RAB28-Related Retinopathy (Cone-Rod Dystrophy 18): A Comprehensive Disease Characterization

Disease: RAB28-Related Retinopathy | **Causal gene: RAB28** | **MONDO:** MONDO:0100448 | **OMIM disease:** 615374 (CORD18) | **OMIM gene:** *612994* | *Category:** Mendelian, non-syndromic inherited retinal dystrophy

Summary

RAB28-Related Retinopathy is a rare, non-syndromic, autosomal-recessive **cone-rod dystrophy (CORD18)** caused by biallelic loss-of-function variants in **RAB28**, a gene encoding a farnesylated small Ras-related GTPase of the Rab family that is highly expressed in photoreceptors and functions at the ciliary apparatus. The disease is cataloged as OMIM 615374, MONDO:0100448, and the causal gene as OMIM *612994 / HGNC:9764 (chromosome 4p15.33). This report focuses on the disease defined by these identifiers and its causal gene RAB28 — not the neighboring PROM1** locus, which maps to the same homozygous interval and has caused diagnostic confusion in at least one consanguineous family.

The clinical phenotype is a progressive, childhood-to-early-adult-onset deterioration of central and color vision, with macular hyperpigmentation, retinal pigment epithelium (RPE) and macular atrophy, photoreceptor-layer thinning on optical coherence tomography (OCT), and a full-field electroretinogram (ERG) signature of severely reduced **cone** responses with milder **rod** reduction (the cone-predominant "cone-rod" pattern). Disease was first established in 2013 through two consanguineous/isolated families (German and Moroccan-Jewish) harboring homozygous nonsense mutations, and has since been reported across European, North-African/Middle-Eastern, Italian, and Korean backgrounds, remaining genetically homogeneous.

Mechanistically, RAB28 localizes to the photoreceptor basal body, connecting cilium and ciliary rootlet, and associates with intraflagellar transport (IFT) trains and the BBSome. Loss of RAB28 function impairs **RPE phagocytosis of (cone) outer segments**, blunts the circadian dawn/dusk peaks of outer-segment phagocytosis (OSP), disrupts **visual-cycle retinoid recycling**

(reduced 11-cRAL, 11cRP, atRP), and dysregulates **ciliary extracellular-vesicle (EV) shedding** via the BBSome. These converging defects culminate in progressive cone-then-rod photoreceptor dysfunction and degeneration. There is currently **no approved therapy**; management is supportive/low-vision rehabilitation plus genetic counseling. Cone-targeted gene replacement rescues the OSP defect in zebrafish, making AAV-based gene supplementation the leading experimental therapeutic strategy.

Key Findings

Finding 1 — RAB28 loss-of-function causes autosomal-recessive cone-rod dystrophy (CORD18)

RAB28-related retinopathy was defined by a combined homozygosity-mapping and exome-sequencing study that identified recessive nonsense mutations segregating with arCRD in two unrelated families. In a German family with three affected siblings, a homozygous **c.565C>T (p.Glu189*)** variant was found; in a family of Moroccan-Jewish descent with two affected siblings, a homozygous **c.409C>T (p.Arg137*)** variant was found. As the original report states: *"A combined approach of homozygosity mapping and exome sequencing revealed a homozygous nonsense mutation (c.565C>T [p.Glu189*]) in RAB28 in a German family with three siblings with arCRD. Another homozygous nonsense mutation (c.409C>T [p.Arg137*]) was identified in a family of Moroccan Jewish descent with two siblings affected by arCRD"* (PMID: 23746546).

All five affected individuals shared a consistent clinical picture: *"All five affected individuals presented with hyperpigmentation in the macula, progressive loss of the visual acuity, atrophy of the retinal pigment epithelium, and severely reduced cone and rod responses on the electroretinogram"* (PMID: 23746546). The recessive inheritance, the nonsense nature of the variants (predicted null alleles), and the shared phenotype together establish RAB28 loss-of-function as the disease cause. Disease OMIM is 615374 (CORD18); gene OMIM is *612994; MONDO:0100448.

