

Mutations in mitochondrial genes

Leber hereditary optic neuropathy

Mitochondrial inheritance • Cellular bioenergetics • Optic neuropathy

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Learning objectives

- Distinguish maternal mtDNA inheritance from nuclear Mendelian transmission.
- Explain heteroplasmy, random segregation, and tissue-specific threshold effects.
- Link mitochondrial respiratory dysfunction to central visual failure.
- Outline phenotype recognition, molecular testing, and family counseling.

Two genetic compartments contribute to mitochondrial function

Nuclear genome

- Biparental inheritance
- Many mitochondrial proteins

Mitochondrial genome

- Maternal inheritance
- 37 encoded genes

- Nuclear chromosomes encode many mitochondrial proteins.
- Mitochondrial DNA (mtDNA) encodes a smaller, essential set.
- Pathogenic variants in either compartment can disturb oxidative phosphorylation.

Why mitochondrial inheritance is non-Mendelian

- Autosomal nuclear alleles are inherited from both parents.
- The embryo normally receives its mitochondrial genome from the oocyte.

- Transmission therefore follows the maternal line, not a dominant/recessive pedigree.

Human mtDNA encodes 37 genes

13

Protein-coding

22

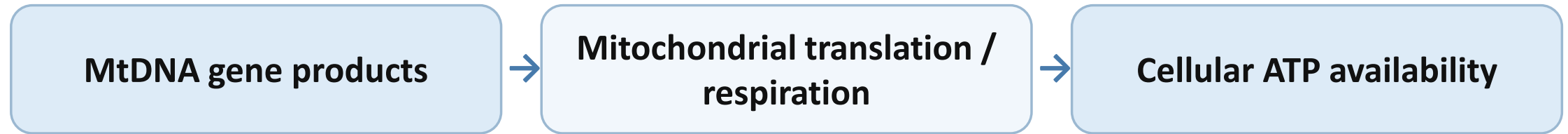
Mitochondrial tRNAs

2

Mitochondrial rRNAs

- 13 encode respiratory-chain polypeptides.
- 22 encode mitochondrial transfer RNAs.
- 2 encode mitochondrial ribosomal RNAs.

Protein synthesis and respiration both require mtDNA products



- Mitochondrial tRNAs and rRNAs support translation within the organelle.
- The 13 protein-coding genes contribute respiratory-chain subunits.
- A genetic defect can therefore impair cellular energy production.

Oxidative phosphorylation creates tissue vulnerability

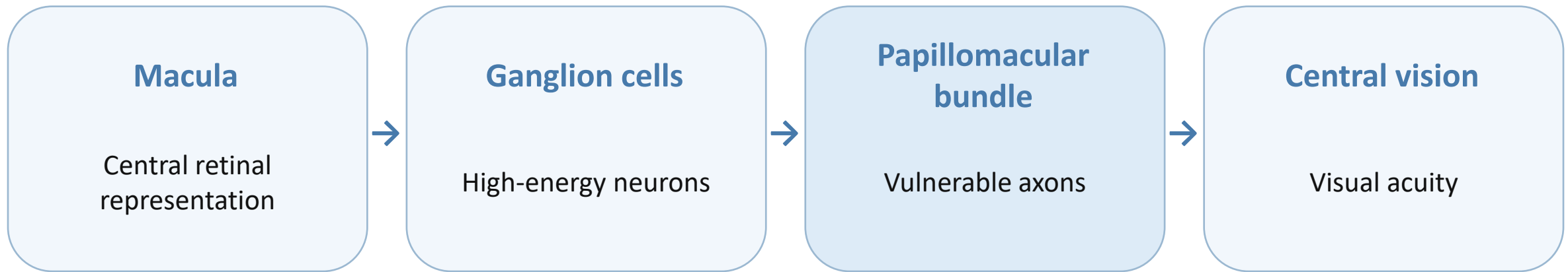
Tissues with sustained ATP demand are susceptible to mitochondrial dysfunction.

The central nervous system, skeletal muscle, heart, liver, and kidneys.

The optic nerve is a clinically important example of neural susceptibility.

Visual axons depend on intact energy metabolism

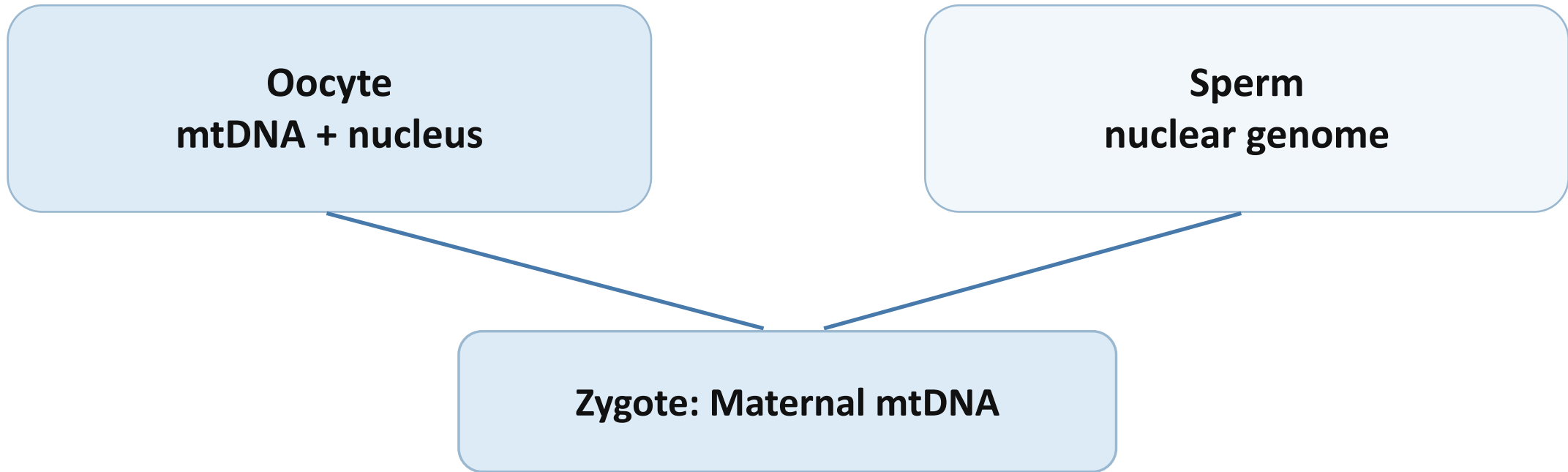
Schematic



- Retinal ganglion cell axons transmit visual information to the brain.
- A sustained mitochondrial energy deficit compromises neural survival.
- Central visual function is especially affected in LHON.

Fertilization establishes maternal mtDNA transmission

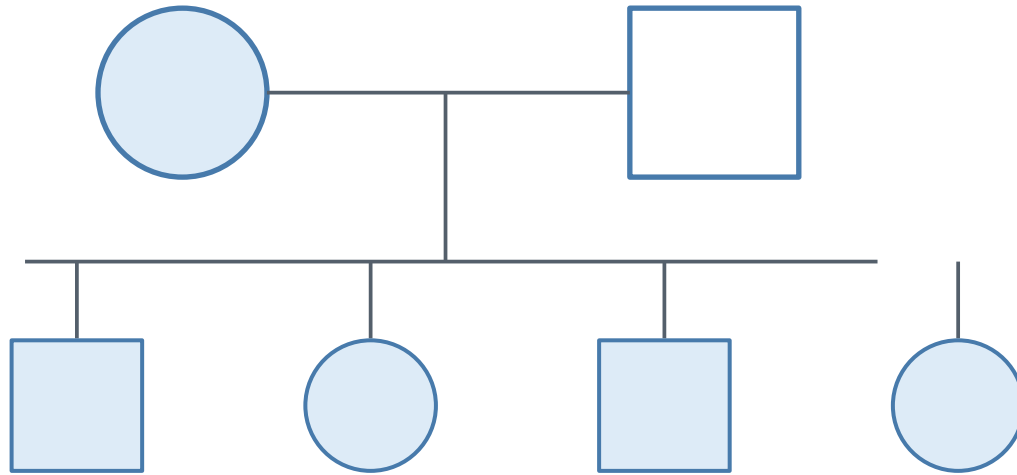
Schematic



- The ovum contributes the mitochondrial population to the zygote.
- Paternal nuclear DNA is inherited; Paternal mtDNA is not normally transmitted.
- Each child of a mother carrying an mtDNA variant can inherit it.

