RDH12-Related Dominant Retinopathy (MONDO:0800100): Comprehensive Disease Characterization

Causal gene: *RDH12* (retinol dehydrogenase 12; HGNC:19977; NCBI Gene 145226; Ensembl ENSG00000139988; UniProt Q96NR8; chromosome 14q24.1).

> **Scope note.** This report concerns the **autosomal dominant** retinopathy caused by heterozygous *RDH12* variants (MONDO:0800100), an allelic but distinct entity from the far more common **autosomal recessive** *RDH12*-associated Leber congenital amaurosis/early-onset severe retinal dystrophy (LCA13; OMIM #612712). Because the dominant form is rare, much of the molecular and mechanistic literature is shared between the two and is drawn from the recessive/cell/animal literature; the distinction is made explicit throughout. Evidence source types are labeled: **[human clinical]**, **[in vitro]**, **[model organism]**, **[computational]**.

---

1. Disease Information

Overview. RDH12-related dominant retinopathy is a rare inherited retinal dystrophy (IRD) transmitted in an autosomal dominant fashion and caused by specific heterozygous C-terminal frameshift variants in *RDH12*. Clinically it is a **comparatively mild, late(r)-onset rod–cone dystrophy / retinitis pigmentosa** with variable expressivity and incomplete penetrance — in sharp contrast to the severe, blinding, childhood-onset recessive disease caused by biallelic *RDH12* loss-of-function. The first dominant family (Fingert et al. 2008,

P 18779497

[human clinical]) had "a mild form of RP" with "late onset and relatively mild severity ... dramatically different from the other disease associated with mutation in this gene, autosomal recessive Leber congenital amaurosis." The most completely characterized dominant pedigree

(Muthiah et al. 2022, P 34031043 [human clinical]) reclassified the phenotype as a rod–cone dystrophy with variable expression.

Key identifiers. - **MONDO:** MONDO:0800100 (RDH12-related dominant retinopathy). - **Gene OMIM:** *RDH12* 608830. **Phenotype OMIM:** no distinct dominant phenotype MIM number is currently assigned; the recessive allelic disorder is "Leber congenital amaurosis 13" OMIM #612712. The dominant RP is described in the literature but not given its own MIM phenotype number (consistent with the template note "OMIM: not recorded"). - **Orphanet:** No dominant-specific ORPHA code; related umbrella entities are retinitis pigmentosa (ORPHA:791) and Leber congenital amaurosis (ORPHA:65). - **ICD-11:** 9B70 Retinitis pigmentosa / hereditary retinal dystrophy (9B70.0). **ICD-10:** H35.52 (pigmentary retinal dystrophy). - **MeSH:** Retinitis Pigmentosa (D012174); Retinal Dystrophies (D058499). - **HGNC:** 19977. **UniProt:** Q96NR8.

Synonyms / alternative names. Autosomal dominant RDH12-related retinal dystrophy; autosomal dominant RDH12 retinopathy; RDH12-associated autosomal dominant retinitis pigmentosa; RDH12 rod–cone dystrophy (dominant).

Information source. Disease-level aggregated resources (OMIM, ClinVar, gnomAD, Ensembl) plus **individual-patient** case series/pedigree studies (Fingert 2008; Muthiah 2022). No EHR-scale datasets exist for this ultra-rare entity.

---

2. Etiology

Primary cause — genetic. The disease is monogenic/Mendelian, caused by **heterozygous pathogenic variants in *RDH12***. Reported dominant alleles are C-terminal single-nucleotide frameshifts clustering around codons 253–260: - **c.776delG (776delG)** — original dominant family (Fingert et al. 2008, P 18779497 [human clinical]. - **c.763delG** — four-generation British pedigree (Muthiah et al. 2022, P 34031043 [human clinical]. - **c.759del, p.(Phe254Leufs*24)** — dominant RP patient used to derive iPSC

line UCLi014-A (Sarkar et al. 2021, P 34216980) [human clinical / in vitro].

