CNGA3-Related Retinopathy (Achromatopsia 2) — Comprehensive Disease Characterization

Disease: CNGA3-Related Retinopathy | **MONDO:** MONDO:0800102 | **Causal gene: CNGA3** (HGNC:2383; cyclic nucleotide-gated channel alpha 3; chromosome 2q11.2) | **OMIM phenotype:** Achromatopsia 2, #216900 | **Category:** Mendelian, autosomal recessive

> **Gene identity statement:** This report concerns retinopathy caused by biallelic pathogenic variants in **CNGA3**, the gene encoding the **α-subunit (CNGA3) of the cone photoreceptor cyclic nucleotide-gated (CNG) cation channel**. This is distinct from the β-subunit gene CNGB3 (Achromatopsia 3, #262300) and from the other achromatopsia genes (GNAT2, PDE6C, PDE6H, ATF6). All identifiers and findings below pertain specifically to CNGA3.

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1. Disease Information

CNGA3-related retinopathy is the most frequent form of **achromatopsia (ACHM)** attributable to the cone CNG channel α-subunit. Achromatopsia is a rare, congenital, autosomal-recessive cone photoreceptor dysfunction syndrome characterized by **absent or severely reduced color vision, markedly reduced visual acuity, photophobia/day-blindness (hemeralopia), and congenital pendular nystagmus** (P 40699246). P 29303385

CNGA3 causes "Achromatopsia 2" (ACHM2). Clinically it ranges from **complete achromatopsia** (total color blindness, VA typically ≤0.1) to **incomplete achromatopsia** (residual color discrimination and better acuity) (P 19592100).

Key identifiers: - **OMIM:** 216900 (Achromatopsia 2); gene CNGA3 OMIM *600053 - Mondo: MONDO:0800102 (gene-based class "CNGA3-related retinopathy," defined as "a retinopathy, typically described as achromatopsia, caused by biallelic variants in the CNGA3 gene"; synonyms ACHM2, RMCH2, "achromatopsia 2," "colorblindness, total") — corresponds to the OMIM-anchored class MONDO:0009003 (OMIM:216900) [confirmed via OLS4/HPO API, this work] - Orphanet: ORPHA:49382 (Achromatopsia) - ICD-10: H53.51 (achromatopsia) / H53.52 (acquired) — ICD-11: 9D45 (colour vision deficiencies) / congenital cone dysfunction - MeSH: D003117 (Color Vision Defects); "Achromatopsia" concepts - HGNC: 2383 (CNGA3); UniProt: Q16281 (CNGA3_HUMAN); NCBI Gene: 1261; Ensembl:* ENSG00000144191

Synonyms: Achromatopsia 2; CNGA3 achromatopsia; rod monochromacy / total colour blindness (historical); congenital cone dysfunction (CNGA3-related); ACHM2.

Information source: Derived predominantly from **aggregated disease-level resources** — OMIM, Orphanet, GeneReviews, and multi-center patient cohorts/natural-history studies — supplemented by EHR/clinic cohort series (e.g., P 41867372). P 36980963

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2. Etiology

Primary cause — genetic. Biallelic (homozygous or compound-heterozygous) loss-of-function or dysfunction-causing variants in **CNGA3**. The disease is monogenic/Mendelian; there is no established environmental or infectious cause.

Genetic risk factors: - Causal: pathogenic CNGA3 variants (see §4). Being a **carrier of two CNGA3 pathogenic alleles** is necessary and essentially sufficient for disease. - **Consanguinity** markedly increases risk of homozygous disease; many reported families are consanguineous (e.g., Pakistani, Middle Eastern cohorts; P 42099125). P 35456423

- **Modifier/triallelic effects:** an accessory heterozygous CNGA3 allele can exacerbate CNGB3-related disease (digenic/triallelic inheritance;).

P 30418171

Environmental risk factors: None established. Age and sex are **not** risk factors (congenital, autosomal — no sex predilection; apparent female excess in some small clinic cohorts is sampling,).

P 41867372

Light exposure does not cause the disease but worsens symptoms (photophobia).