A maternal pedigree identifies the transmission route

Schematic



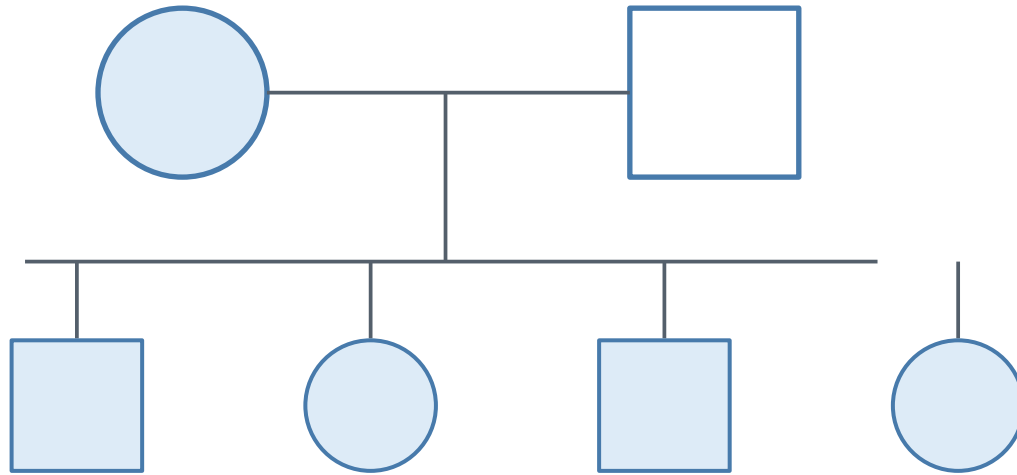
Filled blue: MtDNA variant present Outlined: Variant not shown

Maternal mtDNA can reach sons and daughters

- Individuals of either sex can inherit a maternal mtDNA variant.
- Males do not transmit that variant to their children.
- Female carriers can transmit it to sons and daughters.

An unaffected mother can transmit a pathogenic mtDNA variant

Schematic



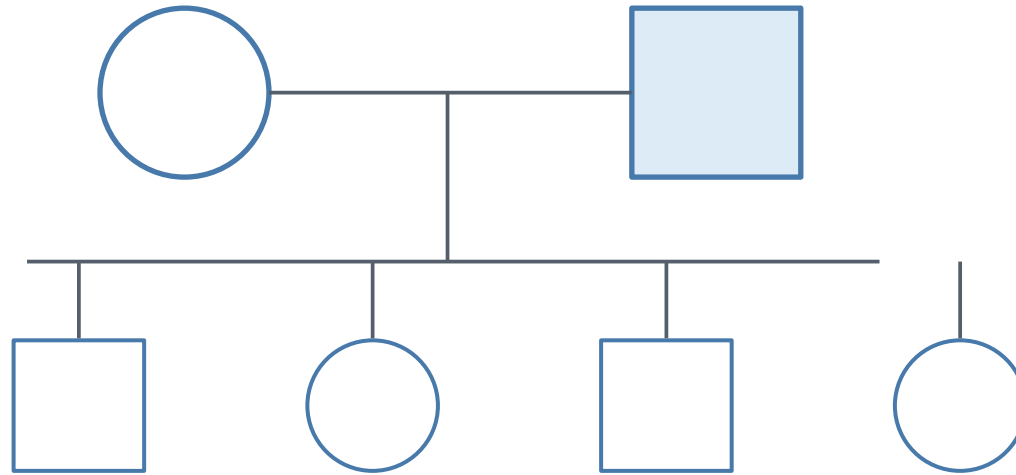
Filled blue: MtDNA variant present Outlined: Variant not shown

Maternal mtDNA can reach sons and daughters

- Variant carriage and clinically manifest optic neuropathy are not equivalent.
- Incomplete penetrance allows a mother to be asymptomatic.
- Her descendants can nevertheless develop visual loss.

Affected fathers do not transmit LHON mtDNA variants

Schematic



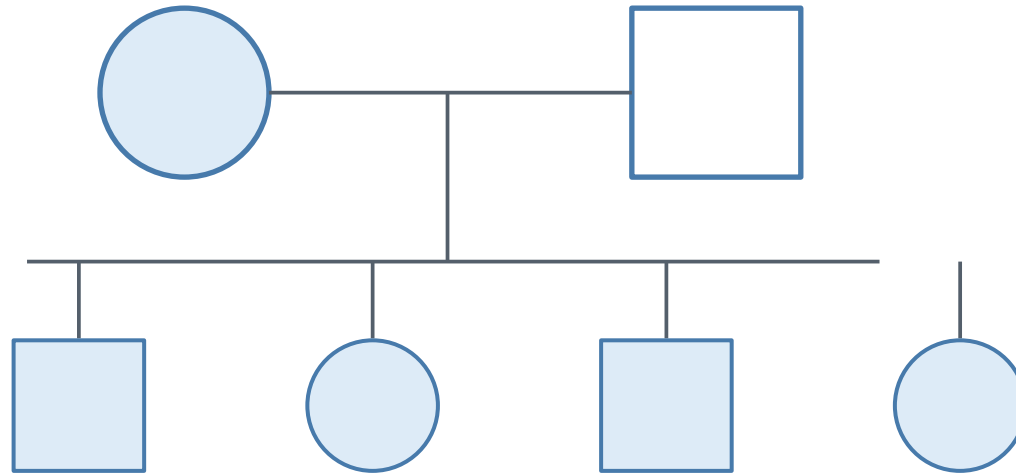
Filled blue: MtDNA variant present Outlined: Variant not shown

Variant-positive father → no paternal mtDNA transmission

- A paternal history of visual loss does not create paternal mtDNA transmission.
- The affected father can transmit his nuclear DNA normally.
- LHON risk from that paternal mtDNA variant is not inherited by his children.

Transmission of a variant is not transmission of blindness

Schematic



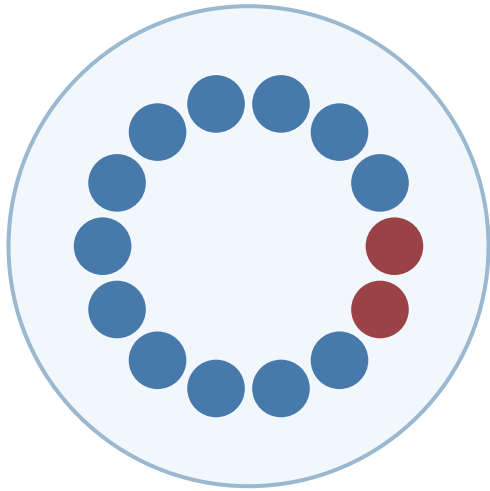
Filled blue: MtDNA variant present Outlined: Variant not shown

Maternal mtDNA can reach sons and daughters

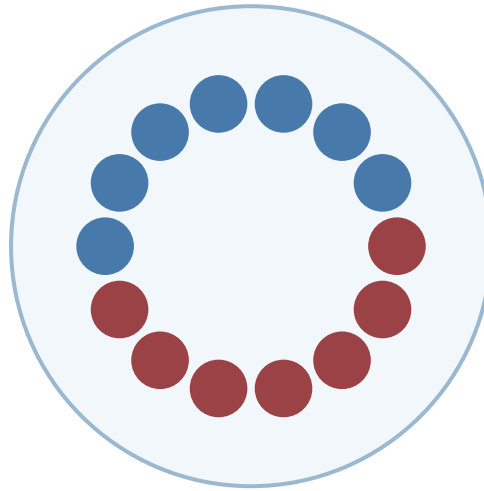
- All children of a homoplasmic maternal carrier may inherit the variant.
- Not all variant-positive relatives develop optic neuropathy.
- Sex, age, other genetic factors, and exposures influence expression.

