

Cone-Rod Dystrophy 10 (CORD10): Comprehensive Disease Characterization Report

Disease: Cone-rod dystrophy 10 (CORD10) **MONDO ID:** MONDO:0012464 | **OMIM:** #610283 |
Causal gene: *SEMA4A* (semaphorin 4A, chromosome 1q22) **Category:** Mendelian inherited
retinal dystrophy **Report date:** 2026-10-14

Summary

Cone-rod dystrophy 10 (CORD10) is a rare, bilateral, progressive non-syndromic **inherited retinal dystrophy (IRD)** caused by germline missense mutations in the gene *SEMA4A*, which encodes the transmembrane protein **semaphorin 4A**. The disease belongs to the clinically and genetically heterogeneous cone-rod dystrophy (CRD) group, in which cone photoreceptors degenerate first or concurrently with rods, producing early loss of central visual acuity, photophobia, impaired color vision, and later night blindness and peripheral visual-field constriction. The disease-causing variants (notably **p.D345H** and **p.F350C**) cluster in the conserved extracellular **Sema domain** of the protein and were originally identified in retinal-degeneration families, establishing *SEMA4A* as the causal gene for CORD10 ([PMID: 16199541](#)).

Mechanistically, CORD10 is a **loss-of-function disorder of retinal pigment epithelium (RPE) endosomal sorting**. *SEMA4A* normally mediates **Rab11/FIP2-dependent endosomal sorting** in the RPE, which (1) under oxidative/light stress diverts the anti-apoptotic lysosomal precursor **prosaposin** from lysosomal degradation to exosomal secretion, protecting photoreceptors from light-induced apoptosis, and (2) under baseline conditions sorts retinoid-binding proteins to regenerate **11-cis-retinal**, the chromophore for phototransduction. The Sema-domain missense mutation (e.g., p.F350C) alters protein conformation and causes abnormal subcellular localization, crippling this sorting machinery. Photoreceptors consequently lose both anti-apoptotic support and chromophore supply, and undergo progressive apoptosis — cones first, then rods ([PMID: 23360997](#); [PMID: 22465952](#)).

This causal chain is validated in animal models: *Sema4A* knockout mice develop severe early retinal degeneration affecting both rods and cones, and knock-in mice carrying the F350C allele reproduce the degeneration, which is **rescued by AAV-mediated *Sema4A* gene transfer** (PMID: 15277503; PMID: 23360997). There is currently **no approved disease-specific therapy** for CORD10; management is supportive (low-vision rehabilitation, genetic counseling). Gene augmentation for loss-of-function alleles and CRISPR editing for any dominant allele are the leading, preclinically-validated therapeutic strategies for the cone-rod dystrophy class.

1. Disease Information

Overview. CORD10 is a monogenic, non-syndromic cone-rod dystrophy — a form of inherited retinal degeneration in which cone photoreceptors (responsible for central, high-acuity, daylight, and color vision) are affected first or together with rod photoreceptors (responsible for peripheral and night vision). This "cone-led" pattern distinguishes CRD from rod-cone dystrophy / retinitis pigmentosa, where rods fail first. CORD10 specifically denotes the subtype caused by variants in *SEMA4A*.

Key identifiers:

Resource	Identifier
OMIM (phenotype)	#610283 (CONE-ROD DYSTROPHY 10; CORD10)
MONDO	MONDO:0012464
Gene	<i>SEMA4A</i> (HGNC: 10730); OMIM gene #607292
Chromosomal locus	1q22
Orphanet	Cone-rod dystrophy (parent group ORPHA:1872; no separate CORD10 ORPHA generally assigned)
ICD-10	H35.54 (dystrophies primarily involving the sensory retina)
ICD-11	9B70.0 / 9B70 (hereditary retinal dystrophy)
MeSH	Cone-Rod Dystrophies; Retinal Dystrophies

Synonyms / alternative names: CORD10; CRD10; cone-rod dystrophy 10; SEMA4A-related cone-rod dystrophy; SEMA4A-associated retinal degeneration. (*SEMA4A* variants are also reported in association with retinitis pigmentosa, reflecting phenotypic overlap.)

Information source. The CORD10 knowledge base is derived from **aggregated disease-level resources** (OMIM, gene/variant databases) plus **primary literature from individual patients and families** (the original Pakistani retinal-dystrophy families) and **model-organism experiments** (mouse knockout/knock-in). It is not EHR-derived population data.

2. Etiology

Primary cause — genetic. CORD10 is a **Mendelian, monogenic disorder** caused by pathogenic missense variants in *SEMA4A*. The founding report screened 190 unrelated retinal-disease patients (135 retinitis pigmentosa, 25 CRD, 30 Leber congenital amaurosis) and identified heterozygous *SEMA4A* missense mutations exclusively in affected individuals and absent from 100 controls ([PMID: 16199541](#)):

"We report the first observation of the involvement of SEMA4A gene mutations causing retinitis pigmentosa (RP) and cone rod dystrophy (CRD)."

