PDE6G-Related Retinopathy (Retinitis Pigmentosa 57, RP57): A Comprehensive Disease Characterization

Disease: PDE6G-Related Retinopathy | **Causal gene: PDE6G** (phosphodiesterase 6G, rod cGMP-specific, γ-subunit; HGNC:8788; NCBI Gene:5148) **MONDO:** MONDO:1040034 (also mapped as MONDO:0013315) | **OMIM:** #613582 | **Synonyms:** Retinitis pigmentosa 57; RP57 **Category:** Mendelian, autosomal recessive

Summary

PDE6G-Related Retinopathy (Retinitis Pigmentosa 57, RP57; OMIM #613582) is a severe, early-onset, autosomal-recessive rod–cone dystrophy caused by biallelic **loss-of-function of PDE6G**, the gene encoding the 87-amino-acid inhibitory γ-subunit (Pγ) of rod photoreceptor cGMP phosphodiesterase (PDE6). PDE6 is the central effector enzyme of the rod phototransduction cascade: light-activated transducin relieves Pγ-mediated inhibition of the PDE6 catalytic dimer (PDE6A/PDE6B), triggering rapid cGMP hydrolysis, closure of cGMP-gated cation channels, and photoreceptor hyperpolarization. When Pγ is lost, this inhibitory control collapses, cGMP homeostasis is dysregulated, and rod photoreceptors degenerate early and rapidly, followed by secondary cone loss — the hallmark of retinitis pigmentosa. The disease was defined in a single consanguineous Muslim Arab-Israeli kindred in which genome-wide homozygosity mapping localized a 4.7-Mb region on chromosome 17q25.3 and identified the pathogenic splice-donor variant **c.187+1G>T** (PMID: 20655036).

The clinical picture is a classic but severe rod–cone dystrophy: markedly constricted visual fields, severely reduced or extinguished scotopic and photopic electroretinograms (ERG), midperipheral bone-spicule pigmentation, optic disc pallor, attenuated retinal vessels, loss of foveal reflex, and cystoid macular edema. Onset is in childhood, and inheritance is strictly autosomal recessive. The official Human Phenotype Ontology (HPO) annotation set for OMIM:613582 comprises ten terms, all sourced to the founding family report.

RP57 is one of the rarest genetic subtypes of a genetically heterogeneous disease group (retinitis pigmentosa, >90 causative genes, overall prevalence ~1/4000). Population genomics (gnomAD v4) show PDE6G is **loss-of-function-tolerant in heterozygotes** (pLI ≈ 0.0004; observed/expected LoF = 0.91), consistent with a recessive gene whose carriers are healthy; the estimated carrier frequency is ~1 in 6,600 and the random-mating affected frequency ~1 in 170 million, explaining why cases essentially require consanguinity. ClinVar documents a small loss-of-function allelic series (nonsense, frameshift, essential-splice, start-loss) plus large 17q25.3 copy-number events. There is currently no approved therapy; management is supportive, but PDE6-related RP is among the most tractable targets for AAV-mediated gene supplementation, which has achieved durable rescue even at advanced disease stages in related PDE6 models. A theoretical pharmacologic caution applies: PDE6-cross-reactive inhibitors (e.g., sildenafil) selectively impair retinal function in PDE6-γ-deficient mice.

Key Findings

Finding 1 — PDE6G loss-of-function causes autosomal-recessive early-onset RP (RP57)

Dvir and colleagues performed genome-wide homozygosity mapping in two sibships of an extended consanguineous Muslim Arab-Israeli family with severe early-onset autosomal-recessive RP, mapping a shared 4.7-Mb homozygous region on chromosome 17q25.3 that contains **PDE6G** (PMID: 20655036). Sequencing of all coding exons and exon–intron boundaries revealed a homozygous single-base change, **c.187+1G>T**, in the conserved intron 3 donor splice site. The variant cosegregated with disease, and an in vitro splicing assay confirmed aberrant splicing. As the authors state: *"Sequencing of all coding exons, including exon-intron boundaries, revealed a homozygous single base change (c.187+1G>T) located in the conserved intron 3 donor splice site of PDE6G."* They further note that *"One of the genes located in this interval is PDE6G, encoding for the inhibitory gamma subunit of rod photoreceptor cyclic GMP-phosphodiesterase."* This established PDE6G as the causal gene of RP57 (MONDO:1040034). **Evidence type:** human clinical/genetic.

Finding 2 — Clinical phenotype: severe rod–cone dystrophy with extinguished ERG and macular edema

In the founding family, affected individuals had *"markedly constricted visual fields"* and *"Both scotopic and photopic electroretinograms were severely reduced or completely extinct,"* indicating combined rod and cone dysfunction (PMID: 20655036). Funduscopy showed *"typical bone spicule-type pigment deposits spread mainly at the midperiphery, as well as pallor of the optic disk."* Macular involvement included loss of the foveal reflex and cystoid macular edema confirmed on optical coherence tomography (OCT). These features situate RP57 within the classic RP clinical spectrum (worldwide RP prevalence ~1/4000) but at the severe, early-onset end. **Evidence type:** human clinical.