Heteroplasmy means mixed mitochondrial genotypes

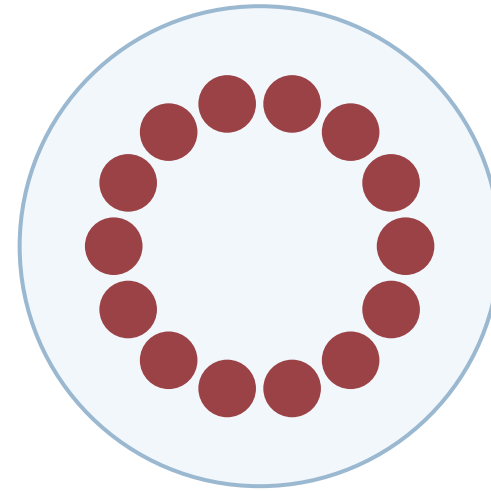
Schematic



Mostly wild-type



Mixed genotypes

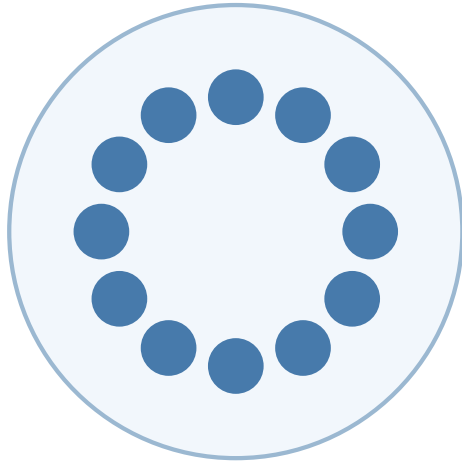


Predominantly variant

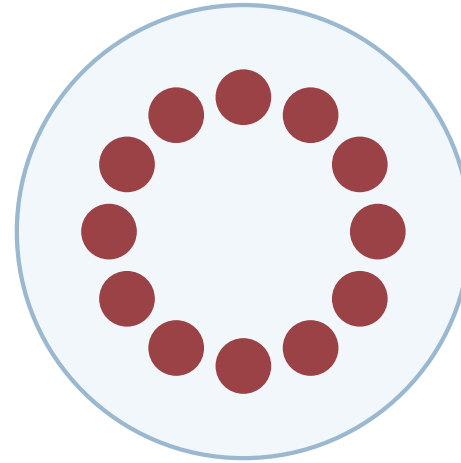
- A cell or tissue contains both wild-type and variant mtDNA.
- The fraction of mutant mtDNA can differ among tissues.
- Variant burden may influence the likelihood of dysfunction.

Homoplasmy does not guarantee clinical disease

Schematic



Wild-type homoplasmy

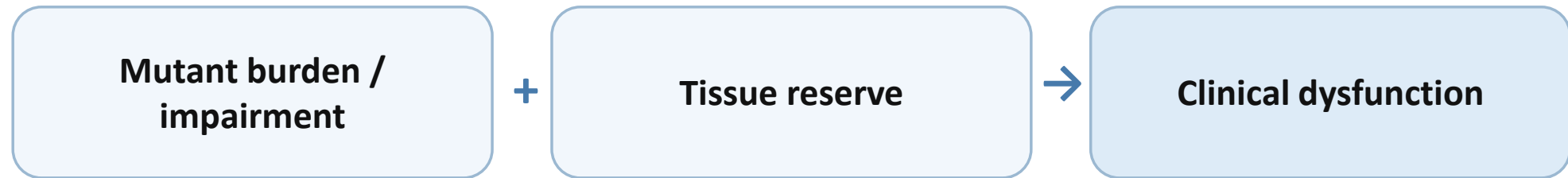


Variant homoplasmy

- Homoplasmy means mtDNA copies are predominantly of one genotype.
- Many individuals carrying a major LHON variant are homoplasmic.
- Clinical penetrance is nonetheless incomplete.

The threshold effect links burden to loss of function

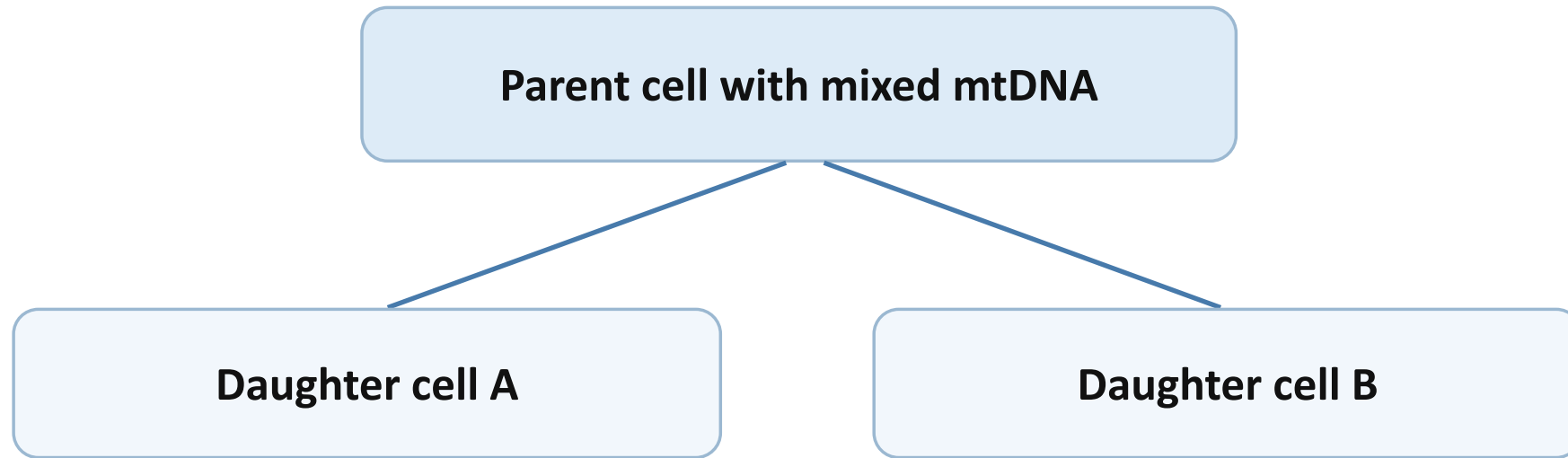
Schematic



- Mitochondrial dysfunction becomes clinically apparent only after a tissue-specific functional threshold is crossed.
- Energy demand and physiological reserve influence that threshold.
- This concept helps explain selective organ vulnerability.

Replicative segregation produces uneven mtDNA distributions

Schematic



Different mutant fractions after division

- Normal and mutant mtDNA copies are not apportioned in fixed Mendelian ratios.
- Daughter cells may receive different proportions of variant mtDNA.
- Cellular lineages can therefore diverge in respiratory capacity.

Within-family severity can differ

Relatives may inherit the same maternally transmitted pathogenic variant.

Their degree of clinical visual loss may still differ greatly.

Mitochondrial segregation and incomplete penetrance provide different levels of explanation.

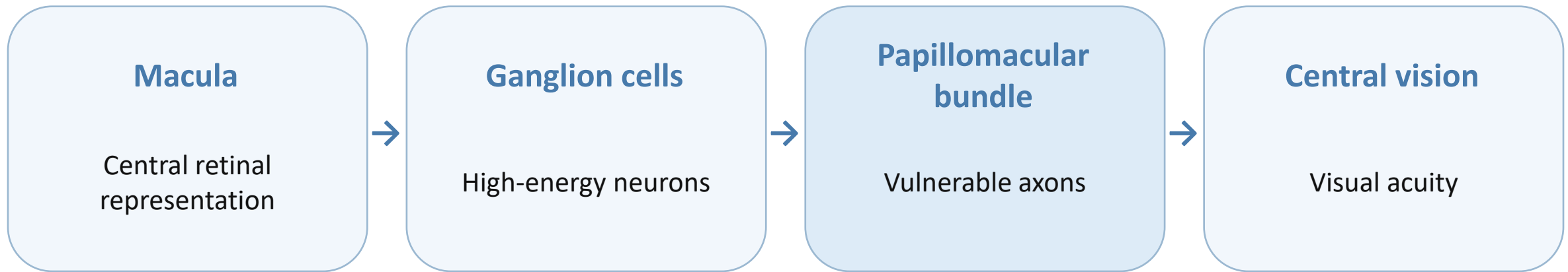
Heteroplasmy is not the sole determinant of LHON risk

- Common LHON variants often occur in a homoplasmic state.
- Sex- and age-dependent penetrance remains important.

- Additional genetic and environmental influences modify expression.

