

Other Retinal Degenerations

Photoreceptor degeneration · Retinitis pigmentosa

Inherited pathology, functional loss and diagnostic localization

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Learning objectives

- Localize retinal degeneration to photoreceptors and the retinal pigment epithelium (RPE).
- Explain the genetic and cellular basis of retinitis pigmentosa (RP).
- Correlate rod–cone loss with functional impairment and morphology.
- Interpret key clinical investigations and distinguish major phenocopies.

Scope: Degeneration is not a single lesion

- The Robbins subsection “Other Retinal Degenerations” specifically discusses retinitis pigmentosa.
- The term encompasses disorders of photoreceptors and/or RPE rather than one uniform molecular defect.
- This lecture develops the RP example, with brief comparisons that establish diagnostic boundaries.

Identify the primarily affected retinal compartment

Vitreous

Nerve fiber / ganglion

Inner plexiform + nuclear

Outer plexiform + nuclear

Photoreceptors: Rods + cones

Retinal pigment epithelium

Bruch membrane / choroid

Outer retinal photoreceptor injury is the central pathologic event.

Retinal vessel narrowing and pigment redistribution develop as degeneration advances.

Retinal microanatomy explains the symptoms

Vitreous

Nerve fiber / ganglion

Inner plexiform + nuclear

Outer plexiform + nuclear

Photoreceptors: Rods + cones

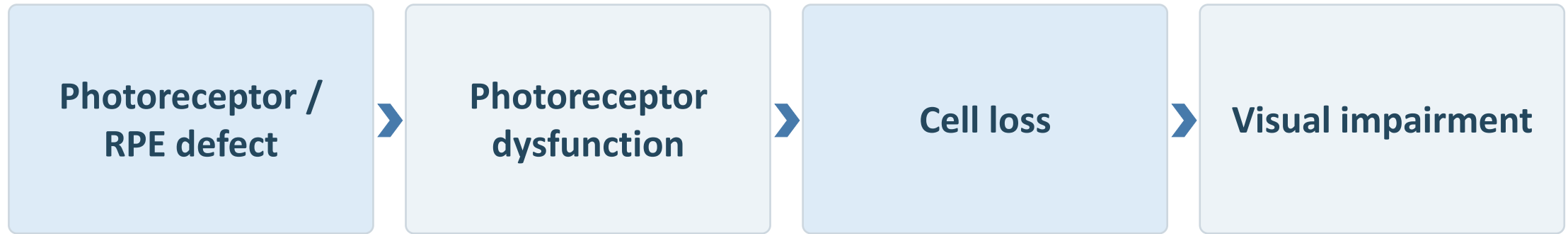
Retinal pigment epithelium

Bruch membrane / choroid

Outer retinal photoreceptor injury is the central pathologic event.

Retinal vessel narrowing and pigment redistribution develop as degeneration advances.

The RPE–photoreceptor relationship



- The RPE forms the outermost retinal epithelial layer adjacent to photoreceptor outer segments.
- The integrity of the photoreceptor–RPE unit is essential for photoreceptor survival.
- Genetic defects affecting either element can culminate in the RP phenotype.

Rods and cones perform distinct visual tasks

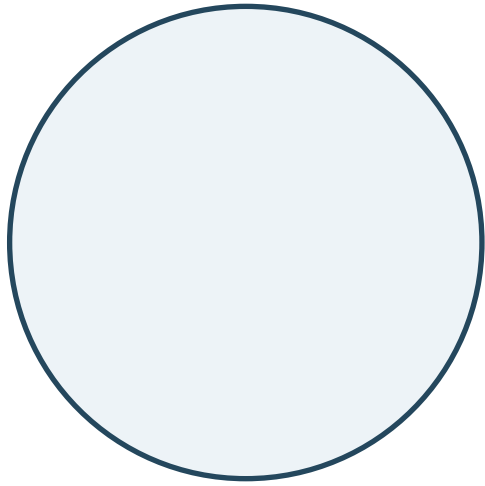
RODS

- Dark adaptation
- Peripheral function

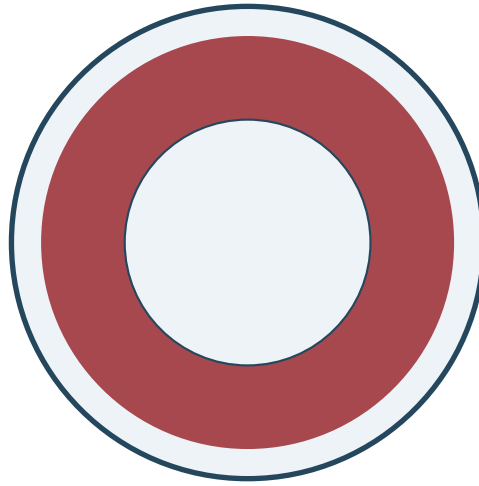
CONES

- Central acuity
- Later involvement in typical RP

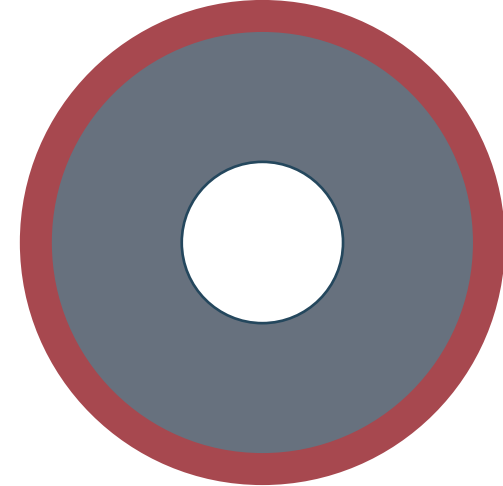
Localizing peripheral versus central vision loss



Intact field (conceptual)



Ring scotoma



Constricted field

Typical RP often begins with rod dysfunction and peripheral field impairment.

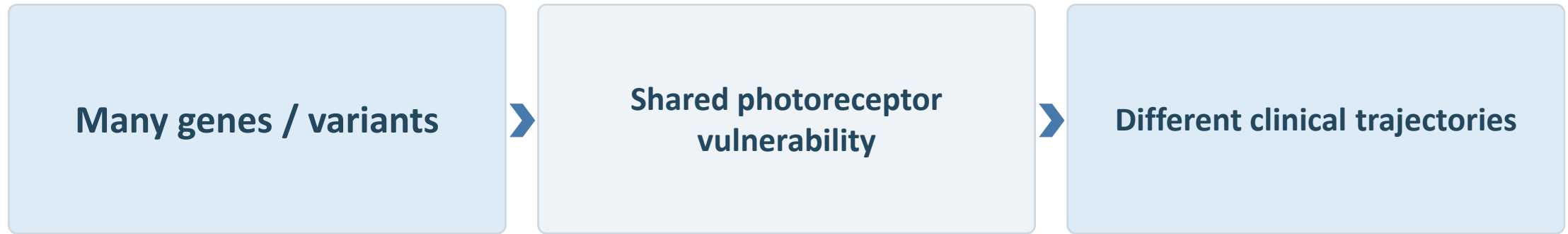
Retinitis pigmentosa: A clinicopathologic definition

- An inherited group of progressive photoreceptor degenerations.
- Pathogenic variants disturb rods, cones, RPE function or associated photoreceptor processes.
- Its expression ranges from mild visual impairment to profound loss of vision.