Finding 3 — Mechanism: PDE6 γ-subunit loss dysregulates cGMP hydrolysis in rod outer segments, driving photoreceptor death

PDE6 is the central effector enzyme of the rod/cone phototransduction cascade — a tetramer of two catalytic subunits (rod PDE6A/PDE6B) and two inhibitory γ-subunits (rod PDE6G). As reviewed, *"As the central effector enzyme of the G-protein coupled visual transduction pathway, activation of PDE6 catalysis causes a rapid decrease in cGMP levels that results in closure of cGMP-gated ion channels in the photoreceptor plasma membrane"* (PMID: 34170501), and *"mutations in PDE6 genes result in various retinal diseases that currently lack therapeutic treatment strategies."* In vivo mouse studies of PDE6γ mutants demonstrate that the γ-subunit normally restrains dark PDE6 activity: ILE86TER rods *"showed a decreased rate of decay of the photoresponse, consistent with decreased inhibition of PDE6 α and β by PDE6γ. Furthermore, ILE86TER rods had a higher rate of spontaneous activation of PDE6 than WT rods"* (PMID: 21920434). Loss of Pγ therefore dysregulates cGMP signaling and reduces holoenzyme stability, the upstream lesion that triggers photoreceptor death. **Evidence type:** in vitro / model organism / review.

Finding 4 — Pde6g-deficient mouse recapitulates early-onset RP; PDE6-RP is gene-therapy-tractable even at late stages

A *Pde6g* preclinical mouse model exhibits *"early onset and rapid rod degeneration, with the vast majority gone by P16,"* leading to retinal remodeling of inner retinal neurons, RPE, and vasculature, including acellular capillaries (PMID: 37363133) — faithfully reproducing the severe, early human phenotype. In the related *Pde6b* RP model, restoring the wild-type gene in rod photoreceptors produced *"stable, sustained rescue of photoreceptor structure and function*

for at least 1 year, demonstrating gene therapy efficacy after onset of degeneration" (PMID: 29721933). A therapeutic window exists: *"when fewer than 13% of rods remain, our genetic rescue halts photoreceptor degeneration, electroretinography (ERG) functional decline and inner retinal remodeling"* at 16 weeks, whereas treatment at 24 weeks failed (PMID: 35195763). **Evidence type:** model organism.

Finding 5 — PDE6G-RP is an ultra-rare subtype within genetically heterogeneous RP (>90 genes)

RP is a group of inherited retinal diseases affecting >1 million people worldwide that *"show tremendous genetic and phenotypic heterogeneity, involving over 90 genes in its causation"* (PMID: 40575766); no curative treatment exists, though gene therapy, stem cells, optogenetics, retinal prosthetics, and pharmacotherapy are emerging. Within this landscape, PDE6G/RP57 is among the rarest causes — the defining disease was described in a single consanguineous Arab-Israeli kindred, against an overall RP prevalence of *"1 in 4000"* (PMID: 20655036). **Evidence type:** review / human clinical.

Finding 6 — Gene–drug interaction: PDE6-inhibiting drugs (sildenafil) selectively impair retinal function in PDE6-γ-deficient mice

In mice heterozygous for the *Pde6g*-null allele (PDEG tm1/+), the PDE5/PDE6 inhibitor sildenafil produced a reversible, dose-dependent decrease in ERG a- and b-wave amplitudes, while wild-type mice were unaffected: *"ERGs of the PDEG:(tm1)/+ mice treated with sildenafil showed a reversible, dose-dependent decrease in a- and b-wave amplitudes. Wild-type mice treated with sildenafil did not show significant differences"* (PMID: 11157892). This reveals heightened sensitivity of PDE6-γ-compromised retina to pharmacologic PDE6 inhibition and motivates a theoretical caution for carriers/patients exposed to PDE5/PDE6-cross-reactive drugs. **Evidence type:** model organism.

Finding 7 — gnomAD: PDE6G is LoF-tolerant in heterozygotes (recessive); carrier frequency ~1/6,600

gnomAD v4 shows PDE6G (ENSG00000185527; chr17:81,650,459–81,663,112; 4 exons) is **not** loss-of-function-constrained: pLI ≈ 0.0004, observed/expected LoF = 0.91 (observed 10 / expected 10.95), LoF Z = 0.24 — consistent with a recessive gene whose heterozygous LoF carriers are healthy. High-confidence truncating alleles are each ultra-rare (AF 1.4×10^{-6} to 6.8×10^{-6}; e.g., p.Arg33Ter AC = 10, AF 6.8×10^{-6}). The founding RP57 allele c.187+1G>T is present at AC = 2/1,461,730 (AF 1.37×10^{-6}). Summing high-confidence LoF alleles gives q ≈ 7.6×10^{-5} →

estimated carrier frequency ~1.5×10^{-4} (**≈1 in 6,600**) and random-mating affected frequency $q^2 \approx 5.8\times10^{-9}$ (**≈1 in 170 million**). This quantitatively explains the ultra-rarity and consanguinity dependence; cases arise via homozygosity-by-descent, as in the founding family (*"Genome-wide homozygosity mapping was conducted in two sibships from an extended consanguineous Muslim Arab Israeli family,"* PMID: 20655036). **Evidence type:** computational / population genomics.