Risk factors. - *Genetic:* The causal heterozygous *RDH12* frameshift is the sole established determinant. A positive **family history** is the dominant risk indicator. No susceptibility loci or validated modifier genes are reported for the dominant form. - *Environmental/other:* No proven environmental, occupational, infectious, lifestyle, age, or sex risk factors. **Light exposure** is a biologically plausible modulator (RDH12 detoxifies light-generated retinaldehyde; Rdh12$^{-/-}$ mice show light-induced photoreceptor apoptosis — Maeda et al. 2006, P 17032653) [model organism]), but no clinical evidence links ambient light to dominant-disease severity.

Protective factors. None established. Genotype itself is protective relative to the recessive disease: within the recessive spectrum, homozygosity for the hypomorphic p.Leu99Ile allele is associated with milder, later disease (Daich Varela et al. 2024, P 37714431) [human clinical]).

Gene–environment interactions. Not formally characterized. The inferred interaction is **light/oxidative load × RDH12 dysfunction → aldehyde-driven photoreceptor stress** (inferred, not demonstrated in dominant patients).

---

3. Phenotypes

The dominant phenotype is a **mild rod–cone dystrophy / retinitis pigmentosa** (Muthiah 2022, P 34031043; Fingert 2008, P 18779497) [human clinical]. Key features, with suggested HPO terms:

Phenotype	Type	Characteristics (onset / severity / course / frequency)	HPO
Rod–cone dystrophy / retinitis pigmentosa	clinical sign	Adult/late onset; mild–moderate; slowly progressive; defining feature	HP:0000510 (Retinitis pigmentosa), HP:0000548 (Cone/cone-rod dystrophy)
Reduced/constricted visual field	sign	Progressive peripheral constriction; present in affected adults	HP:0001133 (Constriction of peripheral visual field), HP:0001123 (Visual field defect)
Relatively preserved central visual acuity	sign	VA −0.1 to 0.2 logMAR in affected (much better than recessive)	HP:0000505 (Visual impairment, mild)
Macular/parafoveal atrophy; perifoveal hypo-autofluorescence with hyper-AF ring	sign (imaging)	Progressive; parafoveal/ peripapillary hyper-AF ring → enlarging perifoveal hypo-AF	HP:0007754 (Macular dystrophy), HP:0030506 (Yellow/altered autofluorescence)
Outer retinal / outer nuclear layer thinning (OCT)	sign (imaging)	Mild foveal total-retinal and ONL thinning	HP:0030466 (Abnormal full-field ERG), HP:0011512 (abnormal photoreceptor)
Reduced cone density (adaptive optics)	sign (imaging)	Reduced along temporal meridian vs normative	HP:0000548
Rod–cone ERG dysfunction	lab/ electrophysiology	Rod-cone pattern; peripheral macular dysfunction on pattern ERG	HP:0000512 (Abnormal electroretinogram), HP:0007984 (abnormal retinal physiology)
Nyctalopia (night blindness)	symptom	Typical of rod-predominant dystrophy	HP:0000662 (Nyctalopia)

Note: The dominant disease generally **lacks** the devastating early features of recessive RDH12-LCA (congenital/early childhood blindness, universal macular atrophy from age 2, non-recordable ERG in infancy, dense bone-spicule pigmentation) documented in Fahim et al. 2019 (P 30979730) and Daich Varela & Michaelides 2022 (P 35491887) [human clinical].

Quality-of-life impact. Progressive peripheral field loss and night blindness impair mobility and night driving; relatively preserved central acuity means reading/face recognition are often retained longer than in the recessive disease. No disease-specific EQ-5D/SF-36/PROMIS data exist for the dominant form; IRDs broadly reduce vision-related QoL (NEI-VFQ).

---

4. Genetic / Molecular Information

Causal gene. *RDH12* (HGNC:19977; OMIM 608830; Ensembl ENSG00000139988; chr14:67,701,886–67,734,451, GRCh38 [computational, gnomAD]). Encodes a 316-aa NADPH-dependent retinal reductase of the short-chain dehydrogenase/reductase (SDR) superfamily (UniProt Q96NR8; Pfam PF00106/adh_short; InterPro IPR002347).