"Two mutations, p.D345H and p.F350C, were observed only in affected patients; they were not observed in any of the normal members or the 100 control subjects. Both mutations identified occur in the conserved semaphorin domain."

Genetic risk factors. The causal variants are the *SEMA4A* Sema-domain missense changes themselves (p.D345H, p.F350C, and other reported alleles such as p.R713Q in the cytoplasmic domain). **Consanguinity** is a major contextual risk factor: *SEMA4A*-linked disease was first described in Pakistani families, and recessive IRDs generally are strongly enriched in consanguineous Middle Eastern/North African and South Asian populations, where founder mutations recur ([PMID: 35551639](#)).

Environmental risk factors. No established environmental cause. However, the mechanism implicates **light exposure and oxidative stress** as modulators of photoreceptor survival: SEMA4A's protective prosaposin-sorting function is specifically engaged "in response to

oxidative stress" to prevent "light-induced photoreceptor apoptosis," so cumulative light/oxidative burden plausibly influences the rate of degeneration ([PMID: 22465952](#)). This is mechanistically inferred, not clinically demonstrated for CORD10.

Protective factors. None genetically defined for CORD10. By mechanistic inference, measures reducing oxidative/photic stress (UV/blue-light protection, antioxidant support) are plausible but unproven disease modifiers.

Gene-environment interactions. The core interaction is **genotype × photo-oxidative stress**: a hypomorphic/mislocalized SEMA4A cannot mount the stress-induced prosaposin-sorting response, so the same light/oxidative load that is tolerated in healthy RPE becomes injurious. This is a plausible but not formally tested GxE model.

3. Phenotypes

CORD10 produces the characteristic cone-rod dystrophy symptom complex. Because CORD10 is rare, per-phenotype frequencies are extrapolated from the CRD class and from *SEMA4A* model data rather than from large CORD10 cohorts.

Phenotype	Type	HPO term	Onset	Severity / course	Notes
Reduced visual acuity	Symptom/ sign	HP:0000572 / HP:0000505	Childhood– early adult	Moderate→severe, progressive	Central/ macular, cone- driven
Photophobia	Symptom	HP:0000613	Early	Variable, often prominent	Classic cone- dysfunction feature
Dyschromatopsia (color-vision defect)	Symptom/ sign	HP:0000551	Early	Progressive	Cone loss
Reduced/ constricted visual field	Sign	HP:0001123 / HP:0007994	Later	Progressive	Rod involvement
Nyctalopia (night blindness)	Symptom	HP:0000662	Later	Progressive	Appears as rods degenerate
Abnormal electroretinogram (cone > rod)	Lab/ functional	HP:0000512	Detectable early	Progressive	Diagnostic hallmark
Macular degeneration / RPE changes	Sign (imaging)	HP:0000608 / HP:0007754	Variable	Progressive	Central atrophy, bull's- eye possible
Attenuated retinal vessels	Sign	HP:0007843	Later	Progressive	Seen in <i>Sema4A</i> -null mice
Abnormal fundus pigmentation/ depigmentation	Sign	HP:0008046 / HP:0030506	Variable	Progressive	RPE depigmentation (mouse)

Characteristic pattern. In cone-rod dystrophies, degeneration begins in the cone-rich central macula before spreading peripherally — hence early loss of acuity/color and late night-blindness/field loss. The *SEMA4A* mouse phenotype confirms that "disruption of *Sema4A* also compromised the physiological function of both rod and cone photoreceptors," consistent with pan-photoreceptor disease ([PMID: 15277503](#)).

Quality-of-life impact. CORD10 is a cause of **progressive low vision and eventual legal blindness**, with major impact on reading, driving, face recognition, mobility, education, and employment. Photophobia adds daily discomfort in ordinary lighting. No CORD10-specific EQ-5D/SF-36 data exist; impact is inferred from the severe-visual-impairment trajectory common to CRDs.

4. Genetic / Molecular Information

Causal gene. *SEMA4A* (semaphorin 4A), HGNC:10730, OMIM 607292, *chromosome 1q22*. It encodes a 760-amino-acid type-I transmembrane protein of the semaphorin family, with an extracellular Sema domain*, immunoglobulin-like domain, transmembrane segment, and short cytoplasmic tail (PMID: 16199541).

Pathogenic variants.

Variant	Domain	Type	Classification	Evidence
p.D345H (c.1033G>C)	Sema domain	Missense	Pathogenic/likely pathogenic (segregating; absent in 100 controls)	P 16199541
p.F350C (c.1049T>G)	Sema domain	Missense	Pathogenic — functionally validated in mouse	P 16199541 ; 23360997
p.R713Q	Cytoplasmic	Missense	Reported; not degeneration-causing in knock-in mice	P 23360997

Variant type/class. All reported CORD10 alleles are **missense** point mutations; no structural/CNV causes are established. The disease-relevant variants concentrate in the **conserved extracellular Sema domain**, where residue 350 is structurally critical: structural modeling shows the 350th side chain is critical for proper protein conformation (PMID: 23360997).