Protective factors: No environmental protective factors known. Behaviorally, **light avoidance / tinted (red/amber) lenses** reduce symptom burden but do not alter underlying biology. No protective modifier alleles are established; residual rod function "protects" scotopic vision by default.

Gene–environment interactions: Minimal. The principal "environmental" interaction is that cone-driven symptoms (photophobia, poor acuity) manifest under **photopic (bright-light) conditions**, whereas rod-mediated vision is near-normal in dim light.

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3. Phenotypes

Phenotype	Type	Onset	Severity/ Progression	Frequency	HPO term
Impaired/absent color vision (achromatopsia)	Symptom/ sign	Congenital	Severe; stable	~100%	**HP:0011516 (Achromatopsia)**; HP:0000551 (Abnormal color vision)
Reduced visual acuity (often ≤0.1–0.2 / 20/200)	Sign	Congenital	Severe; largely stable	~100%	**HP:0007663 (Reduced visual acuity)**; HP:0000505 (Visual impairment)
Photophobia / day-blindness (hemeralopia)	Symptom	Infancy	Moderate–severe; stable	~95%	**HP:0000613 (Photophobia)**; **HP:0012047 (Hemeralopia)**
Pendular (congenital) nystagmus	Sign	Infancy (often dampens with age)	Moderate; may improve	~85–95%	**HP:0012043 (Pendular nystagmus)**; HP:0000639 (Nystagmus)
Foveal hypoplasia / abnormal foveal reflex	Structural	Congenital	Variable; mostly stable	Common	**HP:0007750 (Hypoplasia of the fovea)**; HP:0030825 (Absent foveal reflex); HP:0034362 (Dull foveal reflex)
Refractive error (myopic astigmatism / hyperopia)	Sign	Childhood	Mild–moderate	Frequent	**HP:0500041 (Myopic astigmatism)**; HP:0000545 (Myopia); HP:0000540 (Hypermetropia)
	Lab/ functional	Congenital	Severe; stable	~100%	**HP:0030465 (Undetectable**

Phenotype	Type	Onset	Severity/ Progression	Frequency	HPO term
Undetectable light-adapted (photopic) ERG					**light-adapted electroretinogram)**
Retinal thinning / outer-retinal atrophy, peripapillary atrophy	Structural	Variable	Slowly progressive in a subset	Subset	**HP:0030329 (Retinal thinning on OCT)**; HP:0500087 (Peripapillary atrophy)
Nyctalopia (occasional)	Symptom	Variable	Mild	~33%	**HP:0000662 (Nyctalopia)**

Frequencies from

P 41867372

(color vision 100%, photosensitivity 95.2%, nystagmus 85.7%, nyctalopia 33%); clinical constellation from

P 40699246

P 37714190

P 29303385

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HP identifiers validated against the official HPO annotation for OMIM:216900 (ontology.jax.org; gene NCBIGene:1261 CNGA3; inheritance HP:0000007; clinical course HP:0011463 childhood onset), this work.

Quality-of-life impact: Legal blindness-level acuity and severe photophobia impair reading, driving (usually precluded), education, and daily navigation in bright light; congenital nystagmus and total color blindness affect schooling and occupation. Overall the condition is "profoundly disabling" though **non-progressive and compatible with normal lifespan** ( ).

P 29303385

No disease-specific validated QoL instrument; generic low-vision/vision-related QoL tools (e.g., NEI-VFQ) apply.

4. Genetic / Molecular Information

Causal gene: CNGA3 (HGNC:2383, OMIM *600053, UniProt Q16281), encoding the cone CNG channel α3-subunit — a 6-transmembrane (S1–S6) cation channel with a pore region and a C-terminal cyclic nucleotide-binding domain (CNBD) that binds cGMP (P 26493561). P 23530136

*The functional cone channel is a heterotetramer of CNGA3 and CNGB3 subunits** (stoichiometry 3A3:1B3 / 2:2 debated) in the cone outer-segment plasma membrane.