Pathogenic variants (dominant). Heterozygous **frameshift** C-terminal variants: c.776delG, c.763delG, c.759del p.(Phe254Leufs*24). These lie in the final coding region and are predicted to escape nonsense-mediated decay (NMD), producing a stable, altered truncated protein [computational inference].* - ACMG classification: *dominant alleles are rare/private and functionally supported; recessive frameshifts here are classified Pathogenic/Likely pathogenic in ClinVar.* - Allele frequency: *dominant alleles are essentially absent from population databases (Fingert: not in 158 controls; gnomAD does not list these as recurrent) — consistent with private, family-specific mutations.* - Origin: *germline, segregating through pedigrees (AD). No somatic involvement.* - Functional consequence: *predicted gain of function / dominant-negative (Muthiah 2022,* *):* P *34031043*

"predicted to result in a gain of function, that causes disease in a gene typically associated with

*biallelic (recessive) variants." Supported by gnomAD constraint [computational]: pLI = 7.8×10⁻⁵, LOEUF (oe_lof upper) = 0.889, obs/exp LoF = 0.617 — RDH12 tolerates heterozygous LoF**, so haploinsufficiency is not the mechanism.

Variant landscape (gene-wide, mostly recessive). ClinVar lists 674 variants for RDH12 [computational], dominated by frameshift and missense alleles distributed across the coding sequence (e.g., c.43del p.Leu15Cysfs*4; c.146T>C p.Leu49Ser; c.295C>A p.Leu99Ile; c.701G>A p.Arg234His; c.759del p.Phe254Leufs*24). The recessive common allele **p.Leu99Ile (c.295C>A)** was the most frequent variant (52/… alleles) in a South American cohort (Daich Varela et al. 2024,

P 37714431

) [human clinical].

Modifier genes / epigenetics / chromosomal abnormalities. None established for the dominant disease. No DNA-methylation/histone or large structural (CNV/translocation) mechanisms are implicated; a heterozygous *RDH12* deletion has been reported in the recessive/compound setting (Sarkar et al. 2020,

P 32322264

).

Suggested ontology terms. Gene product GO: GO:0004745 (NAD(P)+-retinol dehydrogenase / all-trans-retinol dehydrogenase activity), GO:0052650 (all-trans-retinol dehydrogenase (NADP+) activity), GO:0042574 (retinal metabolic process), GO:0007601 (visual perception).

---

5. Environmental Information

No established environmental, toxic, radiation, occupational, dietary, lifestyle, or infectious causes/triggers. The only biologically relevant exogenous factor is **light**, which generates the all-trans-retinal substrate that RDH12 detoxifies (inferred modulator; CHEBI:17898 all-trans-retinal). No infectious agents are involved. [No data available for this disease specifically.]

---

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **heterozygous C-terminal frameshift** in *RDH12* (e.g., c.763delG, c.776delG, c.759del) **results in** an mRNA that **escapes nonsense-mediated decay** (last-exon rule) *(inferred)*.
2. This **leads to** expression of a **stable mutant RDH12 protein with an altered/extended C-terminus** (the C-terminus contains the amphipathic membrane-association region) *(inferred; protein-level data limited)*.
3. The mutant protein **acts via a predicted gain-of-function / dominant-negative mechanism** — it is **not** simple haploinsufficiency, because gnomAD shows RDH12 tolerates heterozygous LoF (pLI≈0) and recessive-allele carriers are unaffected **[computational support]**. The mutant is inferred to **mislocalize and/or poison** normal retinoid handling in the photoreceptor inner segment *(inferred)*.
4. Reduced effective RDH12 reductase activity **results in** impaired reduction of **all-trans-retinal (atRAL) → all-trans-retinol (atROL)** in the inner segment **[in vitro: Belyaeva 2005** P 15865448 **; Sarkar 2021** P 34445569 **]**.
5. atRAL and reactive lipid-peroxidation aldehydes (e.g., 4-HNE) **accumulate**, which **leads to** cytotoxicity and disrupted retinoid homeostasis **[in vitro: Lee 2008** P 18396173 **]**.
6. Aldehyde accumulation **induces oxidative stress and the ER unfolded-protein response** (upregulation of sXBP1, CHOP/DDIT3, ATF4) **[in vitro: Sarkar 2021** P 34445569 **]**.
7. Oxidative + ER stress **results in photoreceptor apoptosis**, branching to **rod-predominant degeneration** first (night blindness, peripheral field loss) and **cone/macular involvement** (central atrophy, reduced cone density) **[model organism: zebrafish rdh12; human clinical: Muthiah 2022]**.
8. Progressive photoreceptor loss **manifests clinically as** a slowly progressive rod–cone dystrophy/RP with macular atrophy — milder than the recessive disease because residual wild-type RDH12 and partial function persist *(inferred)*.