Why the optic nerve is a key target

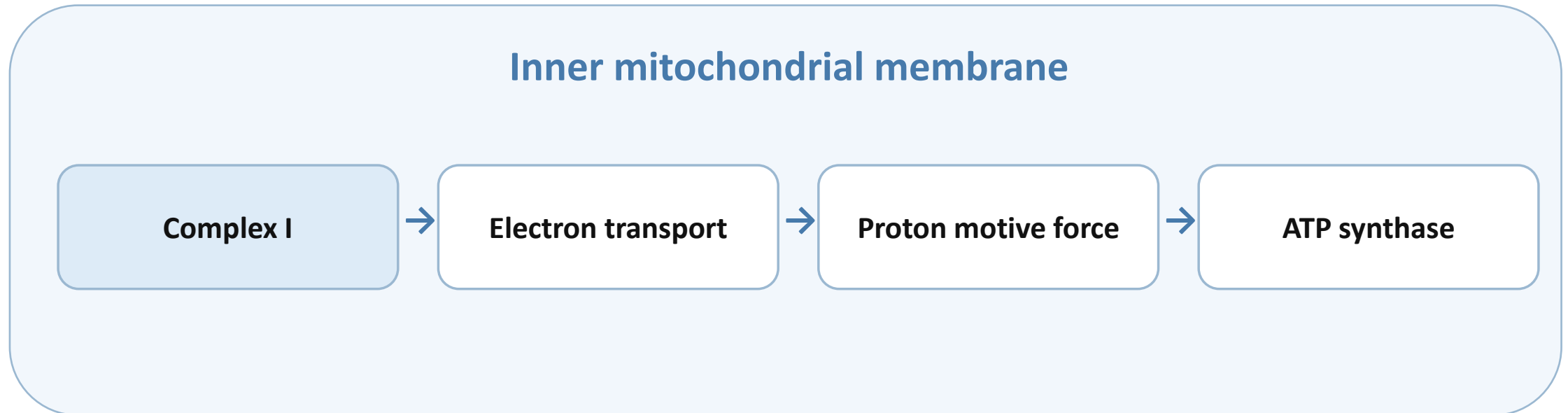
Schematic



- Mitochondrial dysfunction reduces the ability to meet neuronal energy demand.
- Retinal ganglion cells and their axons are especially vulnerable.
- Damage to the papillomacular pathway produces loss of central vision.

Respiratory-chain dysfunction is the mechanistic bridge

Schematic



- The inner mitochondrial membrane contains the electron transport machinery.
- Electron transfer supports the proton gradient used to synthesize ATP.
- LHON-associated complex I variants disrupt this bioenergetic system.

Complex I is central to classical LHON

Schematic

Mitochondrial inner membrane: Complex I

MT-ND1

M.3460G>A

MT-ND4

M.11778G>A

MT-ND6

M.14484T>C

- Complex I participates in entry of electrons from NADH into the respiratory chain.
- Three common LHON-associated mtDNA variants encode complex I subunits.
- Mitochondrial bioenergetic dysfunction contributes to retinal ganglion cell injury.

Three mtDNA variants account for most classic LHON

Primary variant	Affected gene	Respiratory complex
M.11778G>A	MT-ND4	Complex I
M.3460G>A	MT-ND1	Complex I
M.14484T>C	MT-ND6	Complex I

- M.11778G>A affects MT-ND4.
- M.3460G>A affects MT-ND1.
- M.14484T>C affects MT-ND6.

M.11778G>A lies in MT-ND4

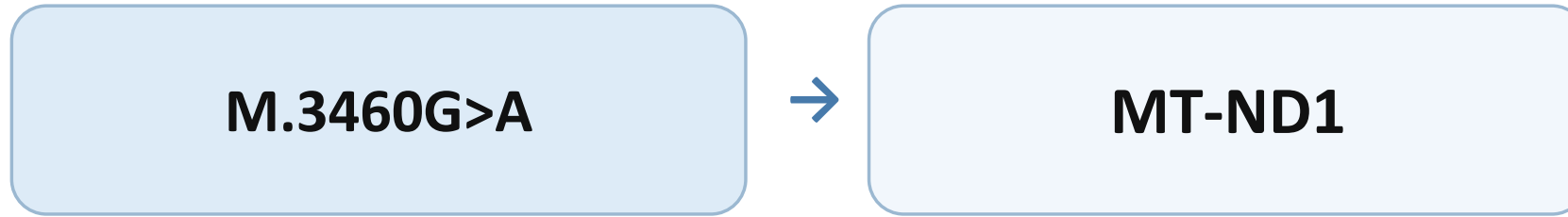
M.11778G>A



MT-ND4

- This is a common primary LHON-associated pathogenic variant.
- MT-ND4 encodes a mitochondrial complex I subunit.
- Its identification supports the diagnosis in a compatible phenotype.

M.3460G>A lies in MT-ND1



- The affected protein is a component of complex I.
- Mitochondrial respiration may be measurably impaired.
- Phenotypic severity still cannot be predicted from the variant alone.

M.14484T>C lies in MT-ND6

M.14484T>C



MT-ND6

- This classic mtDNA variant also affects complex I.
- Visual recovery is relatively more frequent in some affected cohorts.
- Prognosis remains individual and is not a deterministic gene-to-outcome rule.

Mitochondrial variant notation should be read precisely

M.

Mitochondrial genome

11778

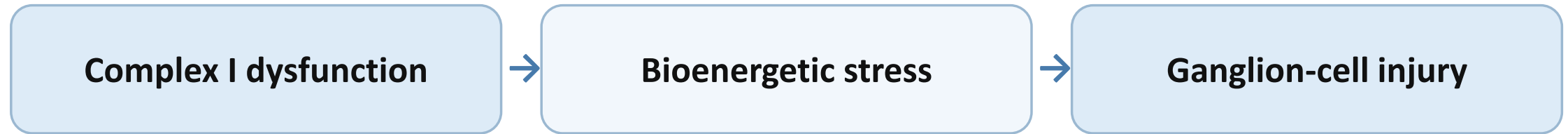
Reference position

G>A

Nucleotide substitution

- The prefix “m.” denotes a mitochondrial sequence position.
- The letters specify the reference and substituted nucleotide.
- Gene symbols such as MT-ND4 identify the affected mtDNA-encoded subunit.

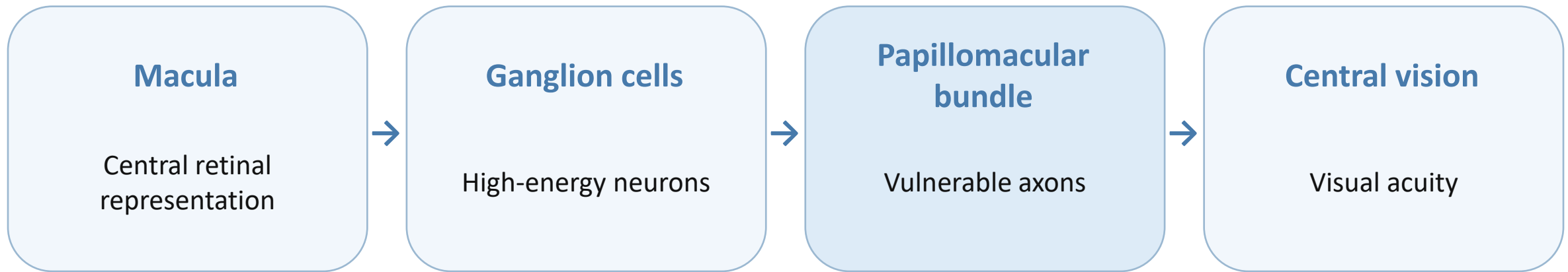
Energy deficit and oxidative stress contribute to cell injury



- Complex I dysfunction perturbs oxidative phosphorylation.
- Altered redox homeostasis and reactive oxygen species can accompany this dysfunction.
- Degeneration of retinal ganglion cells ultimately interrupts visual signaling.

The papillomacular bundle explains central visual loss

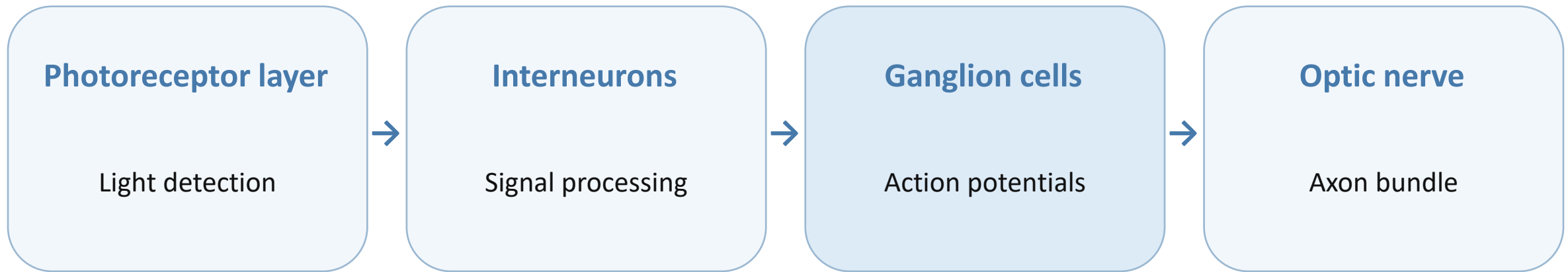
Schematic



- Macular retinal ganglion cell axons project through the optic nerve.
- Injury to these fibers impairs high-acuity central visual function.
- Peripheral visual function may initially be relatively better preserved.