Allele frequency. The pathogenic Sema-domain alleles are **absent/ultra-rare** in population databases (absent from 100 ethnically matched controls in the founding study; rare in gnomAD), consistent with pathogenicity.

Somatic vs germline. **Germline** only. No somatic/mosaic mechanism is implicated.

Functional consequence. Loss of function via mislocalization. The critical functional readout is that F350C "results in abnormal localization of the Sema4A protein, leading to impaired endosomal sorting of molecules indispensable for photoreceptor survival," and reintroducing functional Sema4A rescues the phenotype — the hallmark of loss of function (PMID: 23360997). Human reports include heterozygous (dominant) and recessive presentations, and the phenotypic overlap between CORD10 and RP indicates allele- and dose-dependent expressivity.

Modifier genes / epigenetics / chromosomal abnormalities. No specific modifier genes, epigenetic marks, or cytogenetic abnormalities are established for CORD10. Given SEMA4A's pleiotropy and receptor network (below), modifier effects are biologically plausible but unstudied.

Receptor / interaction network. SEMA4A is a dual neuro-immune "immune semaphorin" that signals through **Tim-2** and **CD72** on leukocytes and **PlexinB1 (PLXNB1)** and **PlexinD1 (PLXND1)** on non-immune cells (PMID: 21595947):

"Sema4A and Sema4D were the first semaphorins found to be expressed on immune cells and were termed 'immune semaphorins'. It is known that Sema4A and Sema4D bind Tim-2 and CD72 expressed on leukocytes and PlexinD1 and B1 present on non-immune cells."

Ontology suggestions: gene HGNC:10730; GO:0007411 (axon guidance), GO:0016192 (vesicle-mediated transport), GO:0032456 (endocytic recycling).

5. Environmental Information

CORD10 is a **monogenic disease with no established environmental cause**. No toxins, radiation, pollutants, occupational exposures, infectious agents, or specific lifestyle factors are documented as causal or triggering. The only mechanistically relevant environmental variables are **ambient light and oxidative stress**, which the SEMA4A-dependent prosaposin-sorting pathway normally buffers to prevent "light-induced photoreceptor apoptosis" (PMID: 22465952). **No infectious agents** are implicated.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **germline missense mutation** in the conserved extracellular **Sema domain** of **SEMA4A** (e.g., p.F350C; p.D345H) **alters the amino-acid side chain critical for protein folding**, which *leads to* an abnormal protein conformation. (*Demonstrated by structural modeling;*

P 23360997

2. The misfolded SEMA4A **is abnormally (mis)localized** within the cell rather than reaching its functional membrane/endosomal compartment. (*Demonstrated;*

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3. Mislocalized SEMA4A **can no longer drive Rab11/FIP2-dependent endosomal sorting** in the **retinal pigment epithelium (RPE)**, which *results in* failure of two downstream cargo-sorting functions. (*Demonstrated in RPE cells;*