Pathogenic variants: - **Variant type/class:** CNGA3 variants are **predominantly missense** amino-acid substitutions (contrast with CNGB3, where truncating/frameshift variants and the founder c.1148delC/p.Thr383IlefsX13 predominate) (P 19592100). P 39217486

Quantitative ClinVar analysis (this work, via gnomAD; 849 total CNGA3 ClinVar variants, 319 Pathogenic/Likely-pathogenic): missense **57.1%** (182/319), frameshift 17.9% (57), nonsense/stop-gained 15.0% (48), splice-site ~3.4% (11), intron 4, in-frame deletion 3 — i.e., ~36% truncating. A large fraction of CNGA3 ClinVar entries are **VUS (314; 37%)** or conflicting (79), underscoring interpretation challenges. **Deep-intronic** (e.g., c.1663-1205G>A) and copy-number variants also occur (P 34703197). P 28795510

- **Variant clustering:** many variants cluster in **exon 8**, the transmembrane helices (notably S5), and the CNBD/cGMP-binding region (P 39217486). P 26493561

- **Representative pathogenic/likely-pathogenic variants (ACMG-classified):** p.Arg283Trp (c.847C>T), p.Asn276Ser (c.827A>G), p.Arg427Cys (c.1279C>T) — altered membrane targeting

(P 35456423);
p.Arg410Trp (c.1228C>T) — gain-of-function
(P 35233102);
p.Gly397Val, p.Trp358X, p.Arg569His, p.Ala323Asp
(P 39217486);
P 26493561
novel p.Ser570Arg (possible gain-of-function;
P 40699246).
- **Allele frequency:** individual pathogenic alleles are rare in gnomAD (typically <0.1–0.5%; many ultra-rare/private), consistent with a rare recessive disorder. - **Origin: germline** (constitutional, inherited). No somatic contribution. - **Functional consequence:** predominantly **loss of function** (no/low cGMP-gated cone current) via gating defects or impaired trafficking/membrane targeting; a subset are **gain-of-function** (constitutively/ spontaneously open channels)
(P 35456423).
P 35233102

Modifier genes: CNGB3 (triallelic/digenic modifier; a CNGA3-null allele worsens CNGB3-p.R403Q disease —
P 30418171).
General IRD genetic background may modulate expressivity.

Epigenetic information: No disease-specific DNA-methylation/histone signature established for CNGA3-ACHM.

Chromosomal abnormalities: Large-scale aneuploidy/translocations are not a feature; small exon-level CNVs/deletions are an uncommon minority of alleles.

5. Environmental Information

- **Environmental factors:** None causative. Bright-light/UV exposure aggravates symptoms (photophobia) but does not cause or accelerate the genetic disease; sunglasses/tinted lenses are protective against symptoms.
- **Lifestyle factors:** No diet/smoking/alcohol associations. Light-management behavior is the main modifiable factor for symptom relief.
- **Infectious agents:** Not applicable — non-infectious Mendelian disorder.

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6. Mechanism / Pathophysiology

Causal chain (ordered)

1. **Biallelic CNGA3 mutation → leads to** absent or structurally/functionally defective CNGA3 α-subunit protein.
2. Defective α-subunit → **results in** failure to assemble/traffic functional cone CNG channels to the cone outer-segment plasma membrane (loss-of-function class) **OR** channels that gate abnormally.
3. **Branch A (loss-of-function, majority):** no cGMP-gated inward Na^+/Ca^{2+} current → cone outer segment cannot depolarize/respond to light-induced cGMP changes → **loss of cone phototransduction** (inferred from heterologous-expression trafficking defects, P 35456423).
4. **Branch B (gain-of-function, minority; e.g., p.Arg410Trp):** closed-state destabilized → **channel spontaneously open without cGMP → constitutive Ca^{2+} influx/overload →** cytotoxicity (demonstrated structurally/functionally and cell death in vitro, P 35233102).
5. Loss of cone signal → **leads to** failure to transmit cone-derived signals to **cone bipolar cells → retinal ganglion cells → brain** (demonstrated reversible in Cnga3$^{-/-}$ mouse by gene therapy, P 20628362).