Anatomic localization: Retina to optic nerve

Schematic



- Photoreceptors detect light; Retinal circuits relay signals to ganglion cells.
- Ganglion cell axons form the optic nerve.
- LHON is an optic neuropathy, not primarily a photoreceptor degeneration.

Functional loss precedes overt chronic optic atrophy

Schematic

Carrier / early

Possible subtle changes

Subacute

Central failure; Variable disc appearance

Chronic

Axonal thinning; Disc pallor

- Acute LHON may have conspicuous optic-disc vascular findings—or a relatively normal fundus.
- Ganglion cell dysfunction reduces central acuity and produces a central scotoma.
- Chronic degeneration eventually produces visible optic atrophy.

LHON is a neurodegenerative optic neuropathy

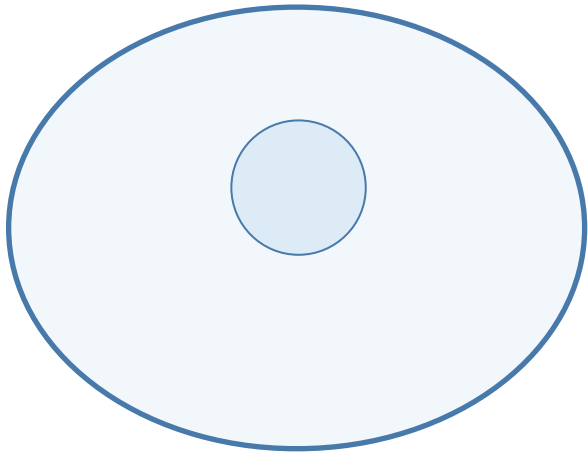
- The defining clinical event is acquired central visual impairment.
- Loss is typically painless and subacute.
- The disease commonly affects both eyes, often sequentially.

Age at onset is concentrated in young adulthood

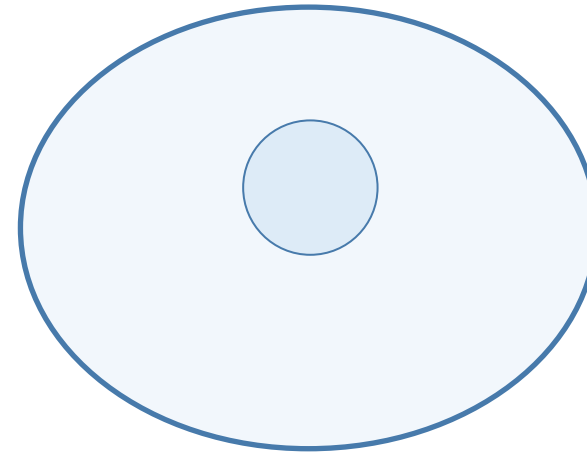
- The ma genetics section describes typical onset at 15–35 years.
- The Robbins eye chapter describes 10–30 years; These are descriptive ranges.
- Presentation outside these intervals is possible and does not exclude LHON.

Visual loss is often sequential but ultimately bilateral

Schematic



Eye 1

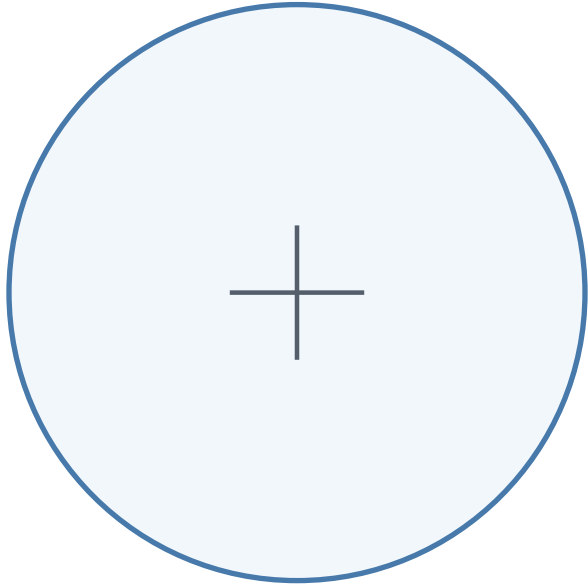


Eye 2

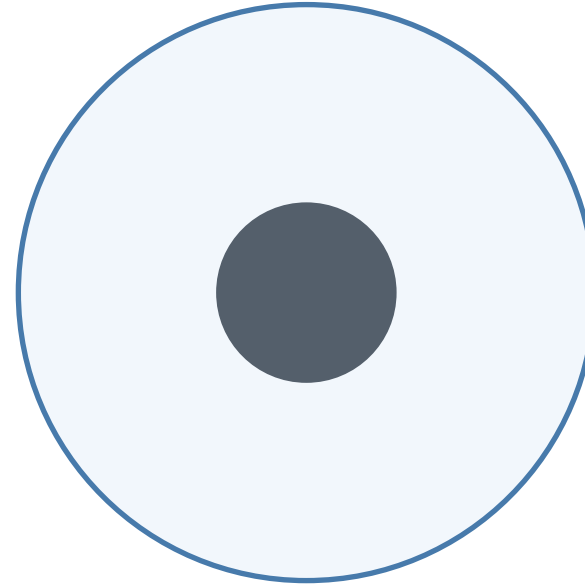
- One eye may become symptomatic first.
- The second eye commonly becomes involved after an interval.
- Purely persistent unilateral optic neuropathy should trigger reassessment.

Central and centrocecal scotomas are characteristic

Schematic



Normal central field



Central scotoma

- Patients lose central field sensitivity corresponding to macular projections.
- The blind region may extend toward the physiologic blind spot.
- Perimetry helps quantify the functional deficit.

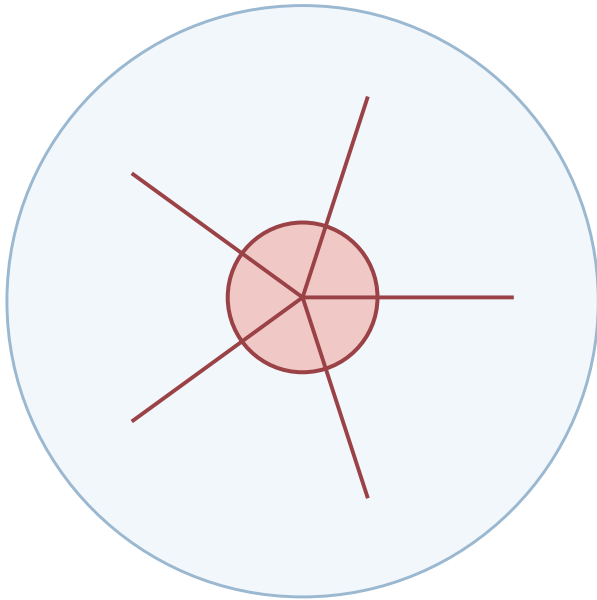
Dyschromatopsia often accompanies central visual loss

- Color discrimination is frequently impaired in optic nerve disease.
- Testing complements acuity and visual field examination.
- These findings are supportive, not independently diagnostic of LHON.

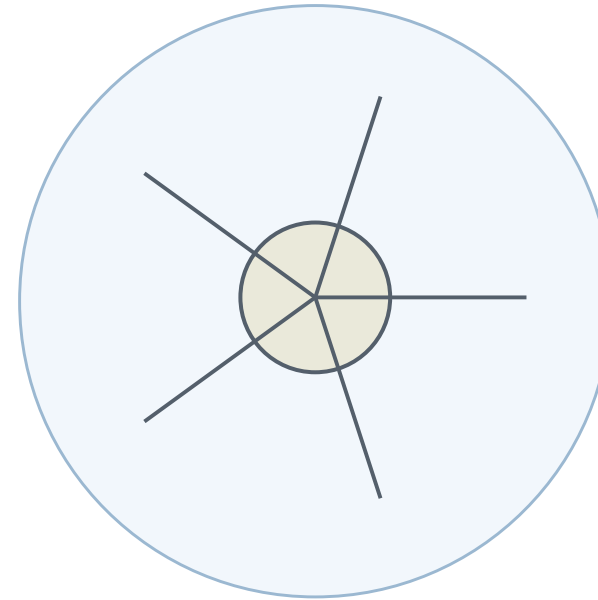
Acute fundus abnormalities can be subtle

Schematic

Schematic optic-disc appearances — not photographs



Subacute / active



Chronic / atrophic

- Reported findings include disc hyperemia and peripapillary nerve-fiber swelling.
- Telangiectatic vessels and vascular tortuosity may be present.
- A normal-appearing disc does not exclude acute LHON.