“Retinitis” is a historical misnomer

Feature	Retinitis pigmentosa	Inflammatory retinitis
Primary process	Hereditary neurodegeneration	Inflammatory injury
Cellular target	Photoreceptors / RPE	Retina affected by inflammation
Interpretive clue	Progressive rod–cone deficit	Assess infection / immune context

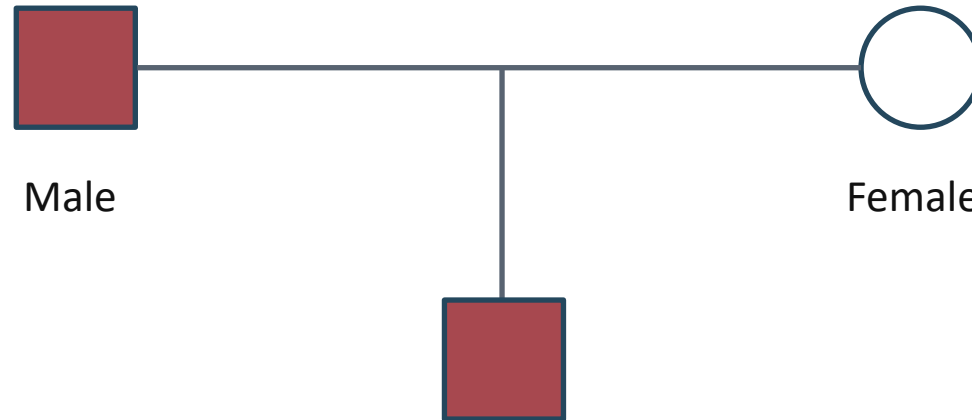
Phenotypic diversity follows genetic diversity



- Different genes can generate a similar rod–cone degenerative phenotype.
- Different variants within one gene may result in different clinical phenotypes.
- Age at onset, rate of decline, and residual central vision are therefore heterogeneous.

Autosomal dominant RP

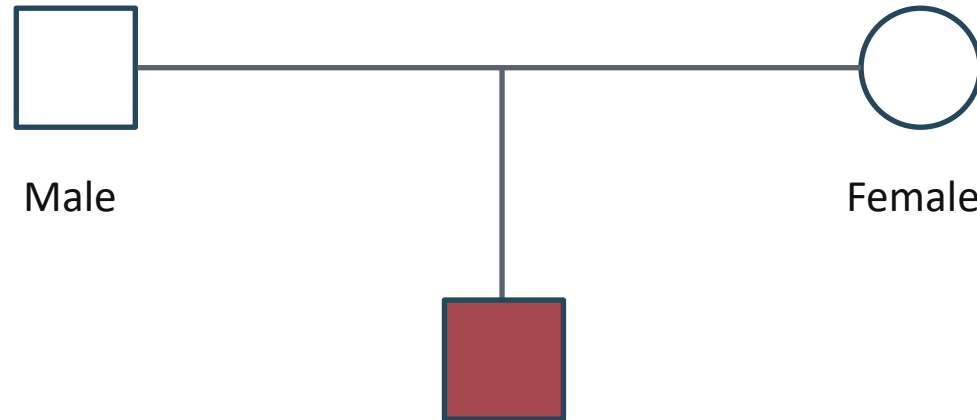
Affected parent → affected child may appear in successive generations



Filled = affected; Illustrative pedigree only

Autosomal recessive RP

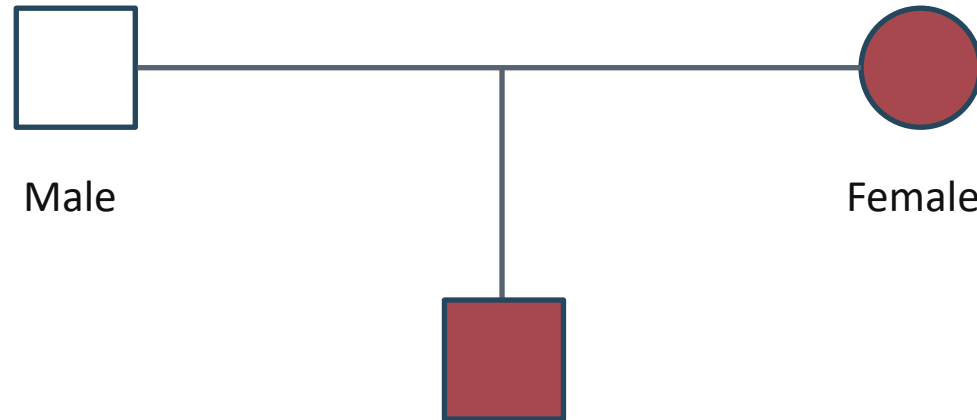
Clinically unaffected parents can have an affected child



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X-linked RP

No male-to-male transmission for an X-linked variant



Filled = affected; Illustrative pedigree only

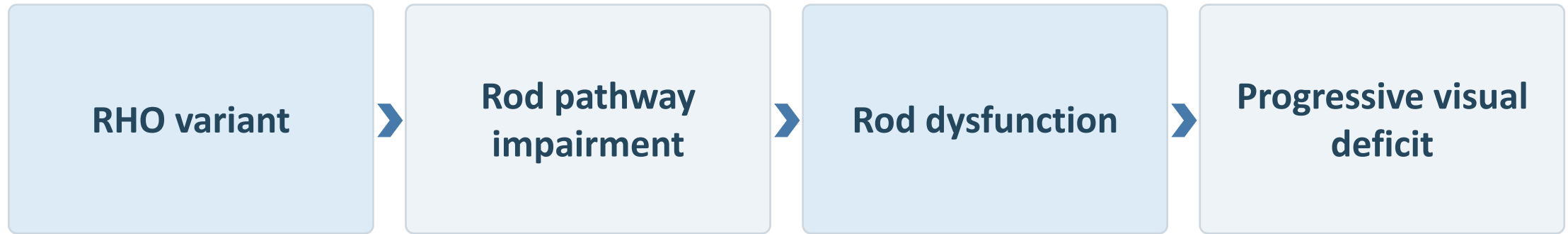
Pedigrees: Interpretation requires caution

- A simplex case is the only known affected individual in a family—not necessarily a recessive case.
- Reduced expression, family size, and incomplete ascertainment may obscure inheritance.
- The clinical phenotype and molecular result must be interpreted together.