Phenotype (HPO) annotations: Cone-rod dystrophy (HP:0000548), abnormal electroretinogram (HP:0000512), abnormality of macular pigmentation (HP:0008061), retinal pigment epithelial atrophy (HP:0007894), reduced visual acuity (decreased), progressive visual loss (HP:0000529), dyschromatopsia (HP:0000551), photophobia (HP:0000613).

Finding 2 — RAB28 is a farnesylated ciliary GTPase at the basal body / connecting cilium, associated with IFT and the BBSome

Unlike most Rab GTPases, RAB28 carries an atypical prenylation signal: *"Opposed to other Rab GTPases that are generally geranylgeranylated, RAB28 is predicted to be farnesylated. Staining of rat retina showed localization of RAB28 to the basal body and the ciliary rootlet of the photoreceptors"* (PMID: 23746546). This farnesyl (C15) lipid anchor is mechanistically relevant because it governs membrane association and trafficking of the GTPase.

Developmental expression profiling in *C. elegans* confirmed a dedicated ciliary role: *"this small GTPase is exclusively expressed in ciliated neurons where it dynamically associates with IFT trains"* (PMID: 27930654). RAB28's distribution along the cilium depends on its GTP/GDP nucleotide state and on BBSome association, placing it within the ciliary intraflagellar transport machinery that is essential for photoreceptor outer-segment maintenance.

Ontology annotations: GTPase activity (GO:0003924), small GTPase mediated signal transduction (GO:0007264), protein farnesylation (GO:0018343), ciliary basal body (GO:0036064), photoreceptor connecting cilium (GO:0032391), intraflagellar transport (GO:0042073), BBSome (GO:0034464). Cell types: retinal cone cell (CL:0000573), retinal rod cell (CL:0000604), ciliated sensory neuron.

Finding 3 — RAB28 is required for RPE phagocytosis of (cone) outer segments and for visual-cycle retinoid recycling

The downstream cellular consequence of RAB28 loss is a defect in the daily renewal of photoreceptor outer segments. In rodent and zebrafish models, *"the absence of Rab28 results in diminished dawn, photoreceptor, outer segment phagocytosis (OSP)"* (PMID: 35471581). The circadian peaks of OSP (dawn for rods, with dusk contributions) are selectively blunted, while basal phagocytosis is preserved — implicating RAB28 in the regulated, high-throughput component of outer-segment turnover rather than constitutive clearance.

This OSP defect is coupled to a measurable disruption of the retinoid (visual) cycle: *"retinoid levels of 11-cRAL, 11cRP, and atRP are significantly reduced in larval and adult rab28 KO retinae ($p < .05$)"* (PMID: 35471581). Reduced 11-cis-retinal (11-cRAL, the chromophore of opsin) directly compromises phototransduction capacity.

The requirement is especially pronounced for cones. In mouse, *"The small GTPase RAB28 is required for phagocytosis of cone outer segments by the murine retinal pigmented epithelium"* (PMID: 30228185), consistent with the cone-predominant ERG deficit seen in patients. In zebrafish, *"Genetic Deletion of Zebrafish Rab28 Causes Defective Outer Segment Shedding, but*

Not Retinal Degeneration" (PMID: 32258030) — a key model limitation indicating that the primary molecular lesion (defective OS shedding/phagocytosis) can be dissociated from overt degeneration in the fish, highlighting species differences in disease tempo.

Ontology annotations: photoreceptor outer segment (GO:0001750), retina homeostasis (GO:0001895), photoreceptor cell maintenance (GO:0045494), visual perception (GO:0007601), retinoid metabolic process (GO:0001523), phagocytosis (GO:0006909). Cell types: retinal pigment epithelial cell (CL:0002586). CHEBI: 11-cis-retinal (CHEBI:16066), retinoid.

Finding 4 — Ciliary Rab28 and the BBSome negatively regulate extracellular-vesicle (EV) shedding

A parallel mechanistic branch emerged from *C. elegans* sensory cilia: *"the ciliary G-protein Rab28, associated with human autosomal recessive cone-rod dystrophy, negatively regulates EV levels in the sensory organs"* (PMID: 32101165). Working with the BBSome, Rab28 restrains the production/shedding of ciliary extracellular vesicles. Because photoreceptor outer-segment disc morphogenesis and shedding share machinery with ciliary EV biogenesis, dysregulated EV shedding offers a complementary explanation for how RAB28 loss perturbs outer-segment homeostasis. This is an inferred bridge between the invertebrate EV finding and the vertebrate OSP defect rather than a directly demonstrated pathway in human retina.