Finding 8 — ClinVar documents a loss-of-function allelic series in PDE6G beyond the founding variant

ClinVar contains 149 PDE6G records (22 Pathogenic, 4 Likely pathogenic, 6 Conflicting, 66 VUS, 41 Likely benign, 8 Benign, 2 Benign/Likely benign). PDE6G-specific pathogenic/likely-pathogenic small variants include the founding splice-donor c.187+1G>T (Pathogenic), a second essential-splice variant c.146+1G>T (Pathogenic), the nonsense c.97C>T/p.Arg33Ter (Pathogenic), the frameshift c.69dup/p.Arg24fs (Pathogenic), and the start-loss c.2T>A/p.Met1Lys (Likely pathogenic); c.95del/p.Gln32fs and c.206del/p.Pro69fs are Conflicting. Large 17q25.3 copy-number gains (×3 duplications) and deletions spanning PDE6G are also catalogued as Pathogenic (contiguous multi-gene events). The founding c.187+1G>T allele anchors this series: *"revealed a homozygous single base change (c.187+1G>T) located in the conserved intron 3 donor splice site of PDE6G"* (PMID: 20655036). The uniform LoF nature of pathogenic alleles confirms a loss-of-function disease mechanism. **Evidence type:** variant database curation.

Finding 9 — Official HPO disease annotations for RP57 retrieved and integrated

The JAX HPO Annotation Network for OMIM:613582 (RP57; gene NCBIGene:5148 = PDE6G) returns ten phenotype annotations, all sourced to PMID: 20655036: Reduced visual acuity (HP:0007663, frequency 6/6), Constriction of peripheral visual field (HP:0001133, 4/4), Rod-cone dystrophy (HP:0000510), Spicular pigmentation of the retina (HP:0007737), Optic disc pallor (HP:0000543, young-adult onset), Absent foveal reflex (HP:0030825), Cystoid macular edema (HP:0011505), Attenuation of retinal blood vessels (HP:0007843), Childhood onset (HP:0011463), and Autosomal recessive inheritance (HP:0000007). The single source documents the constricted fields and extinguished rod+cone ERG that define the phenotype set. **Evidence type:** ontology curation / human clinical.

Section-by-Section Report

1. Disease Information

PDE6G-Related Retinopathy is **Retinitis Pigmentosa 57 (RP57)**, a severe autosomal-recessive, early-onset rod–cone dystrophy caused by biallelic loss-of-function of **PDE6G**. It is an inherited retinal degeneration in which rod photoreceptors degenerate first, followed by cones, producing progressive loss of peripheral and night vision and eventual central visual loss.

Key identifiers:

Resource	Identifier
OMIM (phenotype)	#613582
OMIM (gene PDE6G)	*180073 / 614494
MONDO	MONDO:1040034 (also MONDO:0013315)
Gene (HGNC)	HGNC:8788, PDE6G
NCBI Gene	5148
Ensembl	ENSG00000185527
Locus	17q25.3

Synonyms: Retinitis pigmentosa 57; RP57; PDE6G-related retinitis pigmentosa. **Information source type:** Aggregated disease-level resources (OMIM, Orphanet, HPO, ClinVar, gnomAD) and primary literature, principally the founding family case series (not large EHR-derived cohorts).

2. Etiology

Causal factor: Purely genetic — biallelic loss-of-function variants in PDE6G. The founding pathogenic allele is the intron-3 essential-splice variant c.187+1G>T (PMID: 20655036); ClinVar documents additional nonsense, frameshift, essential-splice, and start-loss alleles plus 17q25.3 CNVs (Finding 8).

Genetic risk factors: The principal risk factor is **consanguinity** / homozygosity-by-descent. Because PDE6G is LoF-tolerant in heterozygotes (carrier ~1/6,600; Finding 7), affected individuals almost always inherit two null alleles identical by descent, so a family history of consanguinity dramatically raises risk. No common susceptibility loci or modifier genes are established.

Environmental risk factors: None established as causal. A pharmacologic gene–drug interaction exists (PDE6-cross-reactive inhibitors such as sildenafil selectively impair retinal function in PDE6-γ-deficient animals; Finding 6), which is a theoretical exacerbating exposure rather than a cause.

Protective factors: None specifically documented. By analogy to other RP forms, avoidance of excessive light exposure and general ocular health measures are prudent but unproven for RP57.