Optic-disc hyperemia is not true inflammatory edema

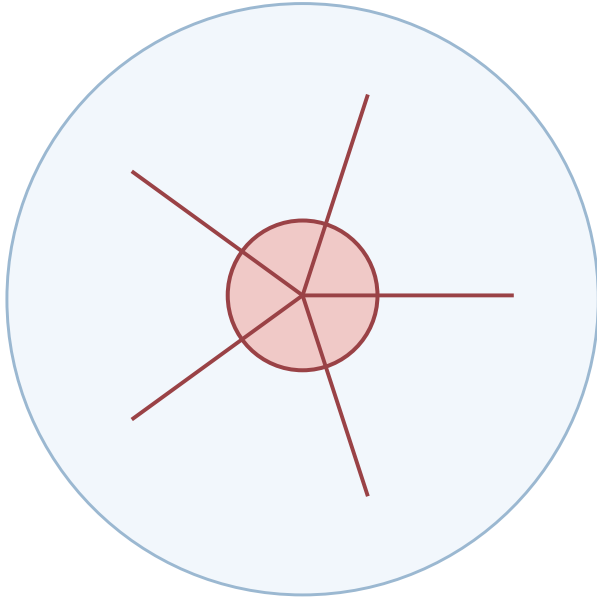
- Acute LHON can produce a pseudoedematous peripapillary appearance.
- Clinical interpretation requires correlation with pain, vision, OCT, and other findings.

- Do not diagnose inflammatory optic neuritis on disc appearance alone.

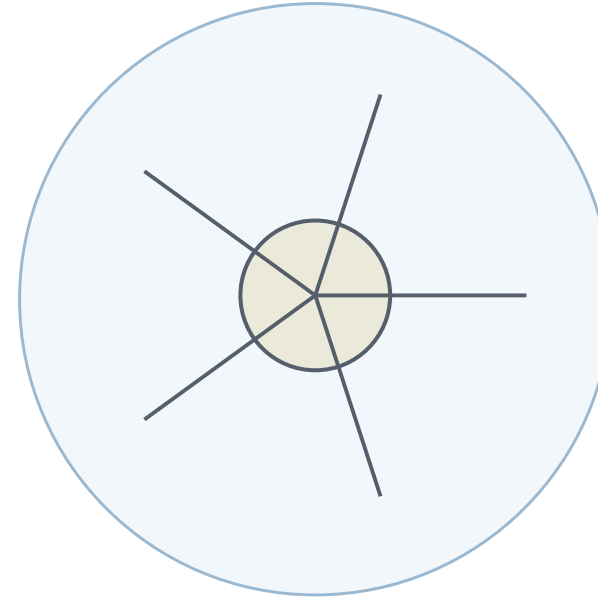
Chronic LHON progresses to optic atrophy

Schematic

Schematic optic-disc appearances — not photographs



Subacute / active



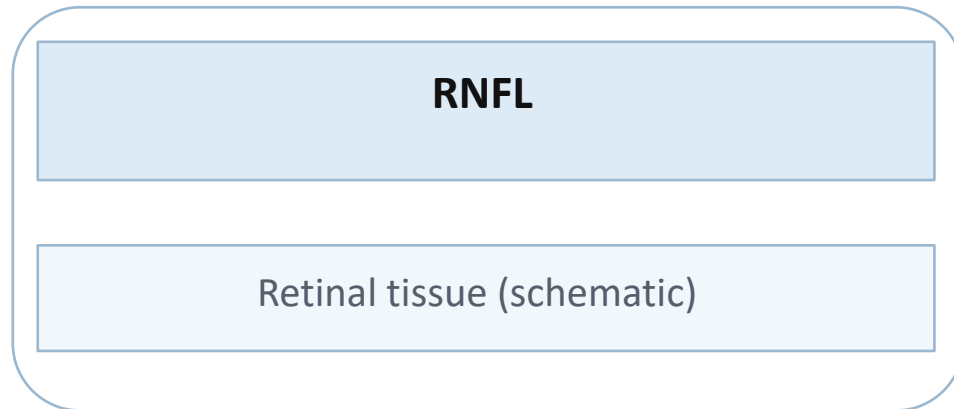
Chronic / atrophic

- Long-standing retinal ganglion cell injury reduces optic-nerve fibers.
- Optic disc pallor becomes a prominent structural clue.
- The degree of atrophy must be interpreted alongside function and disease stage.

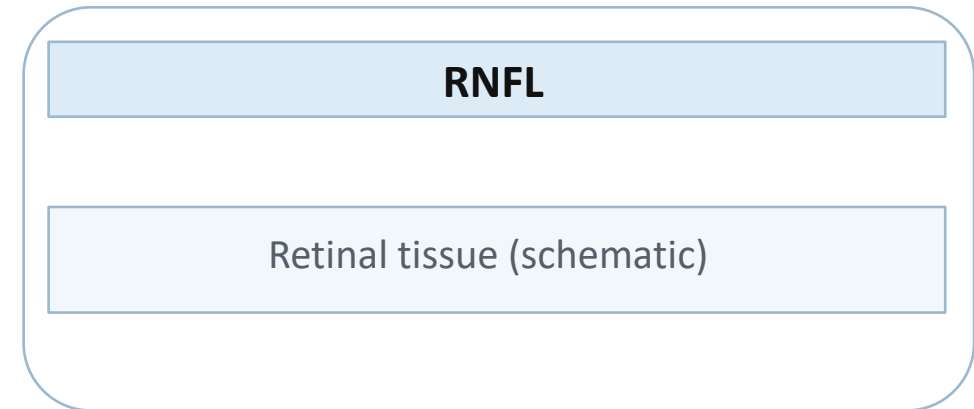
Optical coherence tomography interrogates neural structure

Schematic

Early RNFL thickening



Chronic RNFL loss



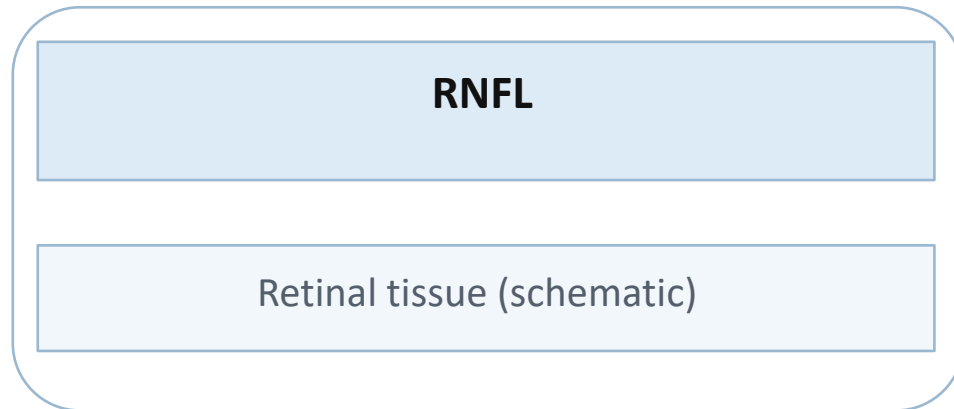
Qualitative layer representation — not acquired OCT measurements

- Retinal nerve fiber layer (RNFL) thickness reflects ganglion-cell axon integrity.
- Macular ganglion cell measurements assess neuronal loss.
- Serial OCT complements—but cannot replace—clinical and molecular diagnosis.