Branch (recessive comparison): biallelic LoF → near-complete loss of RDH12 → severe early atRAL/aldehyde toxicity → fulminant childhood macular atrophy and LCA (Fahim 2019, P 30979730).

Mechanistic detail by category

- **Molecular pathways / biochemistry:** Visual (retinoid) cycle; RDH12 reduces atRAL using NADPH (~2000-fold NADP(H) preference; highest catalytic efficiency for all-trans-retinal kcat/Km ≈ 900 min^{-1} μM^{-1}) (Belyaeva 2005, P 15865448) [in vitro]. KEGG "Retinol metabolism" (hsa00830); Reactome "The canonical retinoid cycle in rods."
- **Cellular processes:** apoptosis (GO:0006915), response to oxidative stress (GO:0006979/GO:0034599), ER unfolded-protein response (GO:0030968), autophagy alteration (reduced atg12), photoreceptor outer-segment phagocytosis disruption.
- **Protein dysfunction:** loss of enzymatic reductase activity in mutants; for dominant alleles, a **gain-of-function/dominant-negative** stable product (vs misfolding/degradation seen with some missense recessive alleles).
- **Metabolic changes:** accumulation of all-trans-retinal (CHEBI:17898) and toxic aldehydes (4-hydroxynonenal, CHEBI:58266); disturbed retinyl ester/retinoic acid balance (Lee 2008, P 18396173).
- **Immune involvement:** none primary.
- **Tissue-damage mechanism:** oxidative stress + aldehyde toxicity + ER stress → photoreceptor cell death.
- **Molecular profiling:** iPSC lines (P 34216980) and HEK/ARPE-19 models (P 34445569; P 41683787) provide expression/functional data; no patient tissue transcriptomics/proteomics/metabolomics for the dominant form.

Cell types (CL): photoreceptor cell (CL:0000210), rod (CL:0000604), cone (CL:0000573); adjacent retinal pigment epithelial cell (CL:0002586). **Subcellular (GO CC):** photoreceptor inner segment (GO:0001917), endoplasmic reticulum membrane (GO:0005789), smooth ER / membrane-anchored.

---

7. Anatomical Structures Affected

- **Organ level:** Eye (UBERON:0000970); specifically the **retina** (UBERON:0000966) and **macula lutea** (UBERON:0005396). Primary disease is confined to the eye; no systemic/secondary organ involvement (non-syndromic).
- **Tissue/cell level:** Neural retina — **photoreceptor layer**; rod and cone photoreceptors (CL:0000604, CL:0000573); secondary RPE changes and inner retinal remodeling. **Peripapillary sparing** and **macular/parafoveal atrophy** are characteristic patterns.
- **Subcellular:** Photoreceptor **inner segment** (RDH12 localization; GO:0001917), ER (stress response).
- **Localization & laterality: Bilateral and symmetric** (HP:0012832 Bilateral). Regional: parafoveal/perifoveal and peripapillary (macula UBERON:0005396; optic disc region).

---

8. Temporal Development

- **Onset:** Adult/late onset for the dominant disease — "late onset and relatively mild severity" (Fingert 2008,

  P 18779497

).
  Variable; some mutation carriers are detectable only subclinically (e.g., on adaptive optics) reflecting **incomplete penetrance** (Muthiah 2022,

  P 34031043

).
  Pattern is **insidious/chronic**. (Contrast recessive: congenital/early-childhood onset, mean 4.1 yr — Fahim 2019,

  P 30979730

  .)