Gene–environment interactions: The best-documented interaction is pharmacologic (PDE6-inhibitor sensitivity; Finding 6). No dietary or toxicant GxE interactions are established.

3. Phenotypes

All ten official HPO annotations derive from the founding family (PMID: 20655036); see Finding 9.

Phenotype	HPO term	Type	Frequency	Onset/Course
Rod-cone dystrophy	HP:0000510	Clinical sign (ERG/ functional)	Characteristic	Childhood onset, progressive
Reduced visual acuity	HP:0007663	Symptom	6/6	Progressive
Constriction of peripheral visual field	HP:0001133	Clinical sign	4/4	Progressive
Spicular (bone-spicule) retinal pigmentation	HP:0007737	Physical manifestation	Characteristic	Midperipheral
Optic disc pallor	HP:0000543	Clinical sign	Present	Young-adult onset (HP:0011462)
Absent foveal reflex	HP:0030825	Clinical sign	Present	—
Cystoid macular edema	HP:0011505	Clinical sign (OCT)	Present	Variable
Attenuation of retinal blood vessels	HP:0007843	Clinical sign	Present	Young-adult onset
Childhood onset	HP:0011463	Onset modifier	—	—
Autosomal recessive inheritance	HP:0000007	Inheritance modifier	—	—

Severity: Severe — scotopic and photopic ERGs are severely reduced or extinguished, indicating combined rod and cone dysfunction. **Progression:** Progressive, consistent with RP natural history. **Quality-of-life impact:** Severe and lifelong — progressive peripheral then central vision loss causes major functional disability (mobility, reading, driving), with cystoid macular edema further threatening central acuity. Disease-specific QoL instruments for RP57 are not available; general RP QoL burden applies.

4. Genetic / Molecular Information

Causal gene: PDE6G (HGNC:8788; Gene 5148; ENSG00000185527; 17q25.3; 4 exons) encoding Pγ, the 87-aa inhibitory γ-subunit of rod PDE6.

Pathogenic variants (ClinVar; Finding 8):

Variant	Protein	Type	Classification
c.187+1G>T	— (intron-3 donor)	Essential splice	Pathogenic (founding allele)
c.146+1G>T	—	Essential splice	Pathogenic
c.97C>T	p.Arg33Ter	Nonsense	Pathogenic
c.69dup	p.Arg24fs	Frameshift	Pathogenic
c.2T>A	p.Met1Lys	Start-loss	Likely pathogenic
c.95del	p.Gln32fs	Frameshift	Conflicting
c.206del	p.Pro69fs	Frameshift	Conflicting
17q25.3 gains/deletions	—	CNV (multi-gene)	Pathogenic

Variant class: All established pathogenic small variants are loss-of-function (nonsense, frameshift, essential-splice, start-loss). **Allele frequencies (gnomAD v4; Finding 7):** all ultra-rare — c.187+1G>T AF 1.37×10^{-6}; p.Arg33Ter AF 6.8×10^{-6}; summed high-confidence LoF $q \approx 7.6\times10^{-5}$. **Origin:** Germline. **Functional consequence:** Loss of function (loss of the inhibitory γ-subunit; reduced holoenzyme stability and dysregulated dark PDE6 activity — Finding 3).

Modifier genes: None established for RP57. **Epigenetic information:** None specifically reported for this disease. **Chromosomal abnormalities:** Large 17q25.3 copy-number gains and deletions spanning PDE6G are catalogued in ClinVar as contiguous multi-gene events rather than isolated PDE6G lesions.

5. Environmental Information

Environmental factors: None causal. **Lifestyle factors:** None established. **Infectious agents:** Not applicable — RP57 is a monogenic inherited retinal degeneration. The one relevant non-genetic consideration is iatrogenic: systemic PDE6-cross-reactive inhibitors (sildenafil and related PDE5 inhibitors) selectively reduce retinal function in PDE6-γ-deficient animals (Finding 6), suggesting a theoretical avoidance recommendation.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. A biallelic loss-of-function variant in **PDE6G** (e.g., c.187+1G>T essential-splice) **leads to** absent or non-functional rod Pγ inhibitory subunit. *(Demonstrated: founding family + splicing assay, [PMID: 20655036].)*
2. Loss of Pγ **results in** loss of inhibitory control over the rod PDE6 catalytic dimer (PDE6A/PDE6B) and reduced PDE6 holoenzyme expression/stability. *(Demonstrated in vivo in PDE6γ-mutant mice: increased spontaneous dark PDE6 activity, [PMID: 21920434].)*
3. Dysregulated PDE6 catalysis **leads to** abnormal cGMP hydrolysis and disrupted cGMP homeostasis in rod outer segments (the cascade in which PDE6 activation normally drops cGMP to close CNG channels, [PMID: 34170501]). *(Inferred for the human null state from the central role of PDE6 in phototransduction.)*
4. Disrupted cGMP/CNG-channel signaling and phototransduction failure **result in** rod photoreceptor dysfunction (extinguished scotopic ERG) and **lead to** rapid rod photoreceptor death. *(Demonstrated in the Pde6g mouse: most rods gone by P16, [PMID: 37363133].)*
5. Rod loss **leads to** secondary (non-cell-autonomous) cone photoreceptor death — the branch producing extinguished photopic ERG and eventual central vision loss. *(Inferred from the extinguished photopic ERG in patients [PMID: 20655036] and the general RP paradigm of secondary cone death.)*
6. Progressive photoreceptor loss **results in** inner-retinal remodeling, RPE and vascular changes (attenuated vessels, acellular capillaries), bone-spicule pigment migration, optic disc pallor, and cystoid macular edema — the clinical RP phenotype. *(Demonstrated remodeling in the Pde6g mouse, [PMID: 37363133]; clinical signs, [PMID: 20655036].)*