Ontology annotations: extracellular vesicle biogenesis (GO:0140112), ciliary membrane (GO:0060170), negative regulation of extracellular exosome assembly.

Finding 5 — An ultra-rare, non-syndromic, childhood-onset, progressive condition with no approved therapy

RAB28-CRD is genetically homogeneous: *"RAB28-associated CRD is genetically homogeneous and results from pathogenic variants in the RAB28 gene, which is essential for photoreceptor function"* (PMID: 42231409). The characteristic electrophysiology is cone-predominant: *"Full-field ERG revealed severely diminished cone responses, while rod responses were mildly reduced"* (PMID: 42231409). Reported patients span European, North-African/Middle-Eastern (Moroccan-Jewish), Italian, and Korean backgrounds, with childhood-to-early-adult onset, progressive central/color-vision loss, macular hyperpigmentation, RPE/macular atrophy, and photoreceptor-layer thinning on OCT (PMID: 23746546, PMID: 33396523, PMID: 42231409). The condition is non-syndromic with normal life expectancy. No formal prevalence, incidence, penetrance, or natural-history figures are established, owing to the disease's rarity (fewer than ~20 reported families worldwide).

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function variant in RAB28** (nonsense/frameshift predominantly; rare missense) **leads to** absent or non-functional RAB28 GTPase protein (predicted null alleles such as p.Glu189* and p.Arg137*). *[Demonstrated in human families,*

   P *23746546*

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2. Loss of the **farnesylated ciliary RAB28 GTPase results in** disrupted RAB28 function at the photoreceptor basal body, connecting cilium and ciliary rootlet, and loss of its nucleotide-state-dependent association with IFT trains and the BBSome. *[Demonstrated: localization*

   P *23746546*

   ;
   IFT/BBSome

   P *27930654*

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3. Impaired ciliary RAB28/BBSome function **branches** into two coupled consequences:
4. **Branch A: leads to** diminished circadian (dawn/dusk) peaks of RPE phagocytosis of photoreceptor — especially **cone** — outer segments (OSP), with basal OSP preserved. *[Demonstrated:*

   P *35471581*

   P *30228185*

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5. **Branch B: leads to** dysregulated (increased) ciliary extracellular-vesicle shedding, since Rab28/BBSome normally negatively regulate EV levels. *[Demonstrated in C. elegans;*

   P *32101165*

   .
   Link to vertebrate photoreceptor is inferred.]
6. Defective OSP **results in** failure to recycle outer-segment retinoids, **leading to** significantly reduced 11-cis-retinal (11-cRAL), 11-cis-retinyl palmitate (11cRP) and all-trans-retinyl palmitate (atRP) — i.e., **visual-cycle disruption**. *[Demonstrated:*

   P *35471581*

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7. Reduced chromophore availability plus accumulating/unrenewed outer-segment material **results in** progressive cone (then rod) photoreceptor dysfunction, **leading to** macular RPE stress and hyperpigmentation, RPE atrophy, and photoreceptor-layer thinning. *[Demonstrated clinically:*

