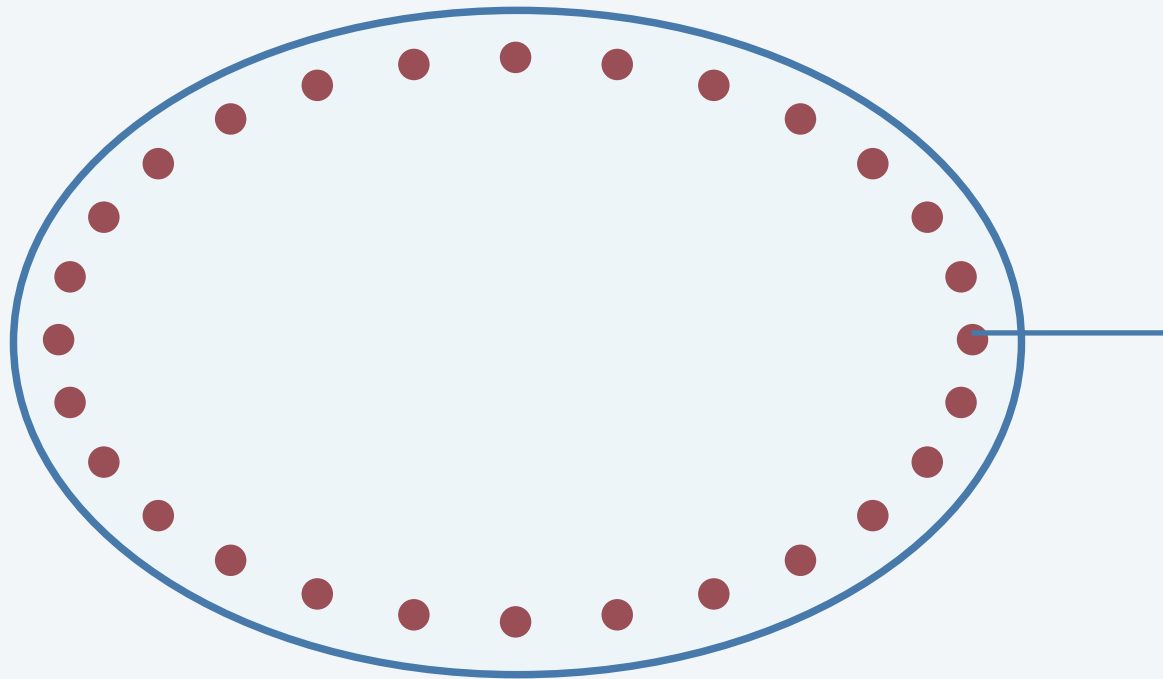


Ragged red pattern



Gomori trichrome pattern comparison — schematic only, not stained tissue.

Subsarcolemmal position is diagnostically relevant



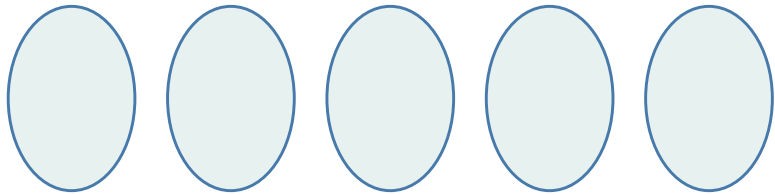
A peripheral rim of aggregates

Beneath the sarcolemma

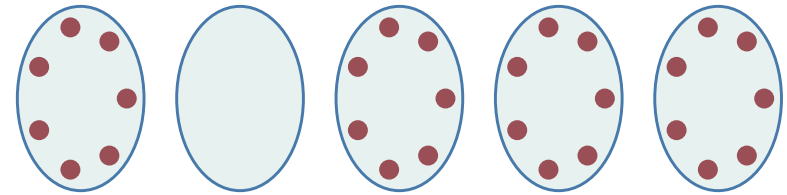
Schematic cross section of a muscle fiber; Not a microscopy image.