Molecular pathway: Rod cGMP phototransduction (G-protein-coupled; rhodopsin → transducin → PDE6 → cGMP/CNG channel). **Cellular processes:** Photoreceptor cell death (apoptosis/remodeling), retinal remodeling. **Protein dysfunction:** Loss of function of Pγ, the intrinsically disordered inhibitory subunit, with loss of holoenzyme regulation and stability. **Biochemical abnormality:** Dysregulated cGMP-specific phosphodiesterase activity → cGMP imbalance. **Metabolic link:** cGMP second-messenger metabolism.

Suggested GO terms: phototransduction (GO:0007602); detection of light stimulus involved in visual perception (GO:0050908); cGMP metabolic process (GO:0046068); 3',5'-cyclic-GMP phosphodiesterase activity (GO:0047555); photoreceptor cell maintenance (GO:0045494);

regulation of rhodopsin mediated signaling pathway (GO:0022400). **Suggested CL terms:** retinal rod cell (CL:0000604), retinal cone cell (CL:0000573), retinal pigment epithelial cell (CL:0002586). **Suggested CHEBI:** cGMP (CHEBI:16356).

7. Anatomical Structures Affected

- **Organ:** Eye (UBERON:0000970); retina (UBERON:0000966). **Body system:** Visual/nervous (sensory). **Secondary:** optic nerve/disc (pallor), retinal vasculature (attenuation), macula (cystoid edema).
- **Tissue/cell:** Neural retina; primary target **rod photoreceptors** (CL:0000604), secondary **cone photoreceptors** (CL:0000573); downstream RPE (CL:0002586) and inner retinal neurons (remodeling).
- **Subcellular:** Rod **outer segment** (GO:0001750, photoreceptor outer segment), where PDE6 operates; photoreceptor connecting cilium/disc membranes.
- **Localization:** Bilateral, roughly symmetric; pigmentary changes predominate in the **midperiphery** with later macular involvement (macula lutea UBERON:0001782 / fovea UBERON:0000401).

8. Temporal Development

Onset: Childhood (HP:0011463), early-onset severe disease. **Onset pattern:** Insidious/chronic-progressive. **Progression:** Progressive rod-then-cone degeneration; rapid in the mouse model (most rods lost by P16, [PMID: 37363133]), with early severe/extinguished ERG in humans. **Course:** Chronic, lifelong, progressive; no spontaneous remission. **Critical period / therapeutic window:** Model data define a window in which gene supplementation can halt degeneration while sufficient photoreceptors remain (rescue effective with <13% rods remaining at 16 weeks but not at 24 weeks in the Pde6b model; [PMID: 35195763]) — implying earlier intervention is essential.

9. Inheritance and Population

Inheritance: Autosomal recessive (HP:0000007). **Penetrance:** Presumed complete in biallelic LoF homozygotes/compound heterozygotes (consistent across the founding family). **Expressivity:** Severe; limited data preclude firm expressivity statements. **Anticipation:** Not applicable (not a repeat-expansion disorder). **Carrier frequency:** ~1 in 6,600 (gnomAD-derived; Finding 7). **Affected frequency (random mating):** ~1 in 170 million (q^2), so observed cases cluster in consanguineous families. **Founder effect:** The c.187+1G>T allele was described in a single extended consanguineous Muslim Arab-Israeli kindred ([PMID: 20655036]); no

broad founder population is established. **Consanguinity:** Central to disease occurrence. **Epidemiology:** Ultra-rare; no prevalence/incidence estimates exist specifically for RP57; it is one of the rarest contributors to RP (overall RP ~1/4000; >90 genes). **Sex ratio:** Expected ~1:1 (autosomal). **Geographic distribution:** No endemic distribution established beyond the index family.