   P *23746546*

   P *42231409*

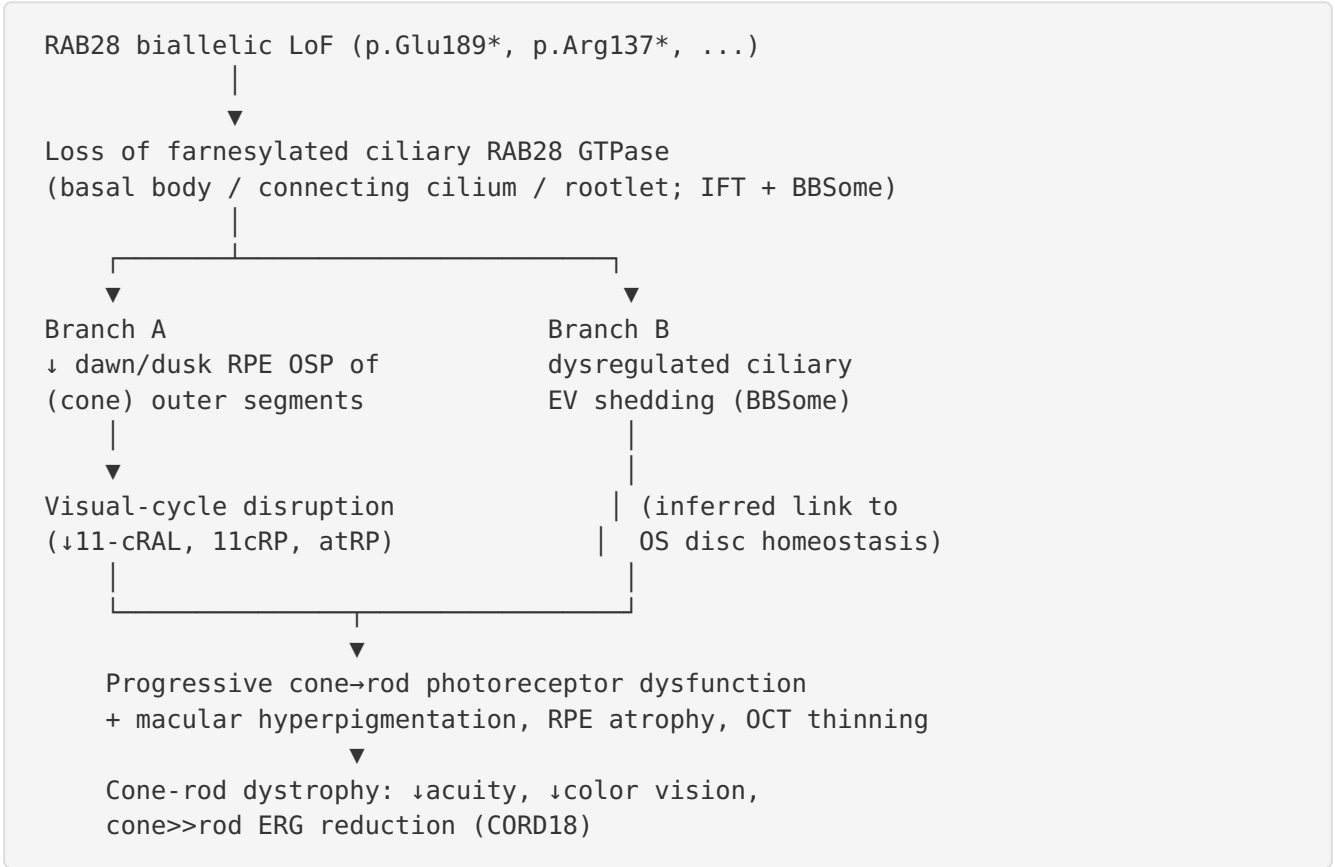
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8. Photoreceptor and RPE degeneration **results in** the clinical phenotype: progressive loss of visual acuity and color vision, macular atrophy, and a cone-predominant ERG deficit. *[Demonstrated:*

   P *23746546*

   P *42231409*

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Schematic



Upstream vs downstream

- **Upstream / initiating:** RAB28 LoF variant → loss of ciliary GTPase function (molecular).
- **Midstream:** OSP failure and EV dysregulation (cellular, RPE-photoreceptor interface).
- **Downstream:** visual-cycle depletion → photoreceptor degeneration → clinical cone-rod dystrophy.

Cell types involved: retinal cone cell (CL:0000573, primary), retinal rod cell (CL:0000604), retinal pigment epithelial cell (CL:0002586). **Anatomy:** retina (UBERON:0000966), macula lutea (UBERON:0005388), photoreceptor outer segment, retinal pigment epithelium (UBERON:0001782). **Subcellular:** connecting cilium / basal body (GO:0032391, GO:0036064), ciliary rootlet, ciliary membrane.