Selected genes named in the Robbins discussion

Gene	Relevant connection
RHO	Rhodopsin / rod pathway
USH2A	Photoreceptor-associated function; Usher association
RPGR	X-linked RP; Verified official symbol
EYS	Inherited photoreceptor degeneration

RHO: A gene–photoreceptor link



- RHO encodes rhodopsin, a core rod phototransduction protein.
- RHO-associated disease illustrates how disruption of a rod-specific function can initiate the RP phenotype.
- Different RHO variants can produce more than one retinal phenotype.

USH2A: Isolated and syndromic disease

Nonsyndromic

- Retinal phenotype
- No established extraocular syndrome

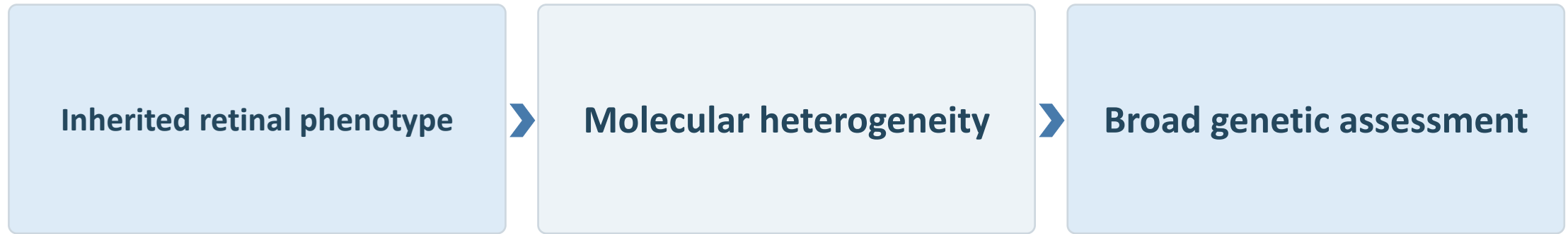
Usher spectrum

- Retinal degeneration
- Sensorineural hearing involvement

RPGR: Reconcile the extracted gene name

- The source conversion displays “RGPR” in the four-gene list.
- The approved gene symbol is RPGR (retinitis pigmentosa GTPase regulator).
- For clinical nomenclature and genetic testing, use verified HGNC/NCBI gene symbols.

EYS illustrates heterogeneous recessive disease



- EYS is explicitly listed among genes linked to RP.
- The involvement of several genes explains why a single negative-gene test cannot exclude RP.
- Comprehensive testing strategies are preferable to arbitrary single-gene exclusion.

Disease-associated pathways are diverse

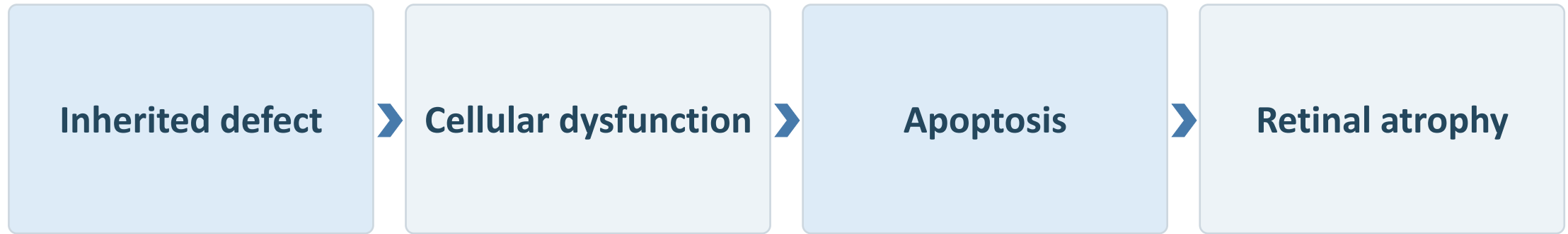
Molecular functions

- Phototransduction
- Visual cycle
- Cell structure

Tissue consequences

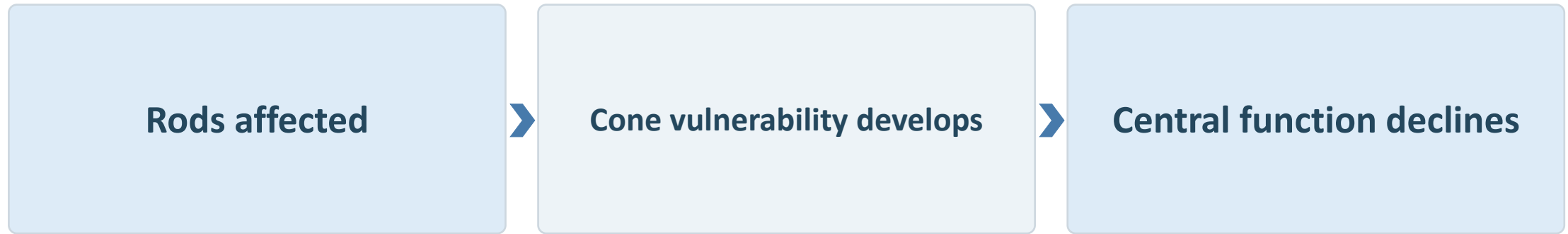
- Reduced function
- Photoreceptor attrition
- Visual disability

The central injury is photoreceptor loss



- Apoptotic death of rods and cones as symptoms develop.
- Photoreceptor loss is progressive rather than an isolated episode of vascular occlusion.
- Loss of the sensory cell population explains reduced retinal responsiveness.

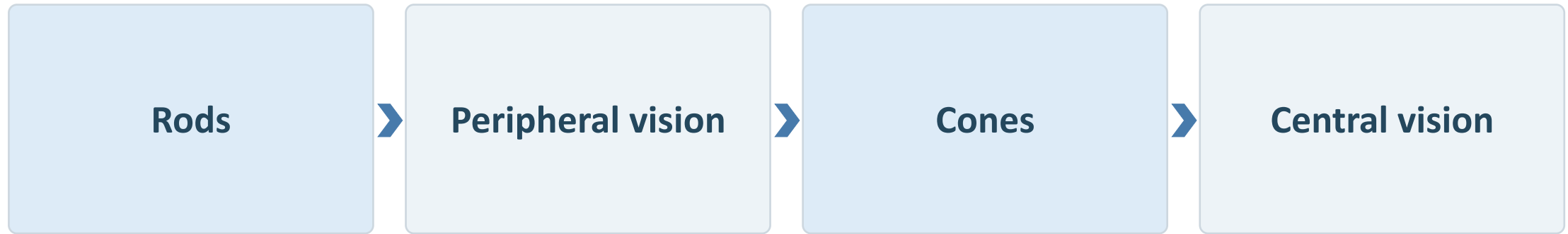
Cone loss involves more than rod loss



- RIP kinase activation as one contributor to cone death.
- This does not imply that one pathway explains all genes or stages.
- Preserved cones can temporarily sustain central vision despite early rod dysfunction.