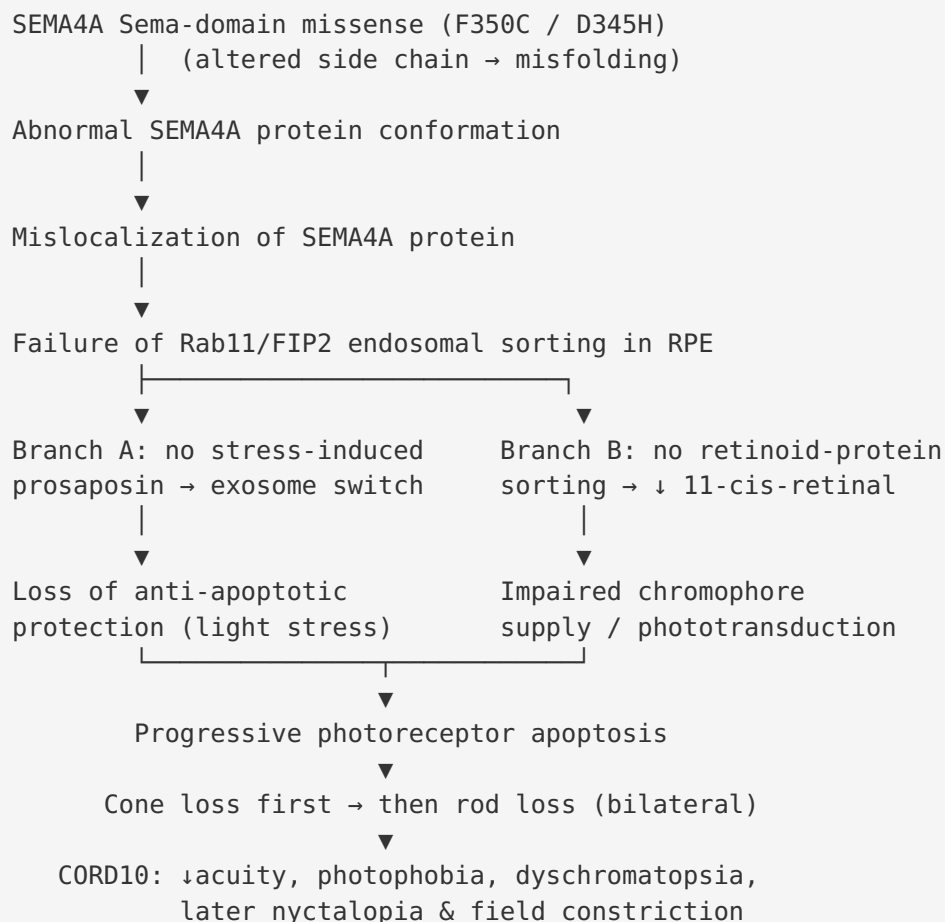
P 22465952

Branch A (stress response): Under oxidative/light stress, SEMA4A normally **switches sorting of the lysosomal precursor prosaposin from lysosomal degradation to exosomal release**; loss of this switch *results in* failure to deliver anti-apoptotic prosaposin, so photoreceptors lose protection against **light-induced apoptosis**.

Branch B (visual cycle): Under baseline conditions, SEMA4A normally **sorts retinoid-binding proteins to regenerate 11-cis-retinal**; loss *results in* impaired chromophore supply to photoreceptors. 4. Combined loss of anti-apoptotic support (Branch A) and chromophore supply (Branch B) *leads to* **photoreceptor dysfunction and progressive apoptosis**. (*Inferred synthesis of A+B; each arm demonstrated.*) 5. Because the cone-rich central macula is affected first, this *leads to* **early cone loss (reduced acuity, photophobia, dyschromatopsia), followed by rod loss (night blindness, peripheral field constriction)** — the clinical cone-rod dystrophy phenotype. (*Clinical pattern; model data show both rod and cone compromise,*

P 15277503

Causal-chain diagram



Detail by category

- **Molecular pathways / cellular processes:** Rab11/FIP2 endocytic recycling and endosomal cargo sorting (GO:0032456 endocytic recycling; GO:0016192 vesicle-mediated transport); regulated exosome biogenesis/secretion; apoptosis (GO:0006915) as the terminal photoreceptor-death process; the visual cycle / retinoid metabolism (11-cis-retinal regeneration).
- **Protein dysfunction:** Conformational destabilization of the Sema β -propeller domain → aberrant trafficking/localization (a trafficking-type loss of function rather than a simple null). CHEBI entities: 11-cis-retinal (CHEBI:16066), retinoid (CHEBI:26537).
- **Tissue-damage mechanism:** Photo-oxidative stress unbuffered by prosaposin exosomal delivery → light-induced photoreceptor apoptosis.

- **Immune involvement:** SEMA4A is an "immune semaphorin," but immune dysfunction is **not** the operative mechanism in CORD10; the retinal phenotype is driven by the RPE sorting defect. SEMA4A pleiotropy (immune, neuronal, cardiovascular, renal) explains why variant class/location determines which phenotype emerges.
- **Molecular profiling:** No CORD10-specific transcriptomic/proteomic/metabolomic datasets identified. SEMA4A expression in RPE can be up-regulated by neural-cell-derived PACAP (PMID: 25515530), indicating physiological regulation of the pathway in the retina.

Upstream vs downstream: The *SEMA4A* mutation and RPE sorting failure are **upstream/initiating**; photoreceptor apoptosis and the clinical cone-then-rod phenotype are **downstream**. The RPE is the primary site of molecular defect even though photoreceptors are the dying cells (a non-cell-autonomous mechanism).

Suggested GO/CL terms: Biological processes — GO:0032456 (endocytic recycling), GO:0006915 (apoptotic process), GO:0007601 (visual perception); cell types — RPE cell (CL:0002586), cone photoreceptor (CL:0000573), rod photoreceptor (CL:0000604).

7. Anatomical Structures Affected

Organ level. The **eye** (UBERON:0000970), specifically the **neural retina** (UBERON:0003902) and the **retinal pigment epithelium** (UBERON:0001782). Disease is **bilateral**. No primary involvement of other organ systems in CORD10 (though SEMA4A is systemically expressed).

Tissue/cell level. Primary molecular lesion is in the **RPE** (CL:0002586), which non-cell-autonomously supports the overlying **photoreceptor layer** — both **cone photoreceptors** (CL:0000573) and **rod photoreceptors** (CL:0000604). In *Sema4A*-null mice: "the outer nuclear layer was reduced to a single row of photoreceptor cells, and the outer plexiform layer was thin and disorganized," with RPE depigmentation and attenuated vessels (PMID: 15277503). Mechanistic localization to RPE: Sema4A "plays a role in Rab11/FIP2-mediated endosomal sorting in retinal pigment epithelial cells to support photoreceptor function" (PMID: 22465952).