Mitochondrial accumulation in a myofiber

Conceptual comparison fiber

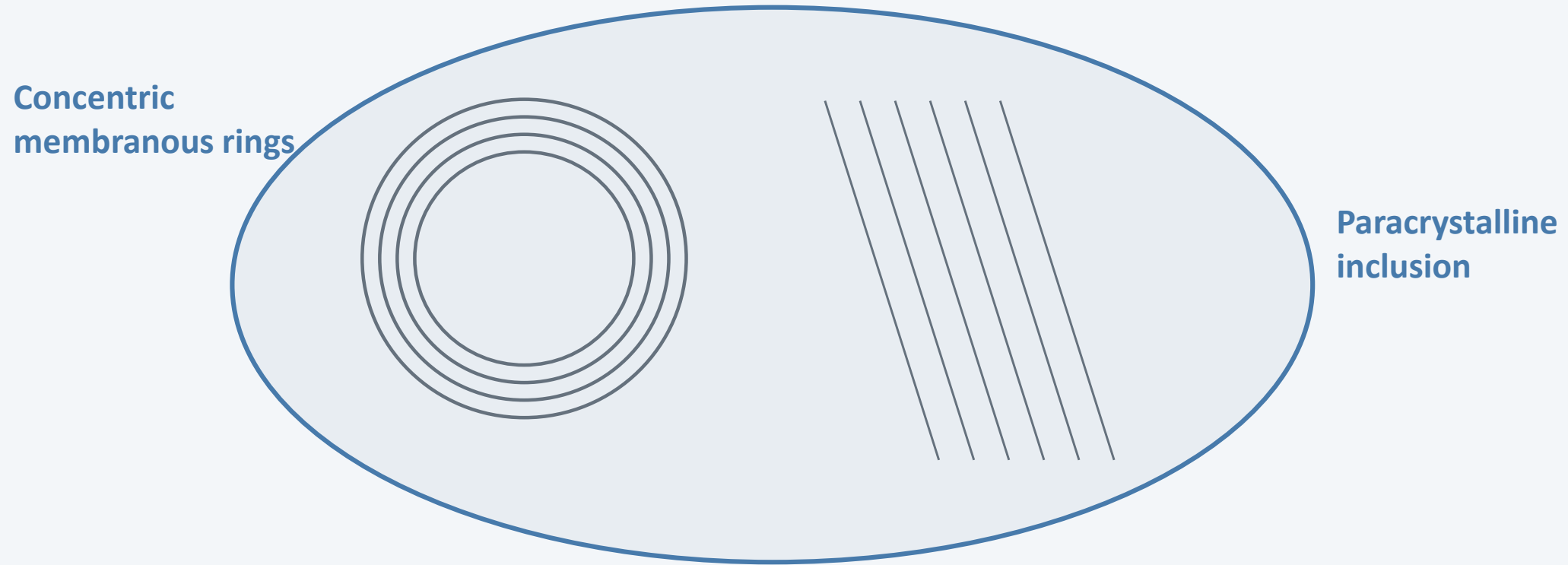


Affected fiber



Conceptual pattern distribution, not a specimen or observed fiber frequency.

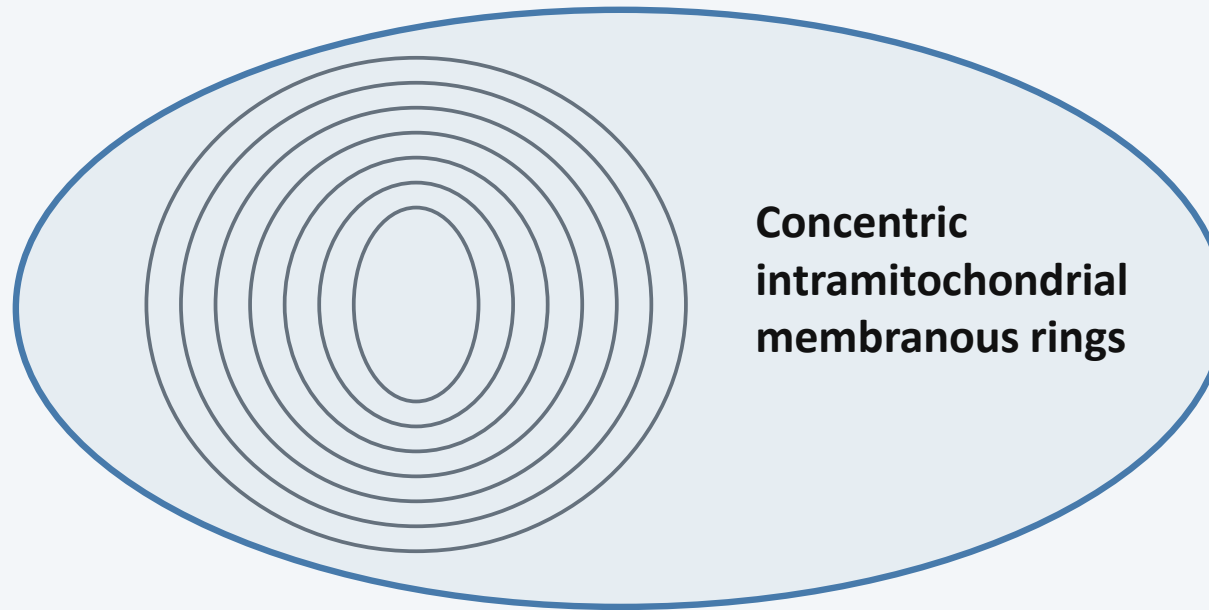
Ultrastructure may reveal abnormal mitochondria