Section-by-Section Reference Content

1. Disease Information

- **Overview:** Non-syndromic autosomal-recessive cone-rod dystrophy with childhood/early-adult onset, progressive central and color vision loss, macular pigmentary changes and RPE atrophy.
- **Identifiers:** OMIM disease 615374 (Cone-Rod Dystrophy 18, CORD18); OMIM gene RAB28 *612994; MONDO:0100448; HGNC:9764 (RAB28). ICD-11: 9B70.0 (cone and cone-rod dystrophies) / ICD-10 H35.5 (hereditary retinal dystrophy). Orphanet: within the inherited cone-rod dystrophy group. MeSH: Cone-Rod Dystrophies / Retinal Dystrophies.
- **Synonyms:** RAB28 retinopathy; RAB28-related cone-rod dystrophy; CORD18; arCRD due to RAB28.
- **Data source:** Aggregated from individual-patient case reports/series and model-organism functional studies — not EHR-derived population data.

2. Etiology

- **Causal factor:** Purely genetic — biallelic (homozygous or compound-heterozygous) loss-of-function variants in RAB28. No environmental or infectious etiology.

- **Genetic risk factors:** The RAB28 pathogenic variants themselves are causal (not susceptibility loci). Consanguinity increases homozygous-variant risk (families reported from consanguineous/isolated populations).
- **Protective factors:** None identified. No modifier alleles or protective variants reported.
- **Gene-environment interactions:** None documented. The circadian light cycle is biologically relevant (OSP peaks are light/dark-entrained) but not established as a modifiable disease modifier.

3. Phenotypes

Phenotype	Type	HPO	Onset	Severity	Progression	Frequency
Cone-rod dystrophy	Clinical sign (ERG)	HP:0000548	Childhood–early adult	Severe (cone)	Progressive	~All
Reduced visual acuity	Symptom	decreased acuity	Childhood on	Moderate–severe	Progressive	~All
Macular hyperpigmentation	Physical sign	HP:0008061	Variable	Variable	Progressive	High
RPE atrophy / macular atrophy	Clinical sign	HP:0007894	Childhood on	Variable	Progressive	High
Photoreceptor-layer thinning (OCT)	Imaging sign	abnormal OCT	Childhood on	Variable	Progressive	High
Dyschromatopsia (color-vision loss)	Symptom	HP:0000551	Early	Variable	Progressive	Common
Photophobia	Symptom	HP:0000613	Variable	Mild–moderate	Stable/ progressive	Variable

- **Quality-of-life impact:** Progressive central and color-vision loss impairs reading, driving, and fine visual tasks; low-vision aids and rehabilitation partially mitigate. No disease-specific QOL instrument data (EQ-5D/SF-36) published.

4. Genetic / Molecular Information

- **Causal gene:** RAB28 (HGNC:9764; OMIM *612994), chromosome 4p15.33; encodes a farnesylated Rab-family small GTPase.
- **Pathogenic variants:** Predominantly **nonsense/null** — c.565C>T (p.Glu189*), c.409C>T (p.Arg137*) (PMID: 23746546); additional alleles expanded the spectrum (PMID: 33396523). A rare **missense** p.Ser23Phe was reported in a sporadic case alongside a de novo 4p16.1p15.33 deletion (PMID: 42231409).
- **Classification:** Null variants are pathogenic (ACMG PVS1 + segregation). Missense/VUS require functional support.
- **Allele frequency:** Pathogenic alleles are ultra-rare/absent-to-very-rare in gnomAD.
- **Origin:** Germline. **Functional consequence:** loss of function (null alleles; hypomorphic for some).
- **Chromosomal abnormalities:** A de novo **4p16.1p15.33 deletion** unmasking a RAB28 variant was reported (PMID: 42231409) — relevant because RAB28 lies on 4p.
- **Diagnostic caveat:** RAB28 and **PROM1** sit in the same homozygous 4p interval; a deep-intronic PROM1 pseudoexon mutation caused CRD in a family initially suspected of RAB28 involvement (PMID: 26153215). Both must be sequenced (including deep intronic regions) when this interval maps.
- **Modifier genes / epigenetics:** None identified.

5. Environmental Information

Not applicable. No environmental, lifestyle, or infectious contributors; disease is monogenic recessive.