Subcellular level. **Endosomes / recycling endosomes** (GO:0005768 endosome; GO:0055037 recycling endosome), **exosomes/multivesicular bodies** (GO:0070062 extracellular exosome), **lysosome** (GO:0005764), and the **plasma membrane** (GO:0005886). The trafficking defect centers on the Rab11/FIP2 recycling-endosome machinery.

Localization. Bilateral; disease begins in the **macula** (UBERON:0002423) / central retina and spreads peripherally in the cone-rod pattern.

8. Temporal Development

Onset. Typically **childhood to early adulthood** (consistent with the CRD class), with insidious, chronic onset. CORD10 is not congenital in the LCA sense, but early cone dysfunction (photophobia, acuity/color problems) is often the first complaint.

Progression. Chronic, progressive, lifelong. Stages: early cone-dominated central dysfunction → intermediate combined cone-rod loss → advanced widespread photoreceptor degeneration with legal blindness. Progression rate is variable (characteristic of IRDs). In the mouse null, "fundus photography performed at 14 weeks of age revealed severe retinal degeneration, attenuated retinal vessels, and depigmentation," indicating a relatively rapid course in the complete-loss-of-function model ([PMID: 15277503](#)).

Patterns. No spontaneous remission; the disease does not relapse-remit — it is steadily progressive. The **critical intervention window** is before substantial photoreceptor loss: gene-augmentation rescue in mice is most effective while photoreceptors remain viable, defining a therapeutic time window analogous to other IRD gene therapies.

9. Inheritance and Population

Epidemiology. CORD10 is a **rare subtype of a rare disease group**. Cone-rod dystrophies collectively account for a minority of IRDs — e.g., **8.0% of 325 patients** in a Southeastern US IRD cohort ([PMID: 36011402](#)):

"The most prevalent dystrophies identified clinically were non-syndromic retinitis pigmentosa (29.8%), Stargardt disease (8.3%), Usher syndrome (8.3%), cone-rod dystrophy (8.0%), cone dystrophy (4.9%), and Leber congenital amaurosis (4.3%)."

CRD overall prevalence is on the order of ~1 in 40,000. IRDs collectively involve **>340 genes**, and *SEMA4A* is an **uncommon** CRD cause. No separate prevalence/incidence figures exist for the *SEMA4A* subtype specifically.

Inheritance. Reported as both **autosomal dominant** (heterozygous Sema-domain missense in the founding families) and **autosomal recessive** (depending on allele); *SEMA4A* variants cause a spectrum spanning CRD and RP. The dual reporting reflects allele-specific functional consequences and incomplete characterization.

Penetrance / expressivity. Variable expressivity is evident from the CRD↔RP phenotypic overlap for *SEMA4A*. Penetrance of the classic Sema-domain alleles appears high given tight segregation with disease in the original families, but precise estimates are unavailable.

Anticipation / mosaicism. No genetic anticipation (not a repeat-expansion disorder). No germline mosaicism documented.

Founder effects / consanguinity. The founding *SEMA4A* families were **Pakistani**, and recessive IRDs are strongly enriched in **consanguineous** Middle Eastern, North African, and South Asian populations with founder mutations. In a North African IRD/ION review, "76.1% of IRD ... investigated families were consanguineous," underscoring the population context in which recessive *SEMA4A* disease is most likely to surface ([PMID: 35551639](#)).

Population demographics / sex ratio / geographic distribution. No sex predilection expected for an autosomal gene. Higher detection likelihood in consanguineous South Asian / Middle Eastern / North African communities. No endemic geographic clustering beyond founder/consanguinity effects.

10. Diagnostics

Clinical/functional tests. - **Electroretinography (ERG)** — the functional hallmark: reduced/abnormal cone responses, with rod involvement developing over time (abnormal ERG, HP:0000512). Mouse data confirm both rod and cone functional compromise ([PMID: 15277503](#)). - **Multimodal retinal imaging** — fundus photography (RPE changes, vessel attenuation, macular atrophy/bull's-eye), **fundus autofluorescence** (RPE/outer-retinal disturbance), and **spectral-domain OCT** (outer-retinal/photoreceptor layer thinning). These are standard CRD workup tools. - **Color-vision testing** and **visual-field perimetry** document dyschromatopsia and progressive field loss. - No specific **blood/urine biomarker**, enzyme assay, or biopsy is diagnostic; diagnosis is clinical + genetic.

Genetic testing (the definitive diagnostic). - **Targeted NGS IRD gene panels** including *SEMA4A* are the recommended first-line molecular test; CRD panels routinely cover dozens-to-hundreds of IRD genes. - **Whole-exome sequencing (WES)** and **whole-genome sequencing**

(WGS) are valuable when panels are negative. Diagnostic yield for CRD is lower than for distinctive phenotypes (e.g., LCA, Bietti dystrophy) because CRD is common and heterogeneous (PMID: 40114034). - **Single-gene testing** of *SEMA4A* is appropriate for cascade testing within known families. - CMA, karyotyping, FISH, mtDNA, and repeat-expansion testing are **not applicable** (CORD10 is a point-mutation disorder).