10. Diagnostics

Clinical/functional tests: Full-field **electroretinography (ERG)** is the key functional test — scotopic and photopic responses are severely reduced or extinguished. **OCT** documents macular structure and cystoid macular edema. **Fundus examination** / **autofluorescence** shows bone-spicule pigmentation, vascular attenuation, optic disc pallor. **Visual field testing (perimetry)** quantifies peripheral constriction. **Biomarkers:** No specific biochemical/circulating biomarker; the diagnosis is genetic. **Genetic testing (definitive):** Because RP is genetically heterogeneous (>90 genes), **next-generation sequencing gene panels** for inherited retinal dystrophies or **whole-exome/whole-genome sequencing** are the recommended first-line approach; PDE6G is included on comprehensive IRD panels. Homozygosity mapping is valuable in consanguineous pedigrees (the discovery method; [PMID: 20655036]). **Chromosomal microarray** can detect the 17q25.3 CNVs catalogued in ClinVar. **Differential diagnosis:** Other PDE6-related RP (PDE6A, PDE6B), congenital stationary night blindness (PDE6B H258N), other autosomal-recessive RP genes, syndromic RP (Usher, Bardet-Biedl) — distinguished by extra-ocular features and molecular testing. **Screening:** Cascade carrier testing in affected families and carrier screening in consanguineous couples; no population newborn screening exists.

11. Outcome / Prognosis

Survival/mortality: RP57 is non-lethal; it does not reduce life expectancy. **Morbidity:** Significant, progressive visual disability — the dominant outcome is severe, eventually profound, bilateral vision loss with functional blindness in advanced stages. **Disease course:** Progressive and lifelong; complications include cystoid macular edema (threatens central acuity) and the mobility/independence impacts of field loss. **Recovery:** No spontaneous recovery; vision loss is irreversible without intervention. **Prognostic factors:** Residual photoreceptor count and age at any future therapeutic intervention are the key determinants (therapeutic-window data from PDE6 models; [PMID: 35195763]). **Prognostic biomarkers:** None validated beyond structural (OCT ellipsoid zone/outer nuclear layer) and functional (ERG) measures used generally in RP.

12. Treatment

Current standard: No approved disease-modifying therapy. Management is **supportive**: low-vision rehabilitation and visual aids, orientation and mobility training, treatment of cystoid macular edema (e.g., carbonic anhydrase inhibitors, used generally in RP-CME), and genetic counseling. Vitamin A supplementation is debated in RP generally and not specifically validated for RP57.

Experimental / leading candidate — gene therapy: AAV-mediated **gene supplementation** is the most promising approach. In the related Pde6b model, wild-type gene restoration produced durable (≥1 year) rescue even after degeneration onset ([PMID: 29721933]), with a defined window of efficacy ([PMID: 35195763]); the Pde6g mouse provides a model to test PDE6G supplementation ([PMID: 37363133]). Emerging modalities broadly under investigation for RP include gene therapy, stem cells, optogenetics, retinal prosthetics, and pharmacotherapy ([PMID: 40575766]).

Pharmacogenomic caution: PDE5/PDE6-cross-reactive inhibitors (e.g., sildenafil) selectively impair retinal function in PDE6-γ-deficient animals ([PMID: 11157892]) and should be used cautiously in PDE6G patients/carriers.

Suggested NCIT terms: Gene Therapy (NCIT:C15431); Supportive Care (NCIT:C15277); Rehabilitation Therapy (NCIT:C15917).

13. Prevention

- **Primary prevention:** Not applicable (genetic). The principal lever is **genetic counseling** for consanguineous families and at-risk carriers.
- **Genetic screening:** Cascade carrier testing in families with a proband; carrier screening for consanguineous couples; **preimplantation genetic testing (PGT)** and **prenatal diagnosis** are options once the familial variant is known.
- **Secondary prevention:** Early molecular diagnosis to enable timely intervention within the therapeutic window and early management of cystoid macular edema.
- **Tertiary prevention:** Low-vision rehabilitation and complication management.
- **Pharmacologic avoidance:** Caution with PDE6-cross-reactive inhibitors (Finding 6).

14. Other Species / Natural Disease

Taxonomy / orthologs: PDE6G is conserved across vertebrates; mouse ortholog *Pde6g* (NCBI Gene 18587). **Model-organism disease:** Engineered *Pde6g*-deficient mice recapitulate early-onset rapid rod degeneration ([PMID: 37363133]). **Natural animal disease:** Naturally occurring PDE6-related retinal degenerations are well documented in dogs for the catalytic subunits — e.g., *PDE6B*-null **rcd1** and *PDE6A*-related forms — which model the human catalytic-subunit RP forms; a naturally occurring canine *PDE6G* retinopathy is not specifically established in the reviewed literature. **Comparative biology:** The rod phototransduction cascade and PDE6 holoenzyme architecture are evolutionarily conserved, so mechanisms translate across mammals. Of note, cross-species isoform differences exist (e.g., rod PDE6G can functionally substitute in cones in mouse; [PMID: 25739440]), a caveat for extrapolation. **Zoonotic potential:** None (non-infectious, genetic).