6. Mechanism / Pathophysiology

See **Mechanistic Model** above. Pathways/processes: ciliary trafficking (IFT/BBSome), RPE phagocytosis (GO:0006909), retinoid/visual cycle (GO:0001523), extracellular-vesicle biogenesis (GO:0140112). No canonical Wnt/MAPK/mTOR involvement reported. Protein dysfunction = loss of GTPase function at the cilium. No immune or metabolic-systemic involvement.

7. Anatomical Structures Affected

- **Organ:** Eye/retina (UBERON:0000966); macula (UBERON:0005388) predominantly affected; RPE (UBERON:0001782).

- **Tissue/cell:** Neural retina photoreceptors — cones (CL:0000573) > rods (CL:0000604); RPE cells (CL:0002586).
- **Subcellular:** Connecting cilium/basal body (GO:0032391/GO:0036064), ciliary rootlet, outer-segment membranes.
- **Localization:** Bilateral, macula-predominant (central), symmetric.

8. Temporal Development

- **Onset:** Childhood to early adulthood; insidious, chronic.
- **Progression:** Slowly progressive; cone dysfunction precedes/exceeds rod. Lifelong, no remission.
- **Critical period:** Therapeutic window exists while photoreceptors survive (pre-end-stage atrophy) — relevant to gene-replacement timing.

9. Inheritance and Population

- **Inheritance:** Autosomal recessive; biallelic. Penetrance appears complete in reported homozygotes; expressivity variable.
- **Epidemiology:** Ultra-rare; no formal prevalence/incidence. <~20 families reported.
- **Populations:** European, North-African/Middle-Eastern (Moroccan-Jewish), Italian, Korean. **Consanguinity** contributes. No established founder variant. Sex ratio ~1:1 (autosomal recessive).

10. Diagnostics

- **Clinical/functional:** Full-field ERG (cone >> rod reduction), color-vision testing, visual-field testing. OCT (photoreceptor/ONL thinning, RPE changes), fundus autofluorescence, fundus photography (macular hyperpigmentation/atrophy).
- **Genetic testing (definitive):** IRD gene panels including RAB28, whole-exome (WES) or whole-genome sequencing (WGS). WGS adds value because deep-intronic variants (e.g., the PROM1 pseudoexon in the same interval, PMID: 26153215) and CNVs (4p deletion, PMID: 42231409) are missed by exon-focused assays. Chromosomal microarray detects 4p deletions. Homozygosity mapping aids consanguineous families.
- **Differential diagnosis:** Other autosomal-recessive cone-rod dystrophies (ABCA4, PROM1, CDHR1, ADAM9, C8orf37, etc.), Stargardt disease, achromatopsia. Distinguished by gene testing; the shared 4p RAB28/PROM1 interval is the key pitfall.

11. Outcome / Prognosis

- **Survival/mortality:** Normal life expectancy; non-lethal, non-systemic.
- **Morbidity:** Progressive low vision / visual disability; central and color vision most affected.
- **Disease course:** Chronic, progressive, no spontaneous remission. Legal blindness possible in advanced disease.
- **Prognostic factors:** Residual photoreceptor survival and macular integrity; earlier/larger atrophy portends worse function. No validated molecular prognostic biomarkers.

12. Treatment

- **Current standard:** No approved disease-modifying therapy. Supportive **low-vision rehabilitation**, optical aids, UV/glare protection, and **genetic counseling**.
- **Experimental — gene therapy:** AAV-mediated RAB28 gene supplementation is the leading strategy. Cone-specific wild-type Rab28 re-expression rescued the OSP defect in zebrafish rab28 mutants (PMID: 37321111). Small gene size and cone-targeting feasibility are favorable for AAV.
- **Gene-agnostic option:** Optogenetic therapy is a universal approach for late-stage degeneration regardless of causal gene (PMID: 33262683), potentially applicable once photoreceptors are lost.
- **NCIT suggestions:** Gene Therapy (NCIT:C15431), AAV Vector-based therapy, Supportive Care (NCIT:C15277), Low Vision Rehabilitation. No pharmacotherapy or pharmacogenomics established.