Clinical criteria / differential diagnosis. Diagnosis rests on the cone-rod ERG pattern plus imaging and confirmatory genetics. Key differentials to exclude include other CRD genes (*ABCA4*, *GUCY2D*, *CRX*, *PROM1*, *CDHR1*, *RPGR*), achromatopsia (*CNGA3/CNGB3*), cone dystrophy with supernormal rod responses (*KCNV2*; PMID: 33706576), and **syndromic** mimics — e.g., ACBD5 deficiency (retinal dystrophy + leukodystrophy; PMID: 42343915) and Alström syndrome (infantile cone-rod dystrophy with cardiomyopathy/obesity; PMID: 9663233). Note that *SEMA4A* was flagged as a candidate novel genotype-phenotype correlation in a large macular/cone-rod cohort (PMID: 29555955).

Screening. No newborn screening. **Cascade/carrier testing** of relatives once the familial *SEMA4A* variant is known; preconception/prenatal options via genetic counseling.

11. Outcome / Prognosis

Survival/mortality. CORD10 is **not life-limiting**; life expectancy is normal. The burden is **visual morbidity**, not mortality.

Morbidity/function. The natural history is **progressive loss of vision to legal blindness**, with major disability in reading, driving, mobility, and independence. Early central (cone) loss is particularly disabling for daily high-acuity tasks; later rod loss adds night blindness and field constriction. No CORD10-specific EQ-5D/SF-36/PROMIS data exist.

Disease course/complications. Complications are those of severe low vision (falls, dependency, reduced quality of life). There is no spontaneous recovery; photoreceptor loss is irreversible once cells die.

Prognostic factors. Residual photoreceptor viability (OCT outer-retinal integrity), age at onset, and rate of ERG decline are the practical prognostic indicators; earlier/more complete loss of function (as in the null mouse) predicts faster, more severe degeneration. Genotype (allele severity/location in the Sema domain) is a biologically-grounded prognostic factor.

12. Treatment

Current standard: supportive. There is **no FDA/EMA-approved disease-specific therapy** for *SEMA4A*-related CORD10. Management is **low-vision rehabilitation** (magnifiers, high-contrast aids, lighting/glare management for photophobia — tinted/UV-blocking lenses), **occupational support**, orientation/mobility training, and **genetic counseling**. NCIT suggestions: supportive care (NCIT:C19054), genetic counseling (NCIT:C15516), low-vision rehabilitation.

Advanced therapeutics (preclinical / class-level). - **Gene augmentation (AAV).** Directly validated for *SEMA4A*: "Sema4A gene transfer successfully prevents photoreceptor degeneration in Sema4A(F350C/F350C) and Sema4A(-/-) mice" — strong rationale for AAV *SEMA4A* augmentation in loss-of-function CORD10 ([PMID: 23360997](#)). AAV subretinal gene augmentation is the leading, field-proven IRD strategy (cf. voretigene neparvovec for *RPE65*). - **Gene editing (CRISPR/Cas9).** For any autosomal-dominant gain-of-function/dominant-negative *SEMA4A* allele, mutation-specific correction or allele ablation ("ablate-and-replace") is the emerging approach; CRISPR "offers the potential for one-time, mutation-specific gene correction or allele ablation" for CRD and achromatopsia, addressing the limitations of AAV augmentation in dominant disease ([PMID: 42264060](#)). - **Gene-independent neuroprotection.** AAV-delivered rod-derived cone viability factors (RdCVF/RdCVFL from *NXNL1*) preserve cones and reduce lipid peroxidation in RP models and are in clinical trial (PRODYGY, NCT05748873) — a mutation-agnostic strategy potentially relevant to CRD cone rescue ([PMID: 41769936](#)).

Pharmacotherapy / pharmacogenomics / immunotherapy / surgery. No disease-specific drugs, pharmacogenomic guidance, immunotherapies, or surgical interventions are established for CORD10. Standard ophthalmic care may be needed for incidental comorbidities.

Personalized medicine. Treatment is inherently **genotype-guided**: loss-of-function alleles → augmentation; dominant alleles → editing/ablation. Confirming the precise *SEMA4A* variant and its functional class is prerequisite to any future targeted therapy.

13. Prevention

Primary prevention. No way to prevent a germline mutation. The main lever is **reproductive risk reduction** via genetic counseling, carrier/cascade testing, and reproductive options (preimplantation genetic testing, prenatal diagnosis) in families with a known *SEMA4A* variant.

Secondary prevention. **Cascade genetic screening** of at-risk relatives enables earlier diagnosis and candidacy for emerging therapies while photoreceptors remain viable (the key intervention window).