Schematic illustration — not a patient electron micrograph.

Concentric rings on electron microscopy

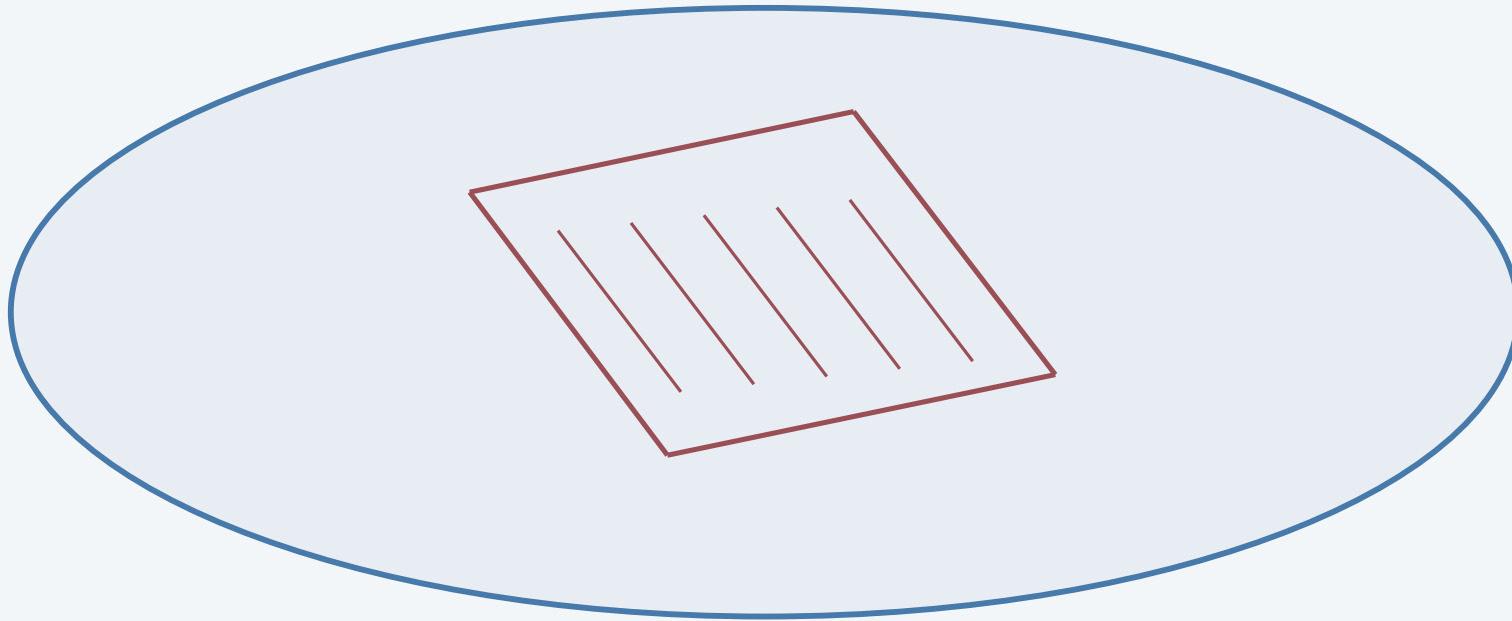
Enlarged native-vector depiction



Schematic; "phonograph record" appearance Fig. 27.13.