- **Progression:** Slowly **progressive** over decades; stages = early (ring of hyper-AF, mild field constriction) → intermediate (enlarging perifoveal atrophy, ONL thinning) → advanced (extensive outer-retinal atrophy, significant field loss) with relative central-acuity preservation until late. Lifelong chronic disease; no remission.
- **Critical periods / intervention window:** Because photoreceptors persist for decades, there is a **wide therapeutic window** for the dominant disease (in contrast to the narrow infantile window in recessive disease, where early macular atrophy limits gene-replacement benefit).

---

9. Inheritance and Population

- **Inheritance: Autosomal dominant** (AD) for MONDO:0800100 (Fingert 2008; Muthiah 2022). The gene far more commonly causes **autosomal recessive** LCA13.
- **Penetrance: Incomplete / age-dependent**; penetrance determination is modality-dependent (subclinical carriers detected only by adaptive optics) (Muthiah 2022, P 34031043).
- **Expressivity: Variable** (Muthiah 2022).
- **Anticipation:** None reported (not a repeat-expansion disorder).
- **Germline mosaicism / founder effects / consanguinity:** No founder effect or consanguinity role for the dominant alleles (private mutations; AD does not require consanguinity). Consanguinity is relevant only to the recessive disease.
- **Carrier frequency:** Not applicable in the AD sense (dominant alleles are private). For recessive disease, heterozygous LoF carriers exist in gnomAD but are unaffected.
- **Epidemiology / prevalence: No reliable prevalence/incidence estimate** exists for the dominant form — it is described in only a handful of pedigrees worldwide (ultra-rare). As gene-level context, **RDH12 accounts for 3.4%–10.5% of LCA/EOSRD** (Fahim 2019, P 30979730) — but these are predominantly recessive cases.
- **Demographics:** Reported dominant families are of European (British/US) ancestry; too few to infer ethnic predilection, geographic clustering, sex ratio (expected ~1:1 for AD), or age distribution.

10. Diagnostics

- **Clinical/imaging tests (core):**
- **Fundus autofluorescence (FAF):** parafoveal/peripapillary hyper-AF ring, perifoveal hypo-AF (Muthiah 2022).
- **Spectral-domain OCT:** foveal total-retinal and ONL thinning; outer-retinal disruption.
- **Adaptive optics scanning light ophthalmoscopy:** reduced cone density (sensitive for subclinical carriers).
- **Full-field & pattern ERG:** rod–cone pattern of dysfunction; peripheral macular dysfunction.
- **Visual fields (perimetry):** peripheral constriction.
- Fundus photography: variable pigmentary changes/macular atrophy.
- **Laboratory/biomarkers:** No blood/urine biomarker or enzyme assay; diagnosis is clinical + genetic. (Research biomarker: all-trans-retinal/aldehyde handling, not clinical.)
- **Genetic testing (definitive): Single-gene / IRD gene-panel next-generation sequencing**, **whole-exome (WES)** and **whole-genome sequencing (WGS)** identify the heterozygous *RDH12* frameshift; segregation analysis across the pedigree confirms dominant transmission (Muthiah 2022 used NGS incl. WGS). Chromosomal microarray/karyotype/FISH/mtDNA/repeat-expansion testing are **not indicated** (point-level frameshift mechanism). RNA studies can confirm NMD escape (research).
- **Clinical criteria / differential diagnosis:** No disease-specific criteria. Differentials: other dominant RP genes (RHO, PRPH2, RP1, PRPF31, NR2E3), cone–rod dystrophy genes (GUCA1A, CRX), and — critically — **recessive RDH12-LCA/EOSRD** (distinguished by congenital/severe early onset, universal early macular atrophy, non-recordable infantile ERG, biallelic variants). Genotyping + segregation resolves these.
- **Screening:** Cascade genetic testing of at-risk relatives in known pedigrees (with adaptive-optics/FAF to detect subclinical carriers). No population newborn/carrier screening (ultra-rare, AD, private alleles).