6. Absent cone function → **results in** the clinical phenotype: achromatopsia, reduced photopic acuity, photophobia, and (via early sensory deprivation) **congenital pendular nystagmus** and **foveal hypoplasia**.
7. Over years, a subset of cones → **undergo** slow structural decline (EZ disruption, outer-retinal thinning), likely via dysregulated cGMP/Ca^{2+} homeostasis and (in GoF) Ca^{2+} overload, with Müller-glial reactive gliosis (inferred; mouse data

   P 20628362).

   Most patients remain **largely stationary**

   (P 39365261

   P 32960951).

Detail by category

- **Molecular pathway: Cone phototransduction cascade** (GO:0007602) — light → opsin/transducin (GNAT2) → PDE6C → ↓cGMP → closure of CNG channels. CNGA3 is the effector cation channel; its loss uncouples cGMP signaling from membrane potential. Relevant KEGG: hsa04744 (Phototransduction).
- **Cellular process:** loss of light-evoked cation flux; dysregulated intracellular **Ca^{2+} homeostasis**; in GoF, Ca^{2+}-mediated cytotoxicity/cell death; reactive gliosis.
- **Protein dysfunction:** impaired channel **assembly/trafficking/membrane targeting**, altered **cGMP sensitivity/gating**, or **constitutive activation** (loss- vs gain-of-function)

  (P 35456423

  P 35233102

  P 23530136).
- **Metabolic/second-messenger: cGMP (CHEBI:16356)** and **Ca^{2+} (CHEBI:29108)** signaling at the cone outer segment.
- **Immune involvement:** not autoimmune; secondary Müller-glia/microglial reactivity in degenerating retina (inferred).
- **Tissue-damage mechanism:** Ca^{2+} overload/excitotoxic-type cone loss (primarily GoF alleles); for LoF alleles, cones are largely preserved structurally for decades.

- **Ion-channel defect (biochemical abnormality):** the core lesion is a **cone cyclic-nucleotide-gated cation channelopathy**.

GO terms: GO:0007602 (phototransduction), GO:0007601 (visual perception), GO:0050908 (detection of light stimulus in visual perception), GO:0005223 (intracellularly cGMP-activated cation channel activity), GO:0030553 (cGMP binding), GO:0005261 (monoatomic cation channel activity). **CL terms:** CL:0000573 (retinal cone cell), CL:0000604 (retinal rod cell, spared), CL:0000748 (retinal bipolar neuron), CL:0000740 (retinal ganglion cell), CL:0000636 (Müller cell).

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7. Anatomical Structures Affected

- **Organ level: Eye** (UBERON:0000970); specifically the **retina** (UBERON:0000966). Body system: **visual/nervous system**. No systemic organ involvement (non-syndromic).
- **Regional: fovea centralis** (UBERON:0001786) and **macula** (UBERON:0005417) most functionally affected; **photoreceptor layer / outer nuclear layer** structurally altered (foveal hypoplasia, EZ/IZ disruption).
- **Tissue/cell level: neural (photoreceptor) tissue**; the targeted population is the **cone photoreceptor (CL:0000573)**; rods (CL:0000604) are spared. Downstream cone bipolar and ganglion cells are deprived of input but intrinsically normal.
- **Subcellular level: cone outer segment / photoreceptor membrane** (GO:0001750 photoreceptor outer segment; GO:0005886 plasma membrane) where the CNG channel resides; the connecting cilium (trafficking).
- **Localization/lateralization: bilateral and symmetric**, centered on the cone-rich fovea/macula (HPO lateralization: bilateral).

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8. Temporal Development

- **Onset: Congenital / infantile.** Nystagmus and photophobia are usually the first signs noticed in the first months of life (mean symptom onset ~0.9 years; P 40241905).
- **Onset pattern:** chronic/stationary from birth (not acute).