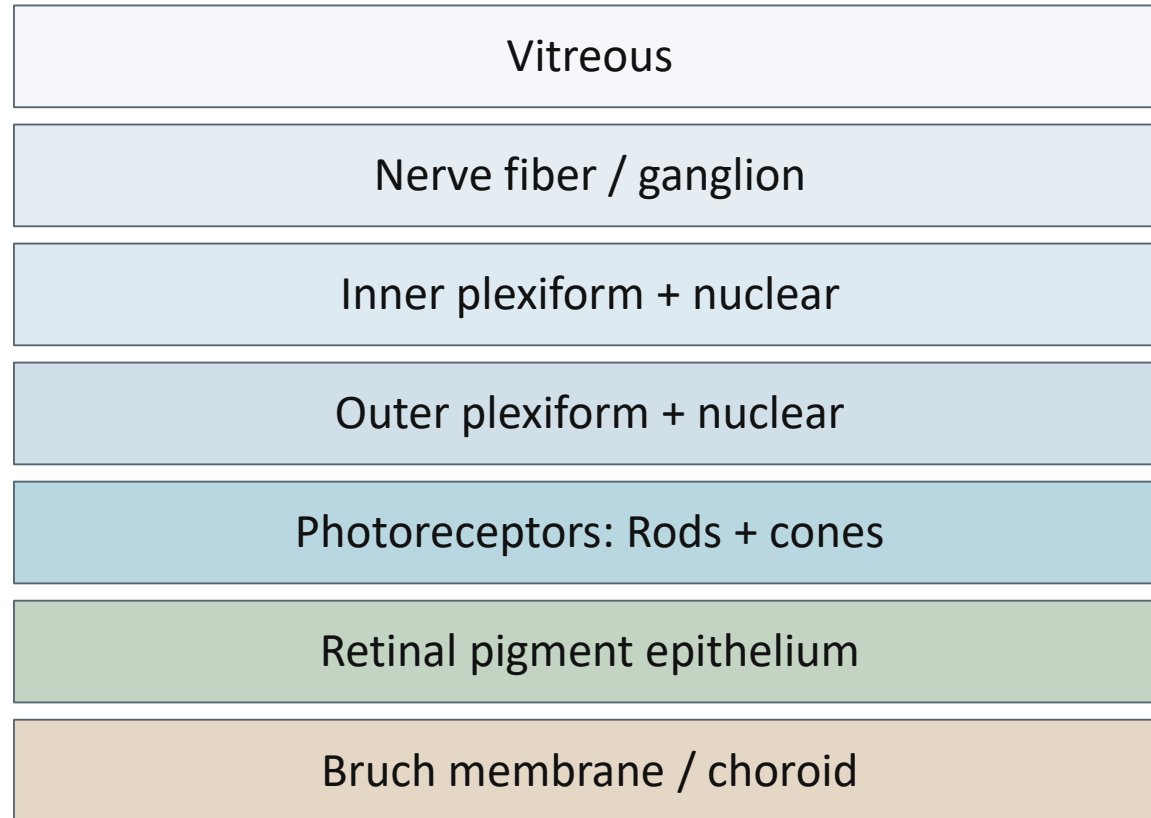
Schematic

Sequence of degeneration maps onto visual deficits



- Initial rod dysfunction → poor dark adaptation.
- Progressive photoreceptor attrition → reduction in peripheral visual field.
- Later cone involvement → impairment of central visual acuity.

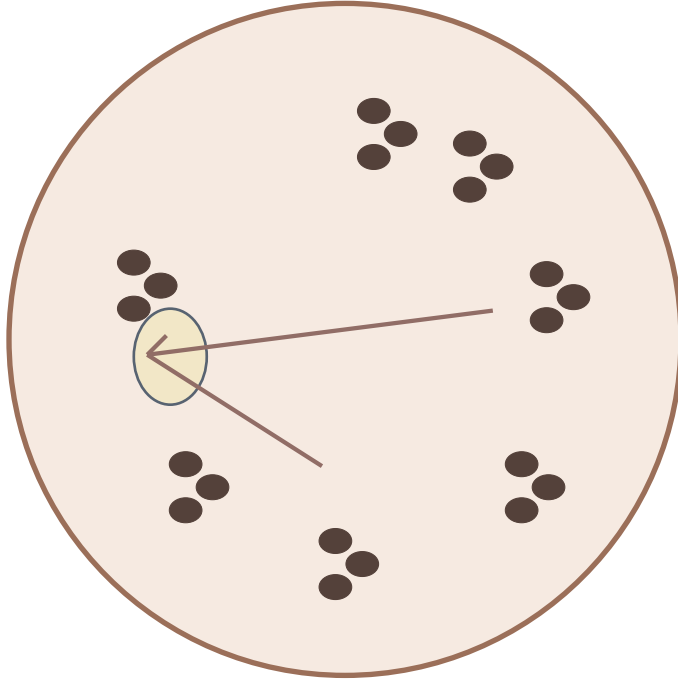
Photoreceptor degeneration remodels the retina



Outer retinal photoreceptor injury is the central pathologic event.

Retinal vessel narrowing and pigment redistribution develop as degeneration advances.

Pigment migration explains “pigmentosa”



Perivascular pigment clumps

Vessel attenuation

Optic disc pallor

Schematic retinal fundus: Not a clinical image

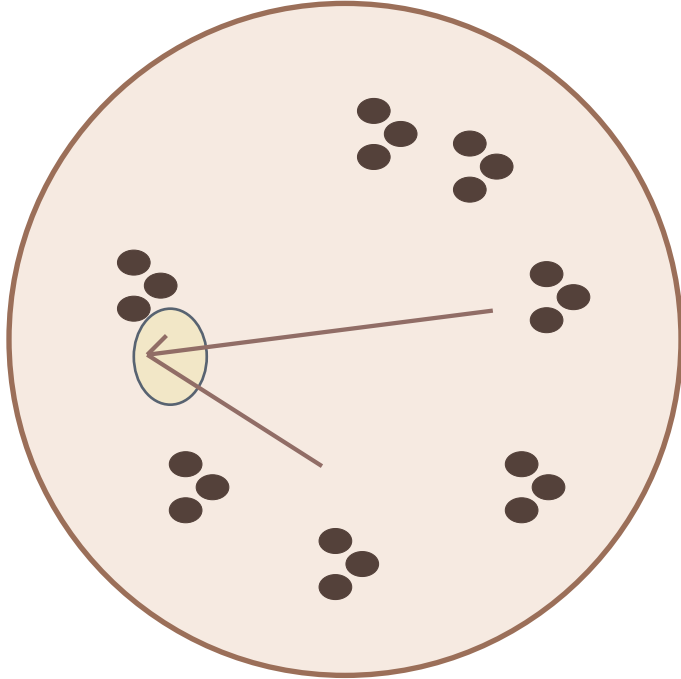
Retinal vessel attenuation in established RP

- Retinal blood vessels appear constricted/attenuated in advanced retinal degeneration.
- Vascular attenuation accompanies retinal atrophy.
- It should not be mistaken for the primary initiating vascular event.