Paracrystalline inclusions are another EM clue

Enlarged native-vector depiction

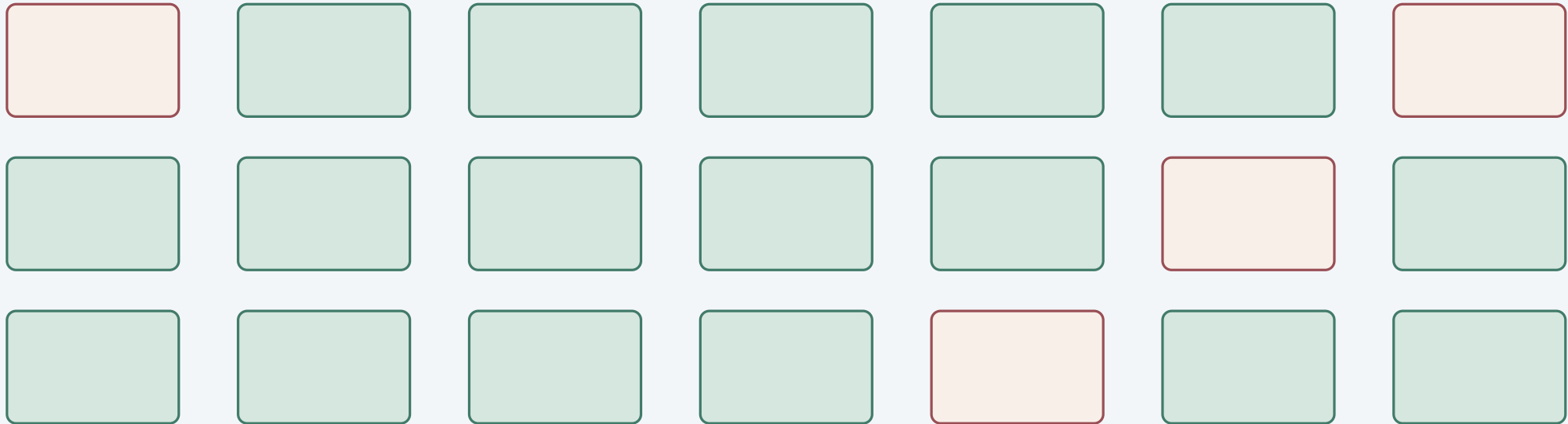


Rhomboïd inclusion with ordered internal pattern

Schematic only; Not an electron micrograph.

Mitochondrial enzyme histochemistry

Cytochrome oxidase histochemistry (conceptual)



Some fibers may show deficient enzyme activity.

Hypothetical staining concept; No patient material or observed counts.

A morphologically normal biopsy may not exclude disease

- Some mitochondrial disorders lack conspicuous histologic changes.
- Enzymatic assays or genetic analysis may be needed to establish diagnosis.
- Do not demand ragged red fibers in every clinically compatible case.

Clinical / conceptual emphasis

**Absent ragged red fibers
≠ excluded
mitochondrial disease.**

Three complementary lines of evidence

Morphology

Visible tissue phenotype

Enzyme activity

Functional mitochondrial
evidence

Genetic analysis

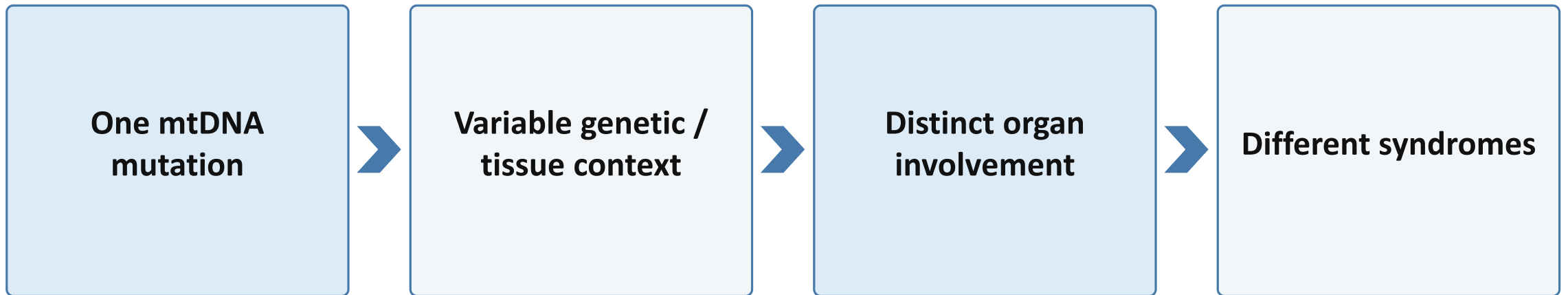
Causative genetic information

Conceptual summary; Categories are not quantitative or exhaustive.