11. Outcome / Prognosis

- **Survival/mortality: Not life-limiting**; normal life expectancy. No disease-specific mortality (eye-restricted disorder).
- **Morbidity/function:** Chronic visual disability — progressive peripheral field loss and nyctalopia with **relatively preserved central acuity**; prognosis is markedly **better than the recessive disease**, which causes childhood legal blindness. Within recessive RDH12, p.Leu99Ile homozygotes reach legal blindness at an older age (Daich Varela 2024, P 37714431) [human clinical].
- **Disease course/complications:** Slowly progressive outer-retinal atrophy; possible late cystoid macular changes/cataract (general RP complications). No spontaneous recovery.
- **Prognostic factors:** Specific variant, age, extent of macular atrophy on OCT/FAF, cone density on AO, residual field/ERG amplitude. No validated molecular prognostic biomarker.
- **QoL measures:** No dominant-form-specific instruments reported; NEI-VFQ-25 applicable clinically.

---

12. Treatment

No approved disease-specific therapy exists for RDH12 retinopathy (Daich Varela & Michaelides 2022, P 35491887: "There is currently no treatment available for RDH12-retinopathy") [human clinical review].

- **Supportive/rehabilitative (standard of care):** low-vision aids, orientation & mobility training, occupational therapy, refraction/glare control (tinted lenses), management of cataract/cystoid macular edema, genetic counseling. NCIT: C15277 (Rehabilitation Therapy), C15296 (Supportive Care).
- **Pharmacotherapy / mechanism-based (experimental, in vitro): Aldehyde/retinaldehyde scavengers — pregabalin** attenuated atRAL-induced ER stress in mutant RDH12 cells (Sarkar 2021, P 34445569)

[in vitro]; conceptually related scavengers (e.g., primary-amine trap drugs). Antioxidants/ER-stress modulators are candidate strategies. No clinical trials for the dominant form. NCIT: C47484 (Pregabalin); C275 (Antioxidant).

- **Gene therapy: AAV-mediated *RDH12* gene augmentation** is in preclinical development (patents held by Ali and Thompson groups per Fahim 2019, P 30979730; in-vitro rAAV-RDH12 functional studies, Pavlova et al. 2026, P 41683787) [in vitro / preclinical]. **Caveat:** gene *augmentation* (adding wild-type) treats loss-of-function recessive disease but may be **insufficient for a dominant gain-of-function allele**, which may instead require **allele-specific knockdown/editing** (ASO, siRNA, CRISPR). NCIT: C15431 (Gene Therapy); C117202 (AAV Vector).
- **Cell therapy / other advanced modalities:** iPSC-derived retinal models exist for drug screening (P 34216980) but no clinical cell therapy. Not applicable: immunotherapy, targeted small molecules, surgery (beyond cataract).
- **Pharmacogenomics:** Not applicable.

13. Prevention

- **Primary prevention:** Not possible for a germline Mendelian disorder. **Genetic counseling** for affected AD families (50% transmission risk) with options for **prenatal diagnosis** and **preimplantation genetic testing (PGT-M)**. NCIT: C15265 (Genetic Counseling).
- **Secondary prevention: Cascade genetic testing** and ophthalmic surveillance (FAF/OCT/AO) of at-risk relatives for early detection; monitor for treatable complications (cataract, CME).
- **Tertiary prevention:** Low-vision rehabilitation; avoidance of excessive light exposure is biologically rational (RDH12 clears light-generated aldehydes) though unproven clinically.
- **Immunization / public-health / behavioral / prophylaxis:** Not applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *RDH12* is conserved in vertebrates — human (NCBI Gene 145226; *Homo sapiens* NCBI:txid9606), mouse *Rdh12* (NCBI Gene 77974; *Mus musculus* NCBI:txid10090), zebrafish *rdh12* (*Danio rerio* NCBI:txid7955). Orthology: Alliance of Genome Resources / HomoloGene.
- **Natural disease in other species:** No well-established naturally occurring *RDH12* retinopathy is cataloged in companion animals (no prominent OMIA entry); disease knowledge is from engineered models rather than spontaneous animal disease.
- **Comparative biology:** The retinoid (visual) cycle and RDH12's atRAL-reductase role are evolutionarily conserved; however, **mice do not recapitulate human severity** (redundancy with other RDHs, lower retinoid flux), a key cross-species difference.
- **Transmission:** Not applicable (non-infectious, non-zoonotic).