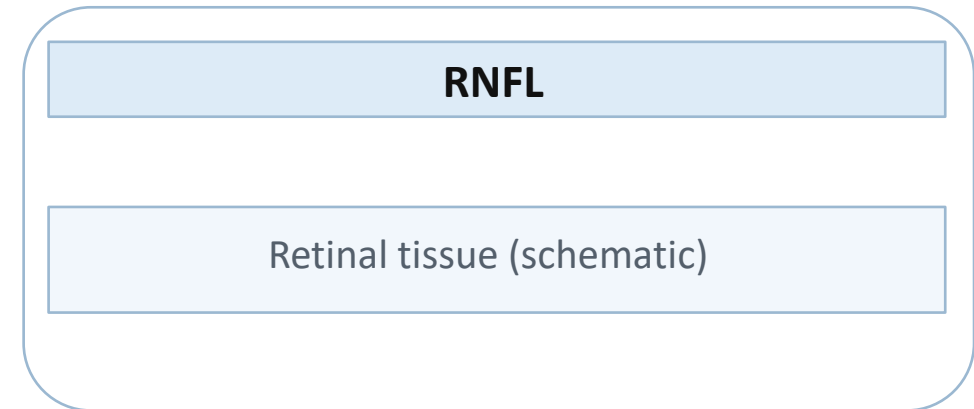
OCT appearance depends on disease stage

Schematic

Early RNFL thickening



Chronic RNFL loss



Qualitative layer representation — not acquired OCT measurements

- Early RNFL swelling may coexist with developing ganglion-cell dysfunction.
- Later RNFL thinning reflects established axonal loss.
- Stage-aware interpretation prevents misreading edema as preserved health.

Visual fields and OCT answer different questions

- Perimetry measures vision function: A central/centrocecal defect.
- OCT measures retinal and peripapillary structure.

- Agreement increases confidence in localization to the optic-nerve pathway.

A typical clinical sequence can be staged

Schematic

Carrier / early

Possible subtle changes

Subacute

Central failure; Variable disc appearance

Chronic

Axonal thinning; Disc pallor

- Carrier state: Pathogenic variant present, with or without subtle ocular findings.
- Subacute phase: Central visual failure with variable disc features.
- Chronic phase: Persistent field deficit and optic-disc atrophy.

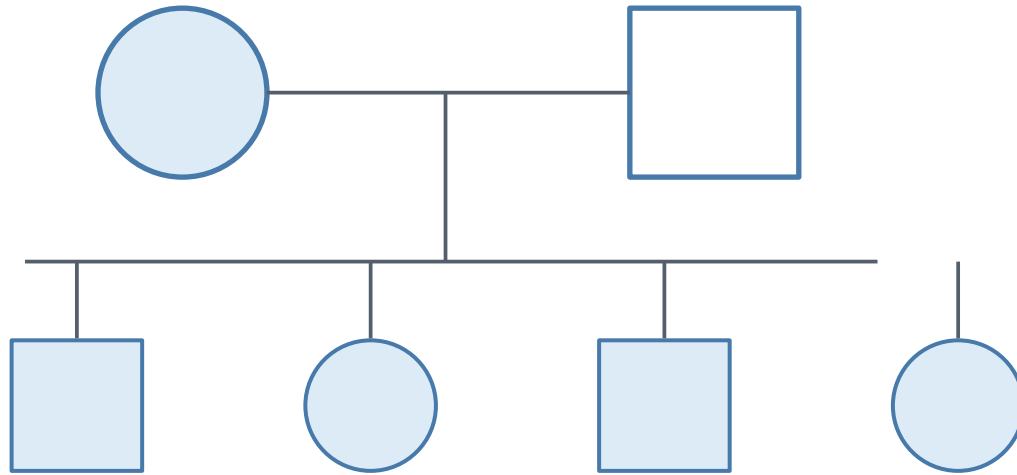
Male predominance does not mean X-linked inheritance

- Males are affected more frequently than females among variant carriers.
- Both sexes inherit the maternal mitochondrial genome.

- The sex bias concerns penetrance, not the route of gene transmission.

Penetrance limits individual risk prediction

Schematic



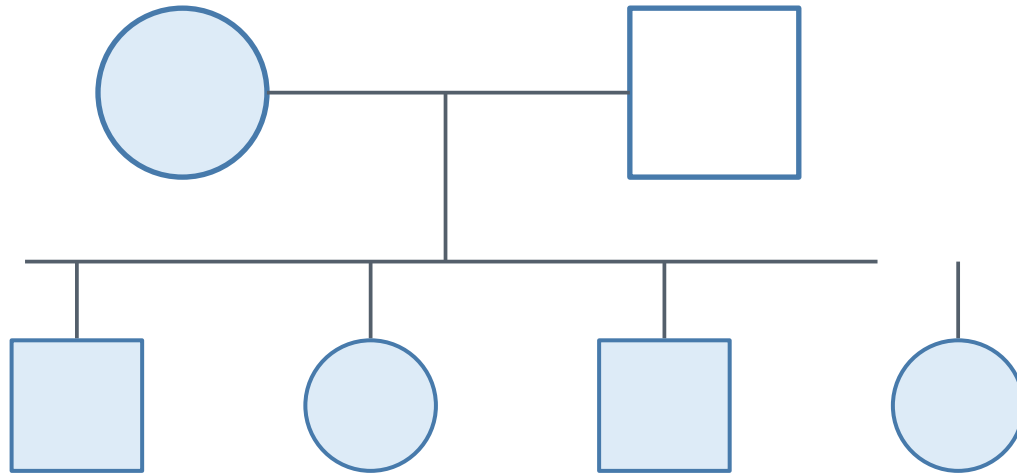
Filled blue: MtDNA variant present Outlined: Variant not shown

Maternal mtDNA can reach sons and daughters

- A pathogenic variant is necessary in classical mtDNA-associated LHON.
- Presence of the variant alone cannot determine future visual loss.
- Family counseling must convey uncertainty rather than a fixed personal prognosis.

A negative family history does not exclude LHON

Schematic



Filled blue: MtDNA variant present Outlined: Variant not shown

Maternal mtDNA can reach sons and daughters

- Maternal relatives may carry the variant without symptoms.
- Smaller pedigrees may contain no previously recognized affected individuals.
- Molecular testing can resolve uncertainty despite an uninformative pedigree.

Extraocular findings occur in some affected families

- Cardiac conduction abnormalities and minor neurologic features.
- GeneReviews also lists tremor, peripheral neuropathy, and movement disorders.

- Such findings require clinical evaluation and should not be assumed in every case.

LHON phenotypes are heterogeneous

Classic LHON predominantly affects the optic nerves.

A minority of patients display additional neurologic or cardiac features.

Atypical systemic involvement warrants broader mitochondrial and neurologic assessment.

Recognize the clinical pattern before ordering genetic tests

Painless central failure



Bilateral optic neuropathy



Consider LHON

- Young adult with painless subacute central vision loss.
- Sequential or simultaneous bilateral optic neuropathy.
- Maternal inheritance, when present, strengthens suspicion.

Core ophthalmic assessment localizes the deficit

Best-corrected visual acuity
and color vision.

Central visual-field evaluation
with perimetry.

Fundus examination and OCT
of RNFL/ganglion-cell layers.

Initial molecular testing targets common mtDNA variants

Primary variant	Affected gene	Respiratory complex
M.11778G>A	MT-ND4	Complex I
M.3460G>A	MT-ND1	Complex I
M.14484T>C	MT-ND6	Complex I

- Test m.11778G>A, m.3460G>A, and m.14484T>C.
- These variants account for approximately 90% of cases in GeneReviews.
- Ensure the laboratory assay reports mitochondrial variant nomenclature clearly.

If primary-variant testing is negative



- Reassess the clinical localization and other treatable etiologies.
- Consider comprehensive mtDNA sequencing or an inherited optic-neuropathy panel.
- Interpret any detected variant using clinical and molecular evidence together.

A variant of uncertain significance is not a diagnosis

- Sequence variation may be benign, pathogenic, or uncertain.
- A VUS must not be treated as molecular confirmation.

- Phenotype, segregation, functional evidence, and expert interpretation matter.

LHON and inflammatory optic neuritis are not synonyms

- LHON usually causes painless central failure, often progressing to the second eye.
- Typical demyelinating optic neuritis may involve pain with eye movements.

- History, examination, imaging, and clinical course guide differentiation.

Consider nutritional and toxic optic neuropathies

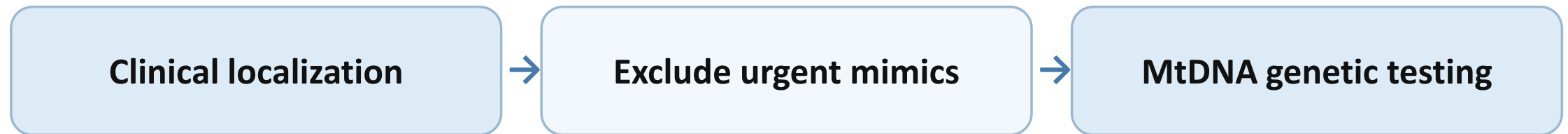
- Central visual loss may result from nutritional deficits or toxic exposure.
- Robbins specifically mentions toxic injury such as methanol exposure.