Morphology, biochemistry and genetics differ

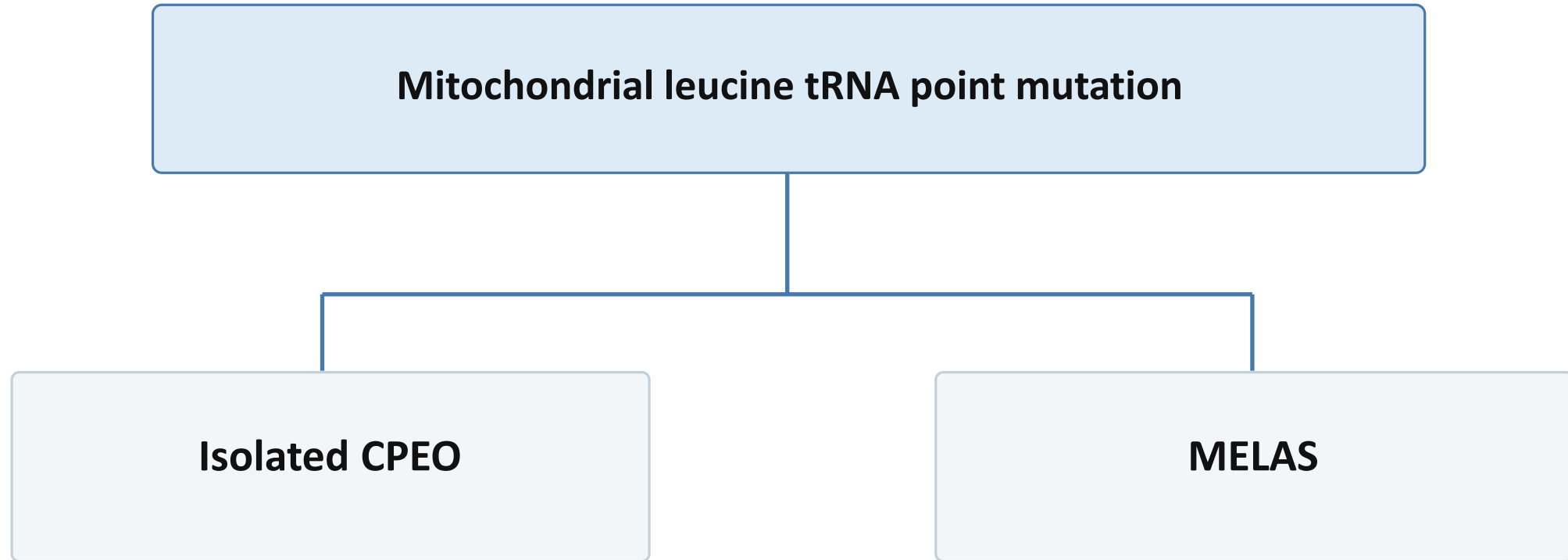
Method	Principal information
Gomori trichrome or ultrastructure	Cytochrome oxidase / genetic assays
Visible mitochondrial accumulation or structural abnormality	Enzyme activity or pathogenic genetic basis
May be absent in some disorders	May clarify otherwise inconspicuous disease

A genotype does not uniquely specify a phenotype



Schematic sequence; Arrows denote conceptual progression.

Leucine tRNA: One mutation, different outcomes



One lesion type can be associated with more than one clinical phenotype.