Optic disc “waxy pallor”

- An atrophic optic nerve head with waxy pallor.
- This finding commonly coexists with vessel narrowing and retinal pigmentation.
- Disc pallor is nonspecific in isolation; Interpretation depends on the broader pattern.

Classical fundus triad



Perivascular pigment clumps

Vessel attenuation

Optic disc pallor

Schematic retinal fundus: Not a clinical image

Early RP may have a normal-appearing fundus

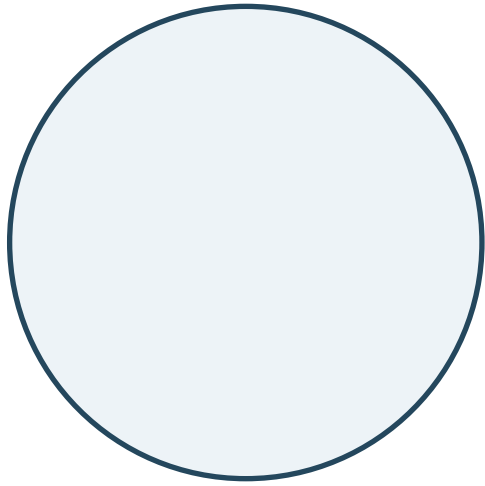
Feature	Early stage	Established stage
Fundus	May be unremarkable	Pigment, vessel and disc changes
Rod function	Often impaired	Markedly reduced
Clinical value	ERG and history	Pattern recognition

Fundus changes and visual disability are related, not identical

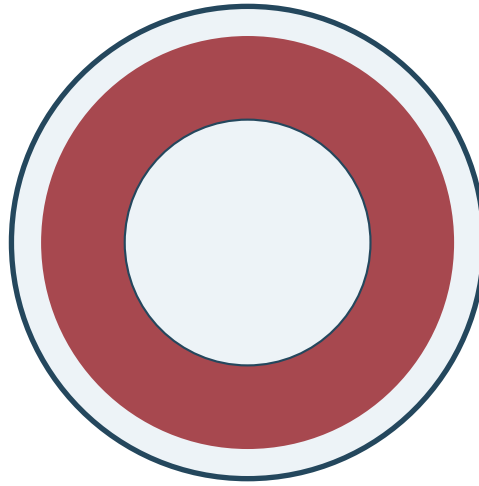


- Clinical symptoms reflect photoreceptor function, not only fundus appearance.
- Peripheral field loss may already impair navigation with relatively preserved central acuity.
- Combine structural, functional, and molecular assessment.

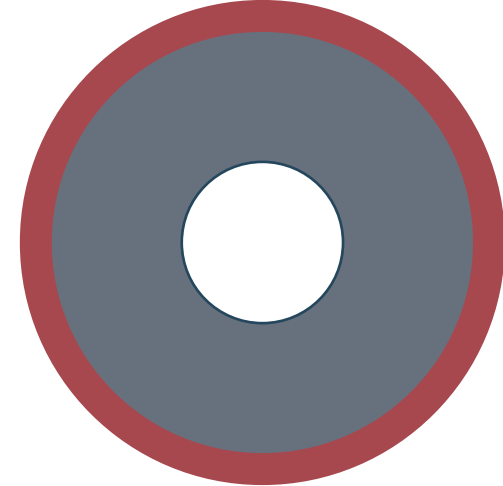
Nyctalopia: The classic initial clue



Intact field (conceptual)



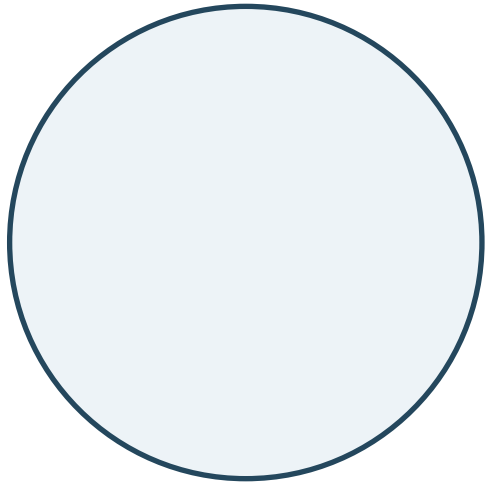
Ring scotoma



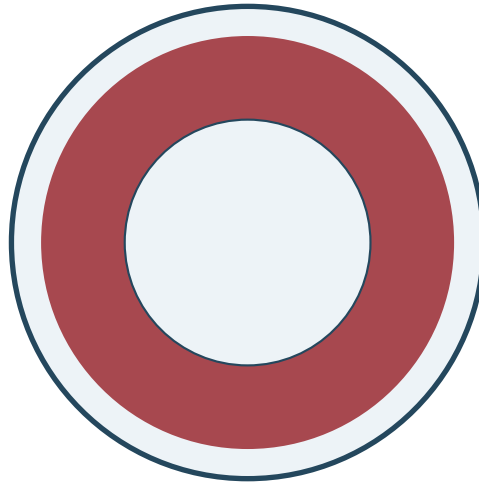
Constricted field

Patients report delayed adaptation after entering dimly lit settings.

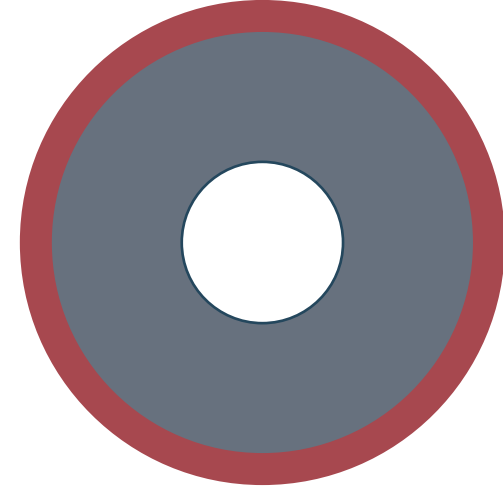
Peripheral visual field loss may go unrecognized



Intact field (conceptual)



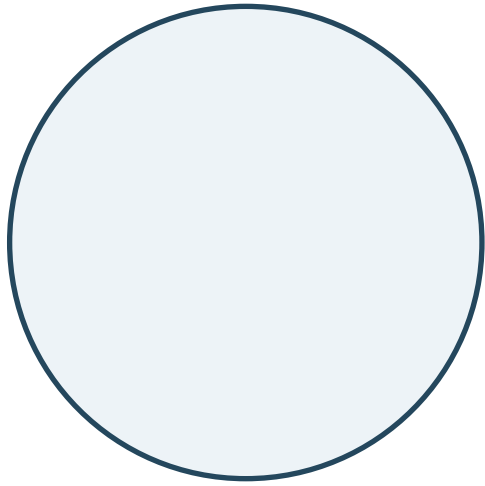
Ring scotoma



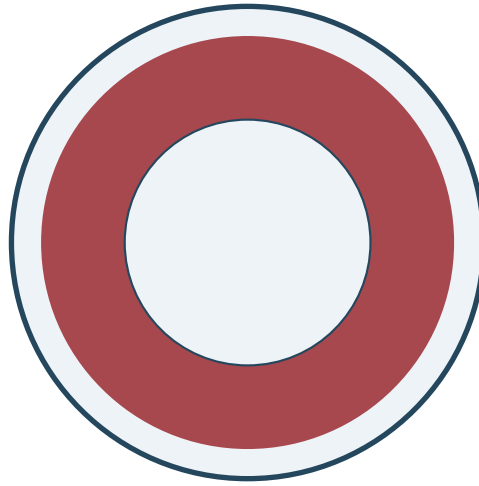
Constricted field

Mid-peripheral field defects can precede the patient's awareness of a field problem.