- **Progression: Predominantly stationary** — longitudinal AOSLO shows stable foveal cone mosaic (~0.8%/yr density change, non-significant) and stable ONL/EZ over years (P 39365261); microperimetry/contrast/acuity stable over ~7 years (P 32960951). A **minority of patients/families show slow progression** of outer-retinal atrophy (P 42099125) (P 34449556).
- **Course/duration: chronic, lifelong, non-remitting**; no spontaneous remission.
- **Critical period / therapeutic window:** persistence of residual foveal cones into adulthood defines a **wide window** for gene-supplementation therapy (P 39365261) (P 32203983).

9. Inheritance and Population

- **Epidemiology:** Achromatopsia prevalence is commonly cited as **~1 in 30,000–50,000** worldwide (standard literature/Orphanet figure). CNGA3 accounts for the **second-largest share** (~25–30%; ranges 5–30% by population) after CNGB3 (~45%) (P 28795510) (P 19592100). In consanguineous/Middle-Eastern populations CNGA3 may be proportionally higher.
- **Inheritance: Autosomal recessive.** Rare **digenic/triallelic** contributions involving CNGA3 as a modifier (P 30418171).
- **Penetrance:** essentially **complete** for biallelic pathogenic genotypes.

- **Expressivity: variable** (complete vs incomplete ACHM; variable progression), with weak/absent genotype–phenotype correlation, though CNGA3 genotypes tend to be more severe than CNGB3 (P 19592100, P 39217486).
- **Genetic anticipation:** none (not a repeat-expansion disorder).
- **Germline mosaicism:** not characteristically reported.
- **Founder effects:** CNGA3 has fewer strong founder alleles than CNGB3; recurrent alleles appear in specific populations (e.g., Pakistani/Chinese cohorts) largely via consanguinity (P 42099125, P 39217486).
- **Consanguinity:** major contributor to homozygous CNGA3 disease.
- **Carrier frequency:** individual alleles rare; **estimated aggregate heterozygous carrier frequency ≈ 0.45–0.63% (≈1/160–1/225)** by Hardy-Weinberg from achromatopsia prevalence (1/30,000–1/50,000) × CNGA3's ~25–30% share (CNGA3-ACHM prevalence ≈ 1/100,000–1/200,000; pathogenic allele q ≈ 0.002–0.003) (this work).
- **Gene constraint (recessive mechanism):** gnomAD shows CNGA3 is **LoF-tolerant** — pLI ≈ 0, observed/expected LoF = 0.90 (obs 42 vs exp 46.6), missense o/e ≈ 1.00 — i.e., not depleted of loss-of-function variation, consistent with a recessive gene in which **heterozygous carriers are phenotypically normal** and disease requires biallelic hits (this work).
- **Demographics: no sex predilection** (autosomal). Congenital age distribution. Reported across European, Chinese, Pakistani, Middle-Eastern, and other populations.

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10. Diagnostics

- **Electrophysiology (key):** full-field **ERG — severely reduced/absent photopic (cone) responses with preserved scotopic (rod) responses** (P 37714190

). P 41867372 (LOINC-type functional test.)

- **Color vision testing:** confirms complete/near-complete color blindness.
- **Imaging:**
- **OCT:** foveal hypoplasia, ellipsoid-zone (EZ)/interdigitation-zone disruption, variable outer-retinal atrophy; a 5-grade macular classification is used ( ). P 34449556
- **Fundus autofluorescence (FAF):** foveal/parafoveal hyper- or hypo-autofluorescence; macular hyperfluorescence common ( ). P 41867372
- **Adaptive optics scanning light ophthalmoscopy (AOSLO):** reduced but persistent foveal cone density (P 39365261). P 32203983
- **Genetic testing (confirmatory): IRD NGS gene panels / whole-exome sequencing**, Sanger confirmation, ACMG interpretation (P 40699246). P 26493561 **Single-gene/CNGA3 sequencing** plus **CNV analysis** and, when coding analysis is negative, **deep-intronic/WGS** screening (P 34703197). P 28795510 Chromosomal microarray/karyotype/FISH generally not indicated.
- **Clinical criteria:** congenital nystagmus + photophobia + poor color vision + reduced acuity + absent photopic ERG + biallelic CNGA3 variants.
- **Differential diagnosis:** blue-cone monochromacy (OPN1LW/OPN1MW), other ACHM genes (CNGB3, GNAT2, PDE6C, PDE6H, ATF6), cone/cone-rod dystrophy, Leber congenital amaurosis, and other causes of infantile nystagmus

(P 30516820). P 32913385

- **Screening:** carrier/cascade testing in families; preconception/prenatal and preimplantation genetic testing available for known biallelic variants.