CPEO and MELAS can share a point mutation

Isolated CPEO

Predominantly extraocular weakness

Chronic progressive ophthalmoplegia

May present without the described multisystem syndrome

MELAS phenotype

Encephalomyopathy

Lactic acidosis

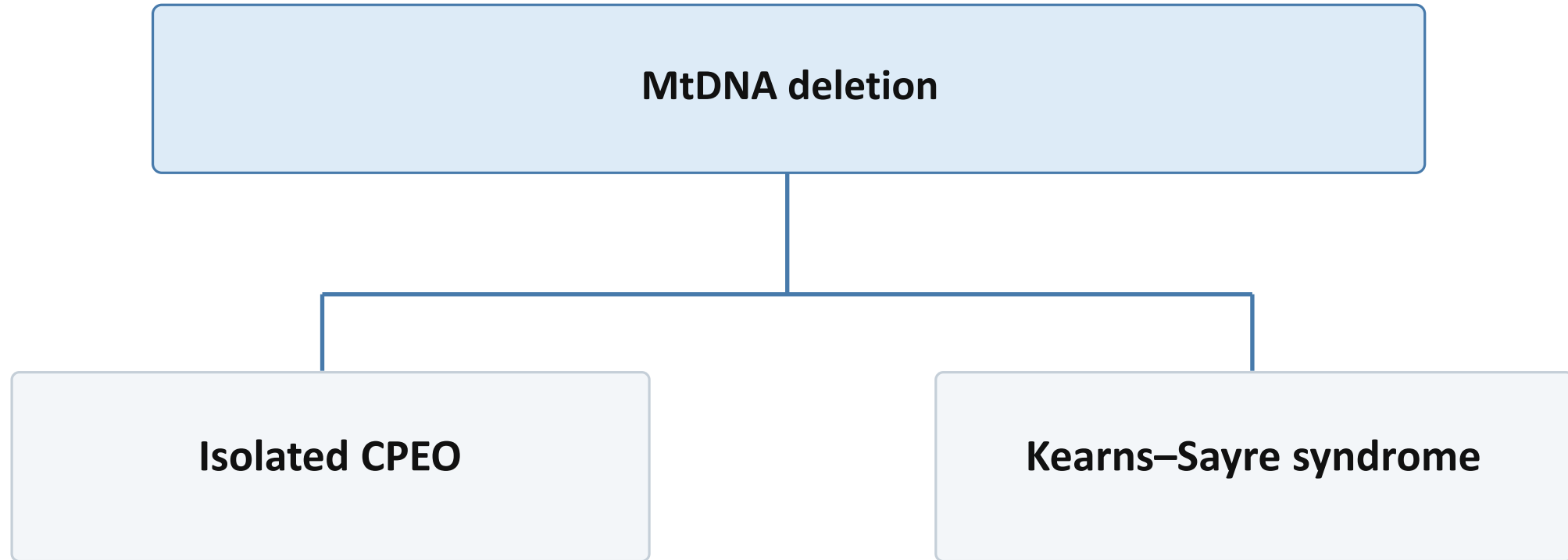
Stroke-like episodes

MELAS: Unpack the name

MELAS

- M: Mitochondrial.
- E: Encephalomyopathy.
- LA: Lactic acidosis; S: Stroke-like episodes.

MtDNA deletions can also yield different syndromes



One lesion type can be associated with more than one clinical phenotype.

Kearns–Sayre syndrome: Characteristic features

Ophthalmoplegia

Chronic progressive
extraocular weakness

Retinal degeneration

Pigmentary degeneration of
retina

Complete heart block

Severe cardiac conduction
manifestation

Conceptual summary; Categories are not quantitative or exhaustive.

CPEO versus Kearns–Sayre

Isolated CPEO

Chronic external ophthalmoplegia

No defining retinal / conduction triad supplied

Narrower phenotype

Kearns–Sayre syndrome

Chronic external ophthalmoplegia

Pigmentary retinal degeneration

Complete heart block

Case 2: Eye, retina and cardiac conduction

Clinical reasoning prompt

- A patient has progressive external ophthalmoplegia.
- The examination identifies pigmentary retinal degeneration and complete heart block.
- Question: Which named mitochondrial syndrome best fits this cluster?

Case 2: The syndromic diagnosis

Interpretation

- The three-feature cluster is characteristic of Kearns–Sayre syndrome.
- This syndrome is due to mtDNA deletions.
- The pattern illustrates why ophthalmoplegia must be evaluated in clinical context.

Myoclonic epilepsy with ragged red fibers

- MERRF is another named mitochondrial disease.
- It among diseases caused by point mutations in mtDNA.
- Its name links a neurologic syndrome to a classic muscle-pathology feature.

Clinical / conceptual emphasis

MERRF: A named mitochondrial syndrome with mtDNA point mutations.