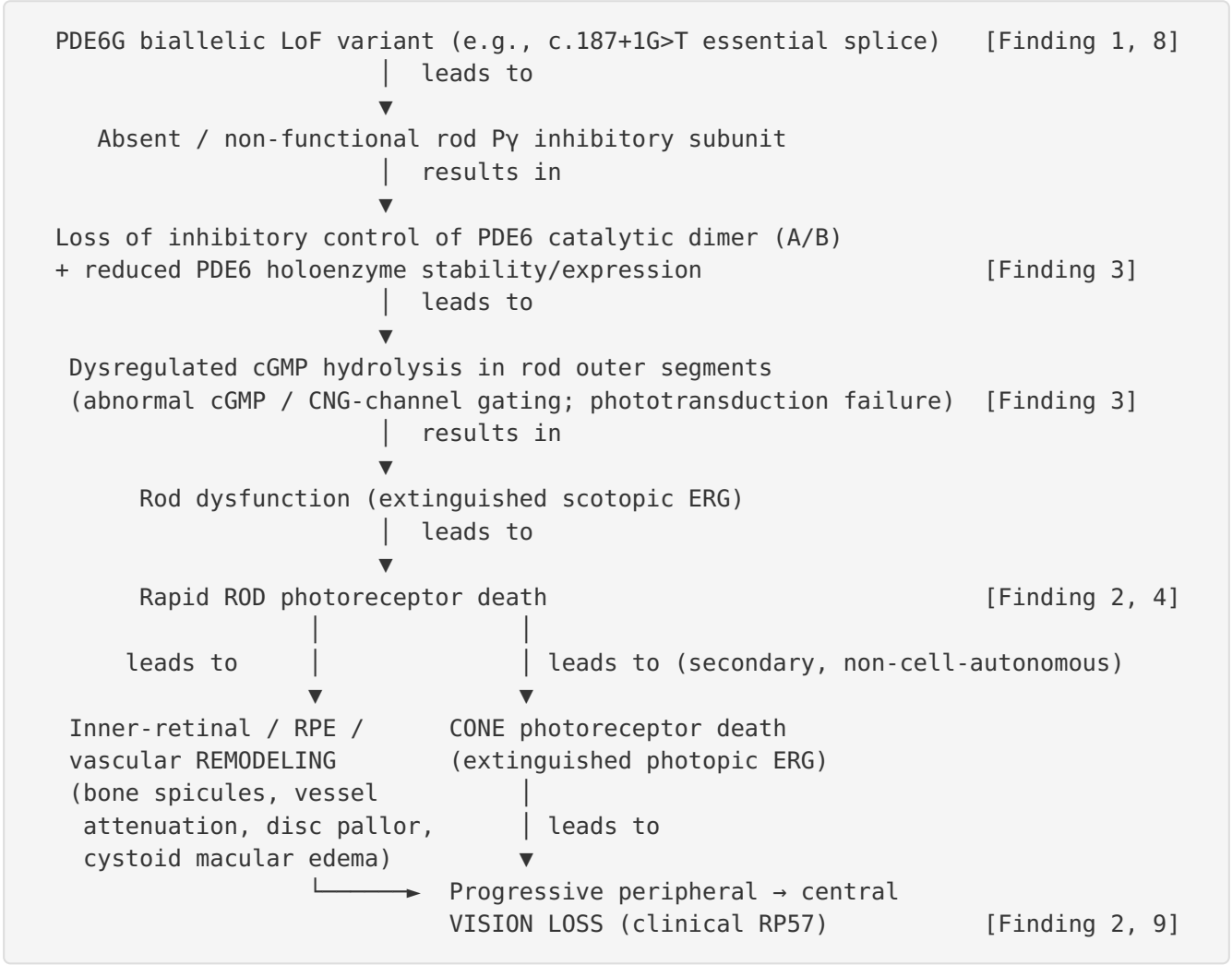
15. Model Organisms

Model	Type	Key features	Reference
Pde6g-deficient mouse (preclinical RP model)	Mammalian, genetic null	Early-onset, rapid rod degeneration (most rods gone by P16); inner-retinal, RPE, and vascular remodeling incl. acellular capillaries	PMID: 37363133
PDE6γ ILE86TER transgenic (on Pde6g-null background)	Mammalian, knock-in/ transgenic	Decreased photoresponse decay, increased spontaneous dark PDE6 activity, reduced PDE6 expression — defines Pγ inhibitory/stabilizing role	PMID: 21920434
PDEG tm1/+ (Pde6g-null heterozygote)	Mammalian	Sildenafil-induced reversible ERG suppression (gene–drug interaction)	PMID: 11157892
Pde6b RP mouse (related subunit)	Mammalian	Gene-supplementation rescue durable ≥1 yr; defined therapeutic window	PMID: 29721933, PMID: 35195763

Phenotype recapitulation: The *Pde6g* mouse strongly recapitulates the human severe, early-onset rod–cone degeneration. **Limitations:** Mouse retinas are rod-dominant and lack a macula/fovea, so cystoid macular edema and foveal phenotypes are not modeled; cross-species

PDE6 isoform substitution ([PMID: 25739440]) can also modify phenotype. **Applications:** Mechanistic dissection of Pγ loss and preclinical testing of AAV gene supplementation and therapeutic-window timing. **Resources:** MGI, IMPC/IMSR for *Pde6g* alleles.