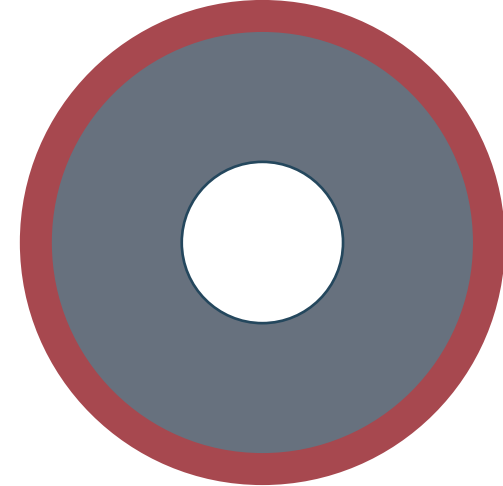
A ring scotoma can progress to field constriction



Intact field (conceptual)



Ring scotoma



Constricted field

An early mid-peripheral ring scotoma may expand with progression.

Central acuity can initially be preserved

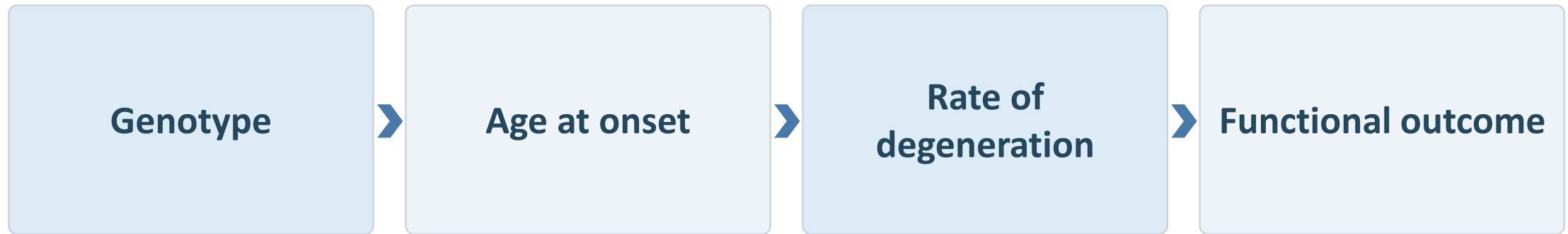
Central visual acuity

- May remain preserved
- Does not measure field width

Peripheral visual field

- Can be markedly constricted
- Critical for mobility

Progression varies across patients

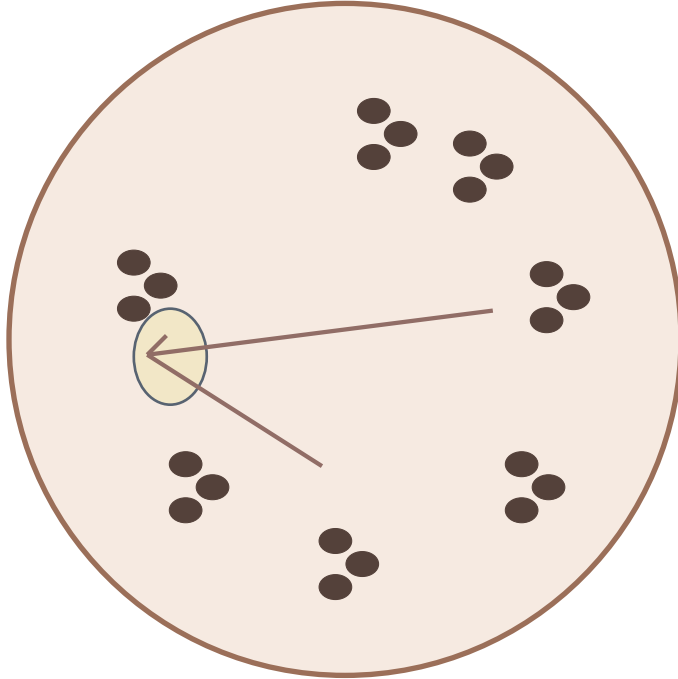


- Inheritance pattern and causal gene influence observed course.
- Autosomal dominant cases with later onset than other patterns.
- Do not predict an individual trajectory from inheritance mode alone.

Clinical evaluation begins with phenotype

- Document nyctalopia, peripheral field complaints, and central visual symptoms.
- Record onset, symmetry, progression, and family history.
- Ask about hearing, neurologic features, renal disease, and systemic manifestations.

Fundus examination tests a pattern hypothesis



Perivascular pigment clumps

Vessel attenuation

Optic disc pallor

Schematic retinal fundus: Not a clinical image

Electroretinography interrogates photoreceptor function

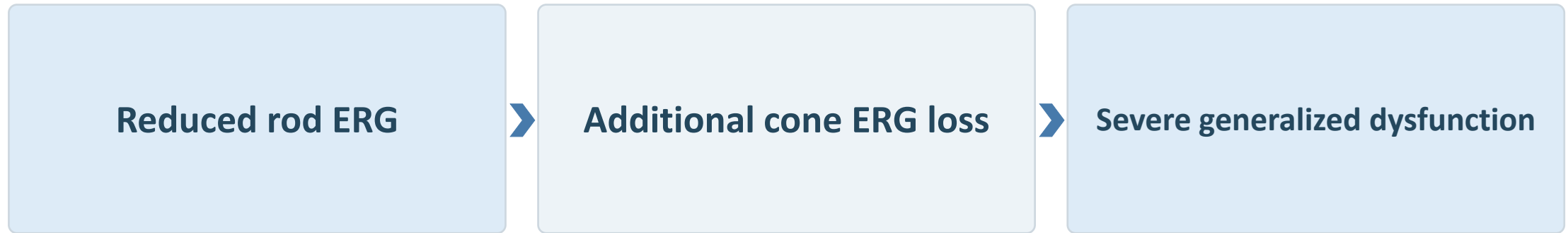
Dark adapted

- Rod-mediated response
- Often affected early

Light adapted

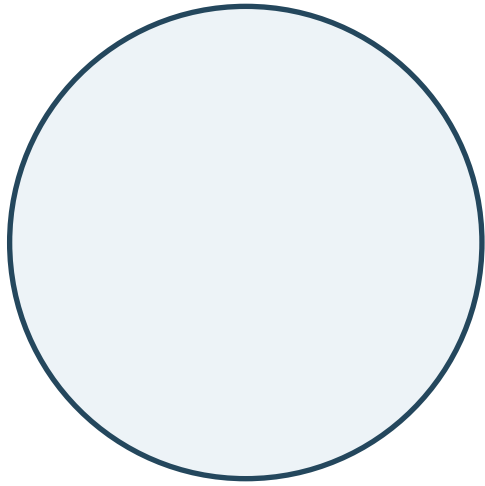
- Cone-mediated response
- May persist longer