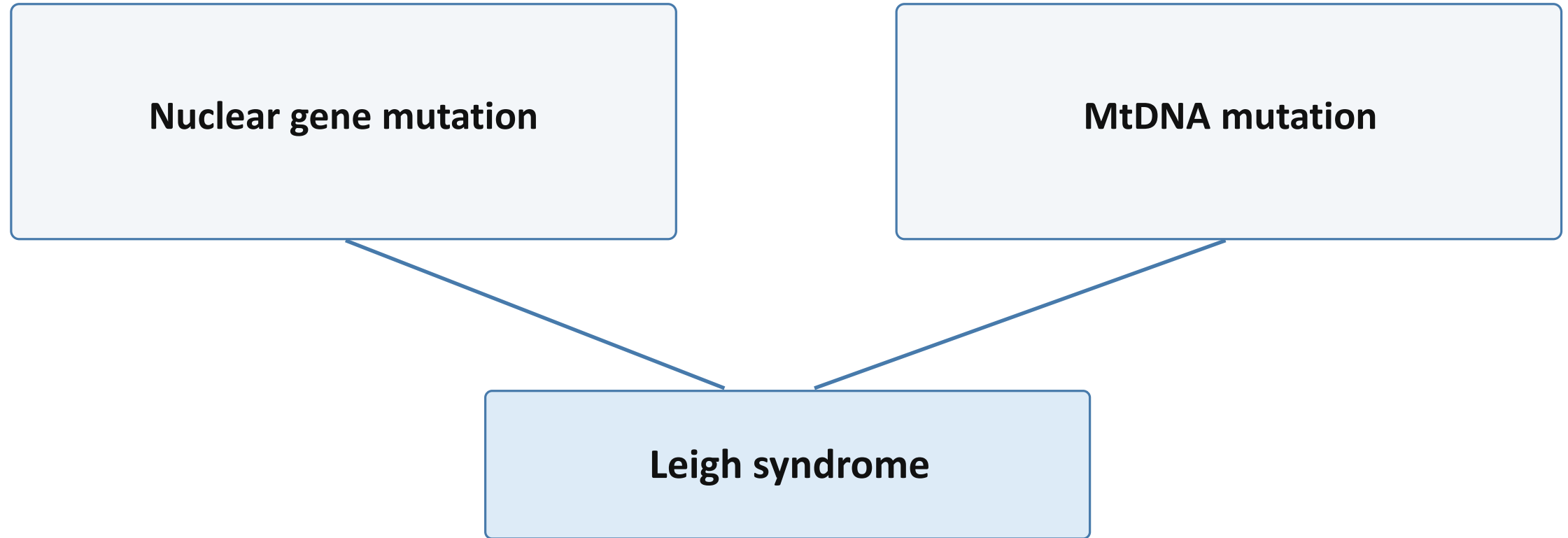
Leber hereditary optic neuropathy

- Leber hereditary optic neuropathy is a mitochondrial disease example.
- It among disorders associated with mtDNA point mutations.
- Its presence in the list reinforces the potential importance of non-muscle organs.

Clinical / conceptual emphasis

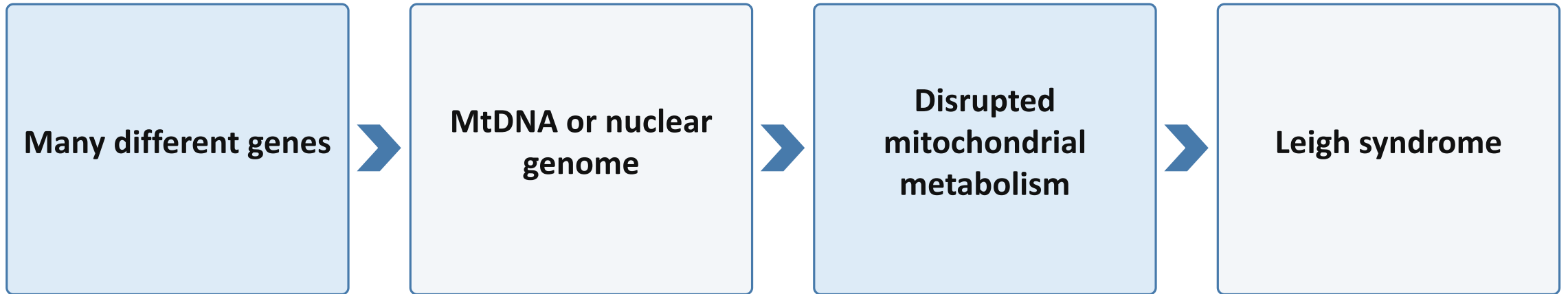
A mitochondrial disease phenotype may be dominated by extra-muscular findings.