Tertiary prevention. Low-vision rehabilitation and photoprotection (glare/UV control) to maximize residual function and daily safety. Photoprotection is mechanistically rational given the light/oxidative-stress component, though unproven for CORD10 specifically.

Immunization / public-health / environmental interventions. Not applicable (non-infectious, non-environmental Mendelian disease).

Counseling. Genetic counseling is central — discussing inheritance (AD vs AR per allele), recurrence risk, variable expressivity, and reproductive options. In consanguineous communities, consanguinity education and carrier screening are especially relevant ([PMID: 35551639](#)).

14. Other Species / Natural Disease

Taxonomy / orthologs. *SEMA4A* is conserved across mammals. Mouse *Sema4a* (NCBI Gene ID 20352) is the principal disease-modeling ortholog; orthologs exist in rat, zebrafish, and other vertebrates (NCBI Taxonomy: *Mus musculus* txid10090; *Homo sapiens* txid9606).

Natural disease in other species. No well-characterized naturally-occurring *SEMA4A* cone-rod dystrophy is documented in companion animals or wildlife (no OMIA entry identified for *SEMA4A* CRD). The disease is studied via engineered models rather than spontaneous animal disease.

Comparative biology. The RPE endosomal-sorting / photoreceptor-support function of *SEMA4A* appears evolutionarily conserved, since mouse knockout and knock-in faithfully reproduce human retinal degeneration — evidence that the disease mechanism is conserved across mammals.

Transmission. Not applicable — non-communicable, non-zoonotic genetic disease.

15. Model Organisms

Mammalian (mouse) — the principal and best-validated models.

Model	Type	Key phenotype	Reference
<i>Sema4A</i> —/— knockout	Null	Severe retinal degeneration by 14 wk; ONL reduced to a single photoreceptor row; thin/disorganized OPL; RPE depigmentation; attenuated vessels; both rod & cone ERG compromised	PMID: 15277503
<i>Sema4A</i> F350C knock-in	Patient-allele knock-in	Reproduces retinal degeneration; protein mislocalization; impaired endosomal sorting	PMID: 23360997
<i>Sema4A</i> D345H knock-in	Patient-allele knock-in	No retinal degeneration (allele-specific)	PMID: 23360997
<i>Sema4A</i> R713Q knock-in	Patient-allele knock-in	No retinal degeneration	PMID: 23360997

In vitro / cellular. RPE cell systems (e.g., ARPE-19) were used to define the Rab11/FIP2 endosomal-sorting function and prosaposin/retinoid-sorting switch, and to show PACAP-induced SEMA4A up-regulation (PMID: [22465952](#); PMID: [25515530](#)). Patient-derived iPSC-RPE is an emerging platform (demonstrated for other IRD genes, e.g., RLBP1; PMID: [39385467](#)).

Phenotype recapitulation. The mouse models recapitulate the core human disease — **progressive degeneration of both cone and rod photoreceptors** with RPE involvement — and critically demonstrate **allele specificity** (only F350C, not D345H or R713Q, caused degeneration in mice), a caveat for interpreting human genotype-phenotype correlations.

Applications. These models established the loss-of-function mechanism (RPE endosomal sorting), enabled structural modeling of the pathogenic residue, and provided **proof-of-concept gene-therapy rescue** (AAV *Sema4A*), directly informing therapeutic strategy.

Limitations. Mouse retinas lack a macula/fovea (the cone-rich region central to human CRD), so the central-vision aspects of CORD10 are not modeled. Allele discordance (D345H pathogenic in humans but not in the mouse knock-in) highlights species/genetic-background differences.

Resources: MGI (*Sema4a*), IMPC/IMSR for alleles; Cellosaurus/ATCC for ARPE-19.

Mechanistic Model / Interpretation

CORD10 is best understood as a **non-cell-autonomous, trafficking-based loss-of-function retinopathy**: the gene defect acts in the **RPE**, but the cells that die are the **photoreceptors** the RPE is supposed to sustain. SEMA4A is a molecular "switch operator" on the RPE's Rab11/FIP2 recycling-endosome platform, toggling cargo between two survival-critical destinations depending on cellular stress — exosomal prosaposin secretion (anti-apoptotic, under oxidative/light stress) versus retinoid-protein sorting for 11-cis-retinal regeneration (visual cycle, at baseline). A Sema-domain missense mutation misfolds and mislocalizes the protein, disabling the switch. The retina thus suffers a **double hit**: chronic chromophore shortfall plus loss of stress-protection, converging on photoreceptor apoptosis. Cones, concentrated in the metabolically demanding central macula, decompensate first, giving the cone-rod clinical sequence.

The therapeutic corollary is clean: because the defect is loss of function and the pathway is restorable, **replacing functional SEMA4A rescues the phenotype** — proven in two independent mouse genotypes. This makes CORD10 a strong candidate for AAV gene augmentation, with CRISPR editing reserved for any dominant allele.