15. Model Organisms

- **Mouse (mammalian):** *Rdh12*-knockout mice (MGI) — **mild phenotype that fails to recapitulate human disease**: slowed atRAL reduction and delayed dark adaptation, accelerated 11-cis-retinal production, and **increased susceptibility to light-induced photoreceptor apoptosis** (Maeda et al. 2006,

  P 17032653

  ); grossly normal retinal histology at 10 months with normal ERG and retinoid levels (Kurth et al. 2007,

  P 17130236

) [model organism]. *Limitation:* no spontaneous severe degeneration → poor efficacy model; useful for light-damage and retinoid-flux studies.
- **Zebrafish:** CRISPR-Cas9 *rdh12* mutant (*rdh12^u533*, c.17_23del; p.(Val6AlafsTer5)) shows disrupted outer-segment phagocytosis, rhodopsin mislocalization, reduced atg12/sod2 — **early rod-predominant degeneration** (Sarkar et al. 2021,

  P 34445569

) [model organism]. Better captures degeneration/oxidative-ER-stress phenotype.

- **Cellular / in vitro:** HEK-293 and ARPE-19 lines expressing WT vs mutant RDH12 for atRAL-toxicity, oxidative/ER-stress, and rAAV-RDH12 functional assays (34445569; 41683787); purified-enzyme kinetics (15865448).
- **iPSC / organoids:** Patient-derived iPSC line **UCLi014-A** from a dominant-RP patient (heterozygous c.759del p.(Phe254Leufs*24)) and UCLi015-A from a recessive-LCA patient (Sarkar et al. 2021,* 34216980 *— enabling retinal-organoid disease modeling, mechanism comparison, and drug screening [in vitro]. This dominant-patient iPSC line is the most directly relevant model for MONDO:0800100.**
- **Model databases:** MGI (mouse), ZFIN (zebrafish), Cellosaurus (iPSC lines), Alliance of Genome Resources.

Summary of Evidence Types & Key Citations

- **Human clinical:**

18779497
(Fingert 2008, first dominant family, 776delG);

34031043
(Muthiah 2022, c.763delG, deep phenotyping, GoF prediction);

34216980
(dominant-patient iPSC, c.759del);

30979730
(recessive natural history; RDH12 = 3.4–10.5% of LCA/EOSRD);

P 37714431

(South American cohort, p.Leu99Ile);

P 35491887

(review, no treatment).

- **In vitro:**

P 15865448

(enzyme kinetics);

P 18396173

(4-HNE/aldehyde toxicity);

P 34445569

(oxidative/ER stress, pregabalin rescue + zebrafish);

P 41683787

(rAAV-RDH12).

- **Model organism:**

P 17032653

(light-induced apoptosis KO mouse);

P 17130236

(KO mouse normal histology).

- **Computational / population genetics:** gnomAD constraint (pLI≈0, LOEUF 0.89) — RDH12 tolerant of heterozygous LoF, arguing against haploinsufficiency.

Limitations

- The dominant entity is **ultra-rare** (a few pedigrees); phenotype, penetrance, natural history, and epidemiology are based on small samples.
- The **gain-of-function/dominant-negative mechanism is predicted/inferred**, not experimentally proven at the protein level for the dominant alleles.
- Most mechanistic/therapeutic data derive from **recessive, cell, or animal** contexts and are extrapolated to the dominant disease.

- No prevalence/incidence, QoL, or clinical-trial outcome data specific to the dominant form.

Future Directions

- Protein-level studies (localization, stability, dominant-negative testing) of c.763delG/c.776delG/c.759del, ideally in patient iPSC-derived retinal organoids (UCLi014-A).
- Allele-specific silencing/editing strategies appropriate to a dominant GoF allele, and testing aldehyde scavengers/antioxidants.
- Natural-history registries and standardized imaging/functional outcome measures for the dominant phenotype.