- A complete exposure, medication, alcohol, and nutrition history is necessary.

MRI is often an exclusion tool, not an LHON biomarker

- MRI may be normal in typical LHON.
- Atypical deficits require evaluation for compressive, inflammatory, and other causes.
- Do not infer that an abnormal MRI automatically proves a mitochondrial etiology.

A safe diagnostic pathway prioritizes reversible disorders



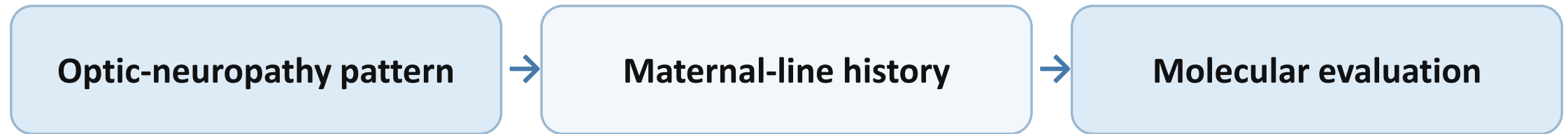
- Establish optic-neuropathy localization and characterize the clinical pattern.
- Exclude urgent treatable mimics based on symptoms and examination.
- Confirm a pathogenic mtDNA variant with appropriately selected testing.

Patient vignette: Bilateral central loss

Constructed educational vignette

- A 22-year-old develops painless central blur in one eye; The fellow eye deteriorates weeks later.
- Perimetry reveals bilateral central scotomas.
- An unaffected mother reports a brother who developed severe visual loss.

Interpretation: Localize before labeling the pedigree



- Sequential painless central loss supports an optic neuropathy.
- The maternal uncle suggests, but does not prove, maternal transmission.
- Targeted testing for primary LHON mtDNA variants is appropriate.

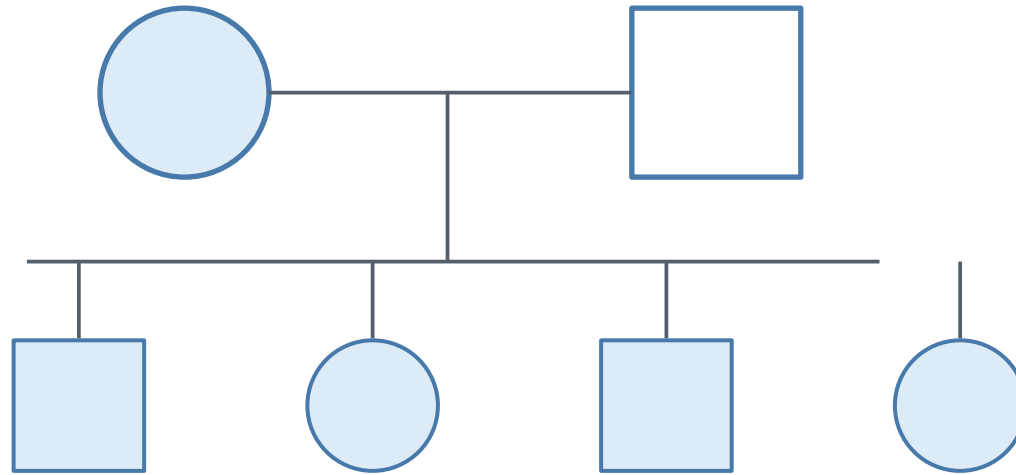
Pedigree exercise: Variant carrier and children

Constructed educational vignette

- A woman carries a pathogenic LHON mtDNA variant but has normal vision.
- Her son and daughter are healthy at the time of consultation.
- Which family members may transmit the mtDNA variant to the next generation?

Pedigree answer: Follow mtDNA, not symptom status

Schematic



Filled blue: MtDNA variant present Outlined: Variant not shown

Maternal mtDNA can reach sons and daughters

- Maternal transmission can occur without maternal visual impairment.
- A variant-carrying daughter can pass it to her children.
- A variant-carrying son cannot pass it through paternal mtDNA.

Genetic counseling separates three distinct questions

Transmission: Which relatives can inherit the variant?

Penetrance: Who is likely to develop optic neuropathy?

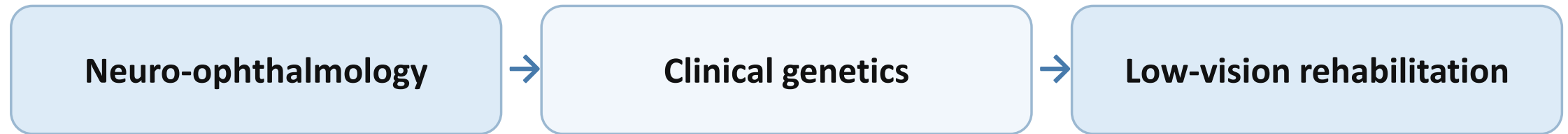
Severity: How much visual impairment might occur?

Risk reduction and clinical support are distinct

- Avoiding smoking is particularly important for known carriers.
- GeneReviews recommends moderation of alcohol and avoidance of binge drinking.

- Functional support requires vision rehabilitation and individualized follow-up.

Management is primarily multidisciplinary

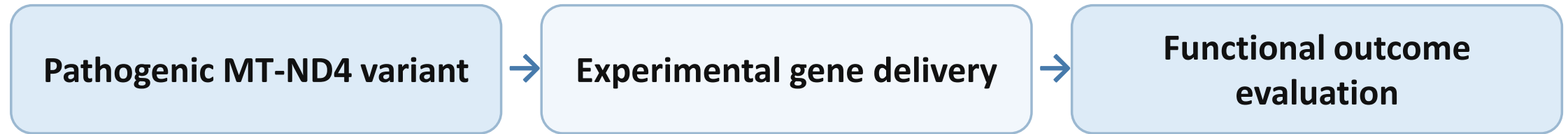


- Neuro-ophthalmology evaluates progression and competing diagnoses.
- Clinical genetics explains inheritance and reproductive implications.
- Low-vision services and rehabilitation address functional disability.

Disease-modifying treatment requires contextual evidence

- Idebenone has a region-specific regulatory history and evidence of benefit in some patients.
- Effect depends on timing and patient characteristics; Responses are variable.
- Therapeutic decisions require current local specialist guidance, not a generic textbook algorithm.

Gene-directed strategies remain an evolving field



- Investigational approaches attempt to restore mitochondrial respiratory function.
- Trials have focused on allotopic delivery of MT-ND4 for selected genotypes.
- Do not equate promising study signals with universally established therapy.

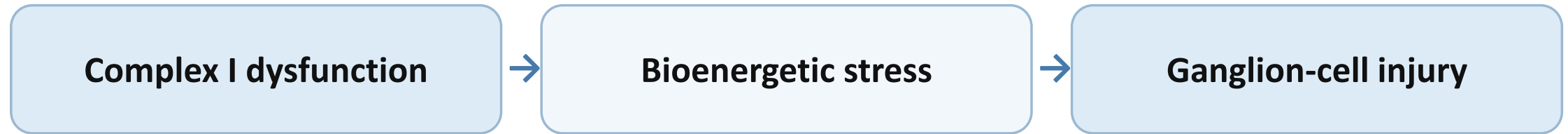
Three high-yield distinctions

Maternal transmission $\neq$ clinical penetrance.

Heteroplasmy threshold $\neq$ sufficient explanation of all LHON cases.

Central optic neuropathy $\neq$ primary disease of retinal photoreceptors.

Integrating genotype, tissue vulnerability, and phenotype



- Maternal mtDNA variant can alter respiratory-chain function.
- Energy-demanding retinal ganglion cells are susceptible to injury.
- Loss of ganglion-cell axons creates bilateral central optic neuropathy.

Selected references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 5, pp. 156–157.
- Robbins, Cotran & Kumar. Other Optic Neuropathies section (eye chapter).
- Yu-Wai-Man P, Chinnery PF. Leber Hereditary Optic Neuropathy. GeneReviews (2021 update).
- Ambika S, Srilekha S. Systematic review of LHON. Indian J Ophthalmol (2026).