13. Prevention

- **Primary:** Not preventable (monogenic). **Genetic counseling**, carrier testing in at-risk families, and reproductive options (preimplantation/prenatal genetic diagnosis) for known familial variants.
- **Secondary:** Cascade testing of relatives; early ophthalmologic surveillance in at-risk children.
- **Tertiary:** Low-vision rehabilitation to limit disability. No immunization or public-health measures apply.

14. Other Species / Natural Disease

- **Orthologs:** Mouse *Rab28* (NCBI Gene 211548), zebrafish *rab28*, *C. elegans rab-28*. Highly conserved ciliary GTPase.
- **Natural disease:** No naturally occurring RAB28 retinopathy documented in companion animals/wildlife (OMIA search negative). All animal data are engineered models.
- **Comparative biology:** Mechanism (ciliary GTPase, OSP) conserved; zebrafish shows OSP defect **without** overt degeneration (PMID: 32258030), a notable cross-species difference. No zoonotic/transmission relevance.

15. Model Organisms

Model	Type	Key phenotype	Recapitulation	Reference
Mouse Rab28 KO	Mammalian, knockout	Loss of cone outer-segment phagocytosis by RPE; blunted dawn/dusk OSP; ↓retinoids	Recapitulates OSP/visual-cycle defect	PMID: 30228185, PMID: 35471581
Zebrafish rab28 KO	Teleost, genetic deletion	Defective OS shedding; **no** overt retinal degeneration	Partial — molecular defect without degeneration	PMID: 32258030
Zebrafish rab28 + cone transgene	Rescue model	Cone-specific WT Rab28 rescues OSP	Proof-of-concept for gene therapy	PMID: 37321111
C. elegans rab-28	Invertebrate	Dysregulated ciliary EV shedding; IFT/BBSome association	Models ciliary/EV mechanism	PMID: 27930654, PMID: 32101165

- **Limitations:** Zebrafish lacks overt degeneration (tempo/species difference); no model fully reproduces human progressive macular atrophy. **Resources:** MGI, ZFIN, WormBase.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
23746546	*Mutations in RAB28 … cause arCRD*	Human clinical + IHC	F1 (causal variants, phenotype), F2 (farnesylation, localization)
33396523	*Expanding the clinical/genetic spectrum*	Human clinical	F5 (variant/phenotype spectrum)
42231409	*Sporadic CRD: RAB28 p.Ser23Phe + 4p deletion*	Human clinical	F5 (homogeneity, cone>rod ERG), missense + CNV
30228185	*RAB28 required for cone OS phagocytosis (mouse)*	Mouse model	F3 (RPE phagocytosis)
35471581	*Dawn/dusk OSP & visual cycle require Rab28*	Mouse + zebrafish	F3 (OSP, retinoids)
32258030	*Zebrafish Rab28 KO: OS shedding defect, no degeneration*	Zebrafish model	F3 (model limitation)
27930654	*RAB-28 ciliary GTPase, BBSome/IFT*	C. elegans	F2 (IFT/BBSome)
32101165	*Ciliary Rab28 & BBSome regulate EV shedding*	C. elegans	F4 (EV shedding)
37321111	*Gene therapy for RAB28: zebrafish*	Zebrafish rescue	Treatment (gene therapy)
26153215	*Deep-intronic PROM1 pseudoexon mimics RAB28 CRD*	Human clinical	Diagnostic caveat (RAB28/PROM1 interval)
33262683	*Optogenetic gene therapy for degenerate retina*	Review	Gene-agnostic therapy option
40869487	*Genetic therapies for retinitis pigmentosa*	Review	IRD gene-therapy landscape

How papers challenge findings: PMID: 32258030 is the main internal tension — zebrafish Rab28 loss produces the molecular OS-shedding defect but **not** degeneration, indicating the OSP lesion is necessary but perhaps not sufficient for rapid photoreceptor death, or that species differ in resilience/tempo. PMID: 26153215 does not challenge RAB28 causation but warns that the co-localized PROM1 gene can masquerade as RAB28 disease.

