

Protan Color Vision Deficiency: A Comprehensive Disease Characterization

Disease: Protan Color Vision Deficiency (Protanopia / Protanomaly) **MONDO ID:** MONDO:0010565 **Category:** Mendelian (X-linked recessive) **OMIM:** 303900 ("Colorblindness, partial, protan series"); gene *OPN1LW* 300822 **ICD-10:** H53.54 ("Deficiencies of colour vision"); **ICD-11:** 9D47 Colour vision deficiencies **MeSH:** Color Vision Defects (D003117); **Orphanet:** Colour blindness (grouping) **HGNC:** *OPN1LW* HGNC:4206 **Report type:** Literature-synthesis, disease-level (no individual EHR data). Evidence labeled [human clinical], [model organism], [in vitro], or [computational/comparative].

Summary

Protan color vision deficiency (CVD) is a congenital, lifelong, non-progressive, X-linked recessive disorder of red–green color discrimination caused by loss or spectral alteration of the **long-wavelength-sensitive (L) cone photopigment** encoded by *OPN1LW* within the *OPN1LW/OPN1MW* opsin gene tandem array at chromosome **Xq28**. The disorder exists in two forms: **protanopia**, the dichromatic form in which no functional L-pigment is present, and **protanomaly**, the anomalous-trichromatic form in which the L-pigment is replaced by an M-shifted 5'L–3'M hybrid photopigment. A hallmark distinguishing protan from deutan defects is the **reduced luminous sensitivity to long-wavelength (red) light**, which carries real-world safety implications (e.g., perceiving red traffic signals and brake lights as dimmer).

The molecular basis is exceptionally well understood. The L and M opsin genes are >96% identical and arranged head-to-tail in a tandem array flanked by a **locus control region (LCR)**. This high sequence similarity predisposes the