Typical RP is rod-predominant on early ERG

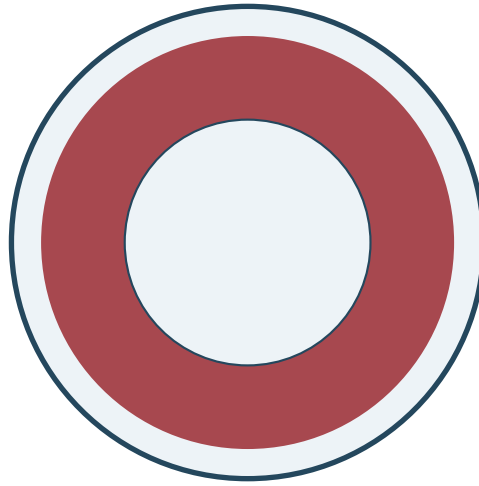


- Rod responses can be markedly diminished before a distinctive fundus pattern appears.
- Cone responses may be less impaired early in rod–cone degeneration.
- In late stages, both response types may be severely reduced or nondetectable.

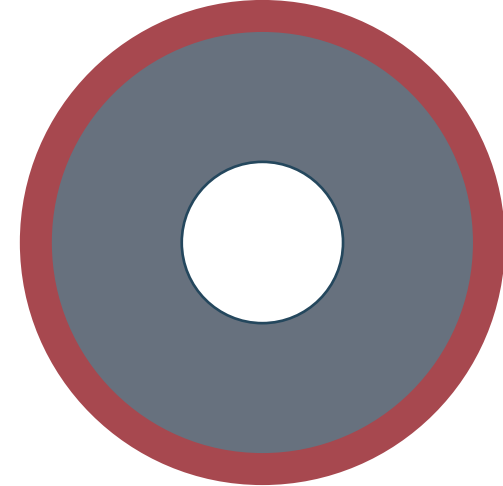
Visual field testing maps functional impact



Intact field (conceptual)



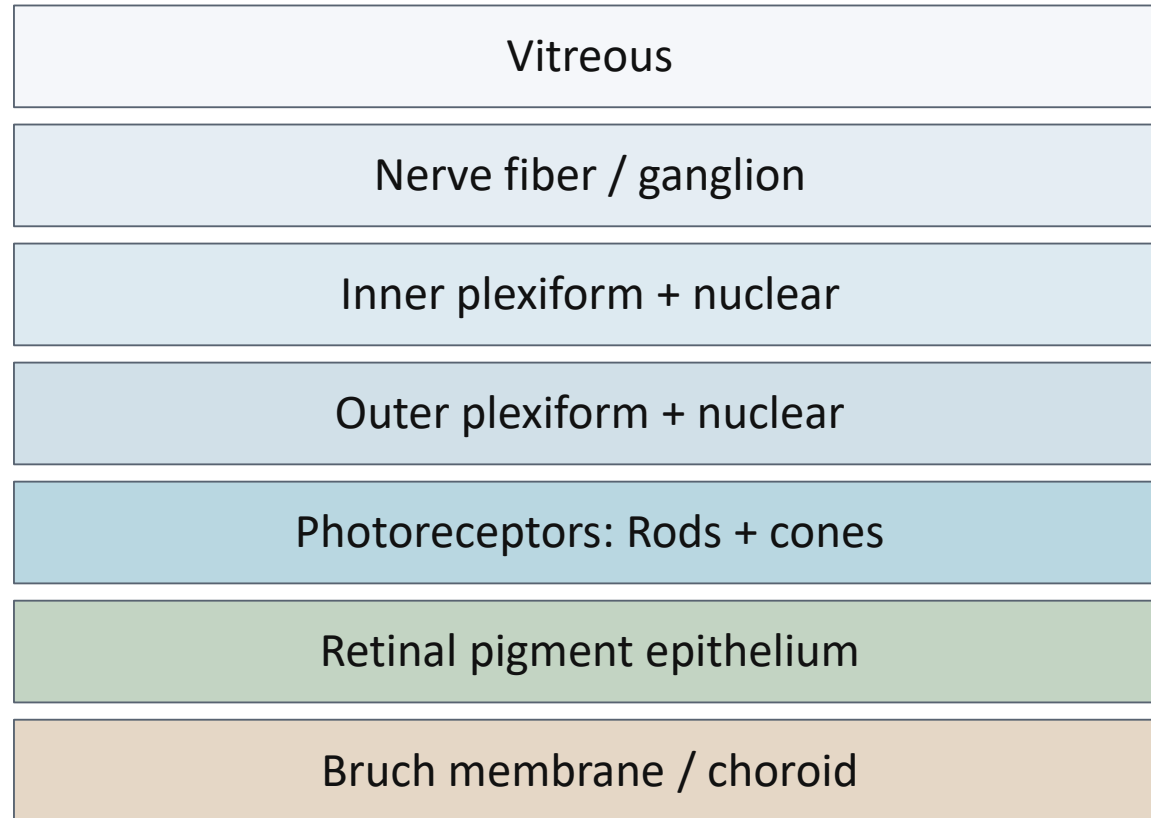
Ring scotoma



Constricted field

Perimetry demonstrates peripheral defects or mid-peripheral scotomata.

Optical coherence tomography localizes layer loss



Outer retinal photoreceptor injury is the central pathologic event.

Retinal vessel narrowing and pigment redistribution develop as degeneration advances.

Fundus autofluorescence adds an RPE-related map

- Fundus autofluorescence is among the clinical imaging modalities used in RP assessment.
- Pattern abnormalities provide information about RPE-related retinal changes.
- Interpret autofluorescence together with OCT and functional testing.

Genetic testing must match the heterogeneity



- An RP multigene panel is generally more informative than sequencing only one presumed gene.
- Exome or genome sequencing may be considered when targeted testing is nondiagnostic.
- Variants of uncertain significance do not independently establish disease causation.