Limitations and Knowledge Gaps

- **Epidemiology unquantified:** No formal prevalence, incidence, penetrance, or natural-history figures — disease too rare; estimates rely on <~20 reported families.
- **Human mechanism inferred from models:** OSP/visual-cycle and EV-shedding mechanisms are demonstrated in mouse, zebrafish, and *C. elegans*; direct human retinal mechanistic data are absent.
- **Model-human discordance:** Zebrafish lacks degeneration, so disease tempo and the sufficiency of the OSP defect for human photoreceptor loss remain uncertain.
- **EV branch under-validated:** The EV-shedding pathway (Finding 4) is established only in *C. elegans*; its contribution to vertebrate photoreceptor pathology is an inference.
- **Genotype-phenotype correlations:** With so few patients and a mix of null and rare missense alleles, severity/progression correlations are not established.
- **No therapy in humans:** Gene-replacement efficacy is shown only in zebrafish; no human trials, dosing, or safety data.
- **No validated biomarkers** for progression or treatment response.

Proposed Follow-up Experiments / Actions

1. **Establish a RAB28-CRD patient registry** to capture natural history, age-of-onset distribution, progression rate, and genotype-phenotype correlations across the reported populations.
2. **Generate a mammalian degeneration model** (e.g., aged/stressed Rab28-KO mouse, or cone-rich model) to test whether the OSP/visual-cycle defect is sufficient for progressive macular-type degeneration, resolving the zebrafish discordance.

3. **Patient iPSC-derived retinal organoids / RPE** to directly test the OSP, visual-cycle, and EV-shedding mechanisms in human cells and validate cross-species inferences.
4. **Preclinical AAV-RAB28 gene-supplementation study** in the mouse model with functional (ERG) and structural (OCT/histology) endpoints, defining the therapeutic window relative to photoreceptor survival.
5. **Dissect the EV-shedding branch in vertebrates** — test whether RAB28/BBSome-dependent EV dysregulation occurs in mammalian photoreceptor cilia and contributes to outer-segment disc defects.
6. **Deep-sequencing diagnostic protocol** for the 4p RAB28/PROM1 interval (WGS + CNV analysis) to avoid misattribution and capture deep-intronic and structural variants.
7. **Biomarker discovery** — longitudinal OCT/autofluorescence and retinoid-related measures as progression/treatment-response surrogates.

References

1. Roosing S, et al. *Mutations in RAB28, encoding a farnesylated small GTPase, are associated with autosomal-recessive cone-rod dystrophy.* PMID: 23746546
2. *Expanding the Clinical and Genetic Spectrum of RAB28-related retinopathy.* PMID: 33396523
3. *Sporadic cone-rod dystrophy caused by a heterozygous RAB28 p.Ser23Phe pathogenic variant and a de novo 4p16.1p15.33 deletion.* PMID: 42231409
4. *The small GTPase RAB28 is required for phagocytosis of cone outer segments by the murine retinal pigmented epithelium.* PMID: 30228185
5. *Dawn and dusk peaks of outer segment phagocytosis, and visual cycle function require Rab28.* PMID: 35471581
6. *Genetic Deletion of Zebrafish Rab28 Causes Defective Outer Segment Shedding, but Not Retinal Degeneration.* PMID: 32258030
7. *Whole-Organism Developmental Expression Profiling Identifies RAB-28 as a Novel Ciliary GTPase Associated with the BBSome and Intraflagellar Transport.* PMID: 27930654
8. *Ciliary Rab28 and the BBSome negatively regulate extracellular vesicle shedding.* PMID: 32101165
9. *Gene therapy for RAB28: What can we learn from zebrafish?* PMID: 37321111

10. *Homozygosity mapping and whole-genome sequencing reveals a deep intronic PROM1 mutation causing cone-rod dystrophy by pseudoexon activation.* PMID: 26153215
11. *Optogenetic Gene Therapy for the Degenerate Retina: Recent Advances.* PMID: 33262683
12. *Genetic Therapies for Retinitis Pigmentosa: Current Breakthroughs and Future Directions.* PMID: 40869487

Evidence source legend: Human clinical (PMIDs 23746546, 33396523, 42231409, 26153215); Mouse model (30228185, 35471581); Zebrafish model (32258030, 35471581, 37321111); C. elegans (27930654, 32101165); Review (33262683, 40869487).