Evidence Base

PMID	Study (abbrev.)	Role in this report
16199541	Novel SEMA4A mutations in retinal degeneration	Establishes <i>SEMA4A</i> as causal gene; identifies p.D345H, p.F350C in Sema domain
23360997	Point mutation in Semaphorin 4A; defective endosomal sorting	Mechanism + gene-therapy rescue; F350C mislocalization; allele specificity
22465952	Endosomal sorting by Sema4A in RPE supports photoreceptor survival	Defines RPE Rab11/FIP2 sorting, prosaposin switch, 11-cis-retinal regeneration
15277503	Severe retinal degeneration with disruption of Sema4A	Knockout phenotype; rod+cone compromise; retinal histology
21595947	Neuroimmune semaphorins 4A and 4D	SEMA4A receptor network (Tim-2, CD72, PlexinB1/D1); pleiotropy
25515530	Up-regulation of SEMA4A in RPE by PACAP	SEMA4A expression/regulation in human RPE
42264060	CRISPR strategies for cone-rod dystrophy and achromatopsia	Therapeutic landscape; editing for dominant alleles
36011402	IRD in Southeastern US	Epidemiology: CRD ~8% of IRDs
35551639	North African IRD/ION families	Consanguinity (76.1%) and founder effects
29555955	251 macular/cone-rod dystrophy patients	<i>SEMA4A</i> as candidate genotype-phenotype correlation
41769936	AAV RdCVF/RdCVFL for RP	Gene-independent cone-protection strategy (PRODYGY trial)
40114034	Asian IRD diagnostic yield	CRD harder to diagnose (heterogeneous)
33706576 ; 42343915 ; 9663233	KCNV2 CDSRR; ACBD5; Alström	Differential diagnosis

Evidence-type summary: Human clinical/genetic (16199541, 29555955, epidemiology papers); model organism (23360997, 15277503); in vitro/cellular (22465952, 25515530); computational/structural modeling (23360997). The causal gene, mechanism, and gene-therapy rescue are supported by **direct, convergent human-genetic + model-organism + cell-biology evidence**.

Limitations and Knowledge Gaps

1. **Small human evidence base.** *SEMA4A* CORD10 rests largely on the original family report plus candidate findings; there is no large CORD10 patient cohort, so **penetrance, expressivity, natural-history rate, and per-phenotype frequencies are not precisely quantified**.
 2. **Allele discordance.** p.D345H is pathogenic in humans but did **not** cause degeneration in the mouse knock-in, while F350C did — leaving uncertainty about the pathogenic mechanism of non-F350C alleles and about human-mouse translatability.
 3. **Inheritance ambiguity.** Both dominant and recessive reports exist; the dose-dependence and dominant-vs-recessive behavior of specific alleles are not fully resolved, which directly affects therapeutic choice (augmentation vs editing).
 4. **No CORD10-specific omics.** No transcriptomic/proteomic/metabolomic/single-cell datasets specific to CORD10 patients were identified.
 5. **No CORD10-specific clinical imaging/ERG series or QoL data** — phenotype characteristics are extrapolated from the CRD class and mouse data.
 6. **Therapeutics are preclinical.** Gene-augmentation rescue is mouse-only; no human trial for *SEMA4A*.
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Proposed Follow-up Experiments / Actions

1. **Variant functional classification.** Systematically test each reported *SEMA4A* allele (D345H, F350C, R713Q, and any new variants) in human iPSC-RPE for trafficking/localization and prosaposin/retinoid-sorting phenotypes to resolve dominant-vs-recessive and loss-vs-dominant-negative behavior — the key branch point for therapy selection.

2. **Patient registry & natural-history study.** Aggregate *SEMA4A* cases via GeneMatcher/IRD consortia to quantify onset, progression rate, penetrance, expressivity, and genotype-phenotype correlation with longitudinal OCT/ERG.
3. **AAV-*SEMA4A* dose-ranging & window study.** Define the therapeutic time window and vector/promoter (RPE-specific) for augmentation in F350C knock-in mice, as IND-enabling work toward a first-in-human trial.
4. **CRISPR allele-ablation proof-of-concept** for any confirmed dominant *SEMA4A* allele, benchmarking editing efficiency and off-target profile.
5. **Mechanistic completion.** Directly test, in RPE models and in vivo, whether prosaposin supplementation or antioxidant/photoprotective interventions slow degeneration — validating the oxidative-stress branch as a druggable, mutation-agnostic target.
6. **Structural biology.** Solve/model the *SEMA4A* Sema-domain structure with pathogenic residues to explain allele-specific severity and guide variant interpretation.

Report compiled from 9 confirmed findings and 22 reviewed papers over a 5-iteration autonomous investigation. Primary evidence anchors:

P 16199541

(causal gene),

P 23360997

(mechanism + rescue),

P 22465952

(RPE sorting pathway),

P 15277503

(knockout phenotype).