Do not overlook the syndromic phenotype

Isolated phenotype

- Retinal degeneration
- No recognized systemic syndrome

Syndromic phenotype

- Retinal degeneration
- Extraocular manifestations

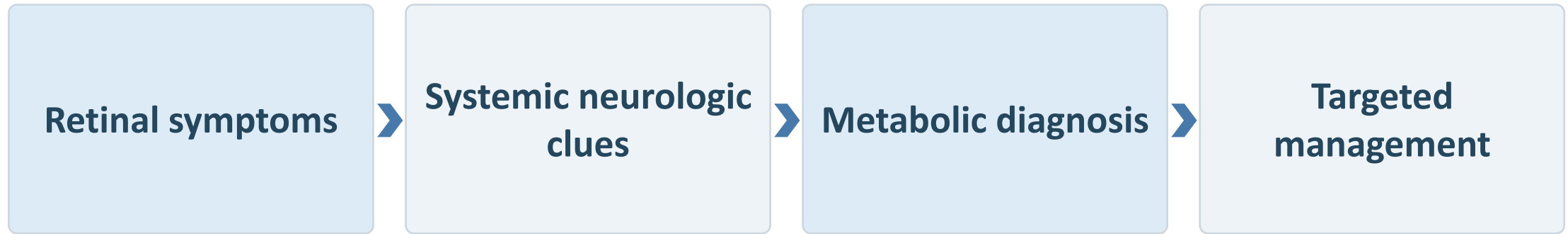
Usher syndrome links retinal and auditory dysfunction

- Robbins explicitly names Usher syndrome as an RP association.
- Sensorineural hearing impairment is an important associated clue.
- Vestibular abnormalities vary across Usher syndrome types.

Bardet–Biedl syndrome: Recognize systemic context

- Bardet–Biedl syndrome as a syndromic RP example.
- Retinal degeneration can accompany a multisystem ciliopathy phenotype.
- A careful systemic and family history should prompt specialist evaluation rather than an eye-only interpretation.

Refsum disease has an actionable metabolic link



- Refsum disease is specifically listed among syndromic RP associations.
- GeneReviews identifies phytanic acid metabolism as the relevant systemic defect.
- Unlike most RP genotypes, this phenotype has an established dietary intervention.

Red flags that warrant expanded differential diagnosis

- Marked asymmetry, atypical onset, prominent inflammation, or prominent central symptoms.
- Hearing loss, neuropathy, ataxia, and other systemic findings.
- History of drug exposure, autoimmune disease, infection, or trauma.

RP versus age-related macular degeneration

Feature	Retinitis pigmentosa	Age-related macular degeneration
Typical deficit	Night / peripheral vision	Central macular vision
Principal locus	Photoreceptors / RPE	Macular RPE–Bruch unit
Signature clues	Rod loss, pigmentary triad	Drusen / CNV

RP versus cone–rod dystrophy

Feature	Rod–cone degeneration	Cone–rod degeneration
Initial dominant deficit	Rods / dark adaptation	Cones / central function
Field pattern	Peripheral constriction	Central abnormalities
ERG	Rod deficit leads	Cone deficit leads

RP versus retinal vascular disease

Feature	Retinitis pigmentosa	Retinal vaso-occlusive pathology
Onset	Usually gradual / progressive	May be acute
Mechanism	Photoreceptor degeneration	Vascular nonperfusion
Primary structures	Rods / cones / RPE	Retinal circulation

RP versus inflammatory or toxic mimics

- Infectious retinitis, autoimmune retinopathy, drug toxicity, and prior injury can mimic retinal degeneration.
- Inflammation or exposure history should prompt consideration of alternative mechanisms.
- Neither bone-spicule pigmentation nor night blindness alone specifies a genotype.

Compare childhood severe-onset retinal dystrophy

Feature	Typical RP	Leber congenital amaurosis
Presentation	Progressive rod–cone loss	Severe early visual dysfunction
Clinical course	Variable onset	Infancy / early childhood
ERG	Rod then cone deficit	Often severely reduced early

Clinical case: The patient with normal central acuity

- An adolescent describes poor dark adaptation and difficulty locating objects to either side.
- Central acuity is relatively preserved; Fundus findings are subtle.
- Question: Which investigation best tests generalized rod-mediated dysfunction?

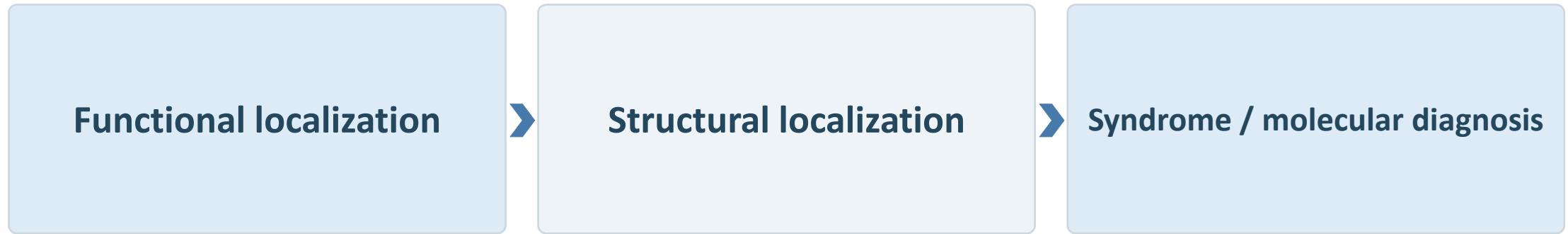
Clinical case: Interpreting the fundus triad

- An adult has constricted peripheral fields, narrowed retinal vessels, perivascular pigment and disc pallor.
- The findings support a chronic pigmentary retinal degeneration.
- Question: Why is vascular narrowing not sufficient to classify the process as vaso-occlusive?

Clinical case: Syndrome or isolated retinal disease?

- A patient with night blindness and progressive retinal degeneration also reports hearing difficulties.
- The retinal phenotype should not be classified as nonsyndromic without further assessment.
- Question: Which syndromic association is especially important?

Three integrated diagnostic decisions



- First: Is the functional pattern rod-predominant, cone-predominant, or another process?
- Second: Do structural features support progressive photoreceptor degeneration?
- Third: Is the condition syndromic, and what genetic evaluation is justified?

Take-home clinicopathologic correlations

- Inherited photoreceptor/RPE dysfunction produces progressive loss of rods and cones.
- Early rod loss explains nyctalopia and peripheral field constriction; Cone loss threatens central acuity.
- Pigment clumping, vessel attenuation and optic-disc pallor are characteristic late clues.
- Testing integrates function, structure, systemic features, and molecular evidence.

Selected references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. 2026. Chapter 29: The Eye.
- Fahim AT, Daiger SP, Weleber RG. Nonsyndromic Retinitis Pigmentosa Overview. GeneReviews. Updated 2023.
- NCBI Gene. RPGR: retinitis pigmentosa GTPase regulator. Gene ID 6103.