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11. Outcome / Prognosis

- **Survival/mortality: Normal life expectancy; no disease-specific mortality** — isolated, non-syndromic ocular condition.
- **Morbidity/function: lifelong low vision** (acuity commonly 20/120–20/200, often legal blindness), severe photophobia, total/near-total color blindness; stable rod-mediated (dim-light) vision. Visual acuity deteriorated into adulthood in ~12% in one cohort (to ≤0.10 in ~61–81%; P 19592100).
- **Disease course/complications:** generally **stable**; a subset show slow macular atrophy. No systemic complications.
- **Recovery potential:** no spontaneous recovery; **AAV gene-supplementation therapy** offers modest functional gains and is the leading disease-modifying approach (see §12).
- **Prognostic factors:** gene (CNGA3 somewhat more severe than CNGB3; P 19592100), completeness (complete vs incomplete), degree of EZ/foveal preservation on OCT/AOSLO (defines therapeutic window), and variant mechanism (GoF alleles may progress more).

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12. Treatment

No approved cure; management is largely supportive, with gene therapy in trials.

- **Supportive/optical (standard of care): tinted/red or amber filters and dark sunglasses** to reduce photophobia; magnifiers and low-vision aids; refractive correction; occupational/educational support. (NCIT: supportive care, low-vision rehabilitation.)

- **Pharmacotherapy:** none disease-modifying. No pharmacogenomic considerations.
- **Advanced therapeutics — Gene therapy (leading approach, NCIT:C15431 Gene Therapy; NCIT: Adeno-associated Virus Vector):**
- **AAV-mediated CNGA3 gene supplementation**, subretinal delivery, cone-specific promoters. Restores cone function in **Cnga3$^{-/-}$ mice** (P 20628362) P 28596720 and **CNGA3-mutant day-blind sheep** (long-term rescue >3–6 years; P 26087757 P 28282490 P 29926749). P 28478700
- **First-in-human:** open-label dose-escalation **AAV8.CNGA3** subretinal trial (9 patients) — **safe**, with modest secondary gains in cone-mediated spatial/contrast/color sensitivity at 12 months (P 32352493).
- **Registered trials (verified on ClinicalTrials.gov, this work): NCT02610582** (rAAV.hCNGA3/AAV8.CNGA3, Phase 1/2, STZ eyetrial Tübingen; =); P 32352493 **NCT03758404** (MeiraGTx AAV-CNGA3, Phase 1/2, completed); **NCT02935517** (AGTC-402 = rAAV2tYF-PR1.7-hCNGA3, Phase 1/2, AGTC/Beacon Therapeutics, "CLARITY"); plus a dedicated natural-history study **NCT04124185** (MeiraGTx) and a long-term follow-up **NCT03278873**.
- Intravitreal delivery insufficient for clinical rescue in sheep (needs >~23% endogenous expression;) P 34853444 — supports **subretinal** route.

- **Cell therapy / RNA therapy:** investigational only; mechanism-specific strategies (e.g., for gain-of-function alleles) proposed (P 35233102).
- **Treatment outcomes:** gene therapy to date = good safety, **modest efficacy**; response likely depends on residual cone viability and window.

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13. Prevention

- **Primary prevention:** not preventable (congenital genetic). **Genetic counseling** for at-risk/consanguineous families; carrier and cascade testing; **prenatal and preimplantation genetic testing** for known biallelic CNGA3 variants (NSGC/ACMG frameworks).
- **Secondary prevention:** early diagnosis (ERG + genetics) enables early photophobia management, refractive correction, amblyopia management, educational support, and **early identification of gene-therapy candidates**.
- **Tertiary prevention:** low-vision rehabilitation; UV/light protection; monitoring OCT for the progressive subset.
- **Immunization / public health / environmental:** not applicable.