Leigh syndrome is genetically heterogeneous



Multiple genes in either genome converge on mitochondrial metabolic dysfunction.

Leigh syndrome: Common pathway, diverse genes



Schematic sequence; Arrows denote conceptual progression.

Clinical syndromes: Pattern comparison

Entity	Core association	Genetic note
CPEO	Chronic progressive external ophthalmoplegia	May be isolated or syndromic
MELAS	Encephalomyopathy, lactic acidosis, stroke-like episodes	MtDNA point mutation example
Kearns–Sayre	Ophthalmoplegia, retina, complete heart block	Associated with mtDNA deletions
MERRF	Myoclonic epilepsy with ragged red fibers	MtDNA point mutations
Leber optic neuropathy	Optic neuropathy phenotype	MtDNA point mutations
Leigh syndrome	Subacute necrotizing encephalopathy	MtDNA and nuclear mutations

Use morphology without overspecifying genotype

Clinical pattern

Ocular, muscle and other
organ findings

Tissue phenotype

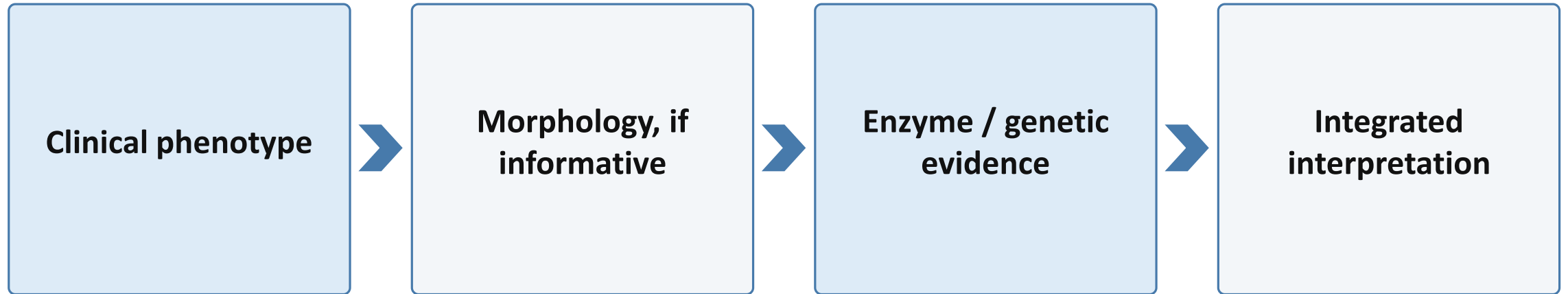
Tissue accumulation or
enzyme defect

Molecular evidence

MtDNA or nuclear variant

Conceptual summary; Categories are not quantitative or exhaustive.

Clinical and tissue evidence must be integrated



Schematic sequence; Arrows denote conceptual progression.

A common diagnostic pitfall

- Absence of ragged red fibers does not rule out mitochondrial disease.
- A classic clinical syndrome may remain recognizable even with subtle morphology.
- Robbins expressly allows enzyme- or genetics-based diagnosis.

Clinical / conceptual emphasis

Histologic visibility and molecular disease are not synonymous.

Case 3: Same mutation, divergent presentation

Clinical reasoning prompt

- Two patients are found to share a pathogenic mtDNA point mutation.
- One has isolated CPEO; The other has MELAS-type multisystem features.
- Question: Must one diagnosis be incorrect?

Case 3: What explains divergence?

Interpretation

- No: Different phenotypes may arise from a shared mitochondrial variant.
- Robbins offers the leucine tRNA point-mutation example.
- Heteroplasmy and tissue threshold effects supply a mechanistic framework.

Synthesis: Five defensible conclusions

- Many mitochondrial mutations interfere with ATP generation.
- Nuclear and mitochondrial genes yield different inheritance patterns.
- Heteroplasmy, segregation and tissue thresholds complicate expression.
- Ragged red fibers are characteristic but not universal.
- CPEO, MELAS, Kearns–Sayre, MERRF, LHON and Leigh illustrate clinical diversity.

Primary reference and source limitations

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Chapter 27, “Peripheral Nerves and Skeletal Muscles,” pp. 1123–1125.
- Source: project-provided Markdown extraction; no original chapter PDF was available.
- Microscopic figures here are native educational schematics, not patient specimens.