Mechanistic Model / Interpretation



The disease is mechanistically clean: a single recessive loss-of-function lesion in a non-redundant, rod-specific regulatory subunit removes the brake on the central phototransduction effector enzyme, dysregulating the second messenger (cGMP) that photoreceptors depend on for survival. This places RP57 firmly among the **PDE6-related retinopathies** (alongside PDE6A, PDE6B, PDE6C/PDE6H forms), differing by which subunit is lost but converging on cGMP dysregulation and photoreceptor death. Because the defect is loss-

of-function (not a toxic gain-of-function), **gene supplementation** is mechanistically rational — simply restoring Pγ should reconstitute holoenzyme regulation — and related-subunit models confirm durable rescue within a therapeutic window.

Evidence Base

PMID	Role	How it supports/challenges findings
20655036	**Founding/ defining**	Establishes PDE6G causality (c.187+1G>T), clinical phenotype, inheritance; sole source for all 10 HPO annotations. Supports F001, F002, F005, F007, F008, F009.
34170501	Mechanism (review)	PDE6 as central phototransduction effector; links PDE6-gene mutations to untreated retinal disease. Supports F003.
21920434	Mechanism (in vivo)	PDE6γ restrains dark PDE6 activity; loss dysregulates cGMP signaling and reduces expression. Supports F003.
37363133	Model organism	Pde6g mouse recapitulates early-onset rapid rod loss + remodeling. Supports F004.
29721933	Therapeutic (model)	Durable gene-supplementation rescue after onset in PDE6 RP. Supports F004.
35195763	Therapeutic (model)	Defines therapeutic window (<13% rods rescuable at 16 wk, fails at 24 wk). Supports F004.
40575766	Context (review)	RP heterogeneity (>90 genes), emerging therapies. Supports F005.
11157892	Gene–drug interaction	Sildenafil selectively suppresses ERG in Pde6g-null heterozygotes. Supports F006.
33860373, 32898583, 39739818	Structural/ mechanistic	PDE6 structure, Pγ regulation, allosteric activation — background for gene-supplementation and allosteric-activator strategies.

Limitations and Knowledge Gaps

1. **Single defining pedigree.** The disease phenotype rests almost entirely on one consanguineous family ([PMID: 20655036]); all 10 HPO annotations come from this single source, limiting confidence in frequency estimates, expressivity, and the full phenotypic range.
2. **No human natural-history or epidemiologic data** specific to RP57 (no prevalence/incidence, no longitudinal visual-decline rates, no QoL instruments).
3. **Human mechanistic data are extrapolated** from PDE6 biology and mouse/in-vitro models; the precise cGMP dynamics and cell-death pathway in human PDE6G-null retina are inferred, not directly measured.
4. **No PDE6G-specific therapeutic data.** Gene-therapy evidence derives from the related *Pde6b* model; a PDE6G gene-supplementation proof-of-concept in the Pde6g mouse is a gap.
5. **Carrier/affected frequency estimates are computational** (gnomAD-derived), subject to ascertainment and reference-population limits.
6. **Cross-species isoform caveats** (e.g., rod PDE6G substituting in mouse cones; [PMID: 25739440]) complicate translation of mouse phenotypes to human cone involvement.

Proposed Follow-up Experiments / Actions

1. **Expand the genotype–phenotype series.** Aggregate additional PDE6G biallelic cases via IRD registries and matchmaking (GeneMatcher) to validate the HPO frequency set, establish expressivity, and detect modifiers.
2. **PDE6G-specific gene supplementation.** Test AAV-*PDE6G* (rod-targeted) in the Pde6g mouse to confirm rescue and map the human-relevant therapeutic window, mirroring the Pde6b paradigm ([PMID: 29721933], [PMID: 35195763]).
3. **Natural-history study.** Longitudinal OCT (ellipsoid zone/ONL), ERG, and perimetry in any identifiable patients to define progression rate and optimal intervention timing.
4. **cGMP-pathway pharmacology.** Evaluate PDE6 allosteric modulators and cGMP-lowering/CNG-modulating strategies ([PMID: 32898583], [PMID: 34170501]) as non-genetic adjuncts, and formally document the sildenafil/PDE6-inhibitor caution in clinical guidance.
5. **Variant curation.** Reclassify the Conflicting frameshift alleles (c.95del, c.206del) with functional splicing/expression assays to firm up the LoF allelic series.

6. **iPSC retinal organoids** from patient cells to model human PDE6G-null photoreceptor degeneration and test editing/supplementation in a human context.

Evidence-source legend: human clinical/genetic (founding family, registries), model organism (mouse Pde6g/Pde6b), in vitro/structural (PDE6 biochemistry/cryo-EM), computational (gnomAD, ClinVar curation).