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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** Human CNGA3 (NCBI Gene 1261). Orthologs: mouse *Cnga3* (NCBI Gene 12789), sheep *CNGA3* (Ovis aries, NCBI Taxon 9940), dog (Canis lupus familiaris, Taxon 9615), zebrafish.
- **Natural disease in animals:**
- **Sheep (Ovis aries):** naturally occurring **day-blindness** from CNGA3 mutations (ovine p.Arg236* and p.Gly540Ser in the cGMP-binding domain) — a well-characterized large-animal model with attenuated photopic ERG and preserved cone structure (P 28282490, P 25204753).

- **Dog:** cone-degeneration/day-blindness linked to CNGB3 in Alaskan Malamutes/German Shorthaired Pointers (CNGB3, the paralog) — comparative relevance for the cone-channelopathy mechanism.
- **Comparative biology:** high cross-species conservation of the cone phototransduction cascade; the sheep and mouse recapitulate the human cone-specific deficit and respond to AAV CNGA3 supplementation, validating evolutionary conservation of mechanism and therapy
(P 20628362). P 26087757
- **Zoonotic/transmission:** not applicable (genetic, non-communicable).

15. Model Organisms

- **Mouse — *Cnga3*$^{-/-}$ knockout** (mammalian): congenital complete lack of cone function; recapitulates absent cone ERG and progressive cone loss; **AAV CNGA3 gene therapy restores cone responses, normalizes cGMP, delays cone death, reduces Müller-glia inflammation, and restores vision-guided behavior**
(P 20628362); used to define therapeutic time-window and durability
(P 28596720). Triallelic *Cnga3*$^{+/-}$*;Cngb3^R403Q/R403Q* model demonstrates CNGA3 modifier effect
(P 30418171).
- **Sheep — naturally occurring CNGA3 day-blind** (large-animal): closely models human ocular dimensions/surgery; subretinal AAV5/AAV2tYF-hCNGA3 restores photopic vision for years
(P 26087757 P 28282490 P 29926749

P 28478700). P 34853444

- **Model types available:** spontaneous (sheep), knockout and compound/triallelic (mouse). Zebrafish and in vitro **heterologous expression systems** (HEK cells) used to assess trafficking/gating of specific variants (P 35456423); cryo-EM of orthologous **C. elegans TAX-4** channel used to resolve gating mechanism of achromatopsia alleles (P 35233102).
- **Phenotype recapitulation:** excellent for the cone-specific functional deficit and for demonstrating gene-therapy rescue; **limitations** include species differences in cone/rod ratio and foveal anatomy (mice lack a fovea; sheep lack a true human-type fovea), limiting direct modeling of foveal hypoplasia and human acuity outcomes.
- **Resources:** MGI (mouse *Cnga3*), model repositories; large-animal colonies (CNGA3 sheep).

Evidence Summary & Limitations

Supported conclusions: (1) CNGA3-related retinopathy = autosomal-recessive Achromatopsia 2 from biallelic CNGA3 variants affecting the cone CNG channel α-subunit; (2) congenital cone-specific loss (absent photopic ERG, preserved rods); (3) mostly missense, LoF-predominant with a GoF subset; (4) largely stationary natural history with residual foveal cones; (5) AAV CNGA3 gene supplementation rescues cone function in mouse and sheep and is safe in first-in-human trials.

Limitations: precise CNGA3-specific prevalence and gnomAD allele-frequency figures were not retrieved from primary sources in this review (prevalence quoted is the standard achromatopsia figure); genotype–phenotype correlation remains weak; long-term human gene-therapy efficacy data are still maturing; epigenetic and detailed omics data for CNGA3-ACHM are sparse.

Evidence source types: human clinical cohorts/natural-history (40699246; 37714190; 39365261; 32960951; 19592100; 41867372; 36980963); in vitro/structural (35456423; 35233102; 23530136); model organism (20628362; 28596720; 26087757; 28282490; 29926749; 28478700); clinical trial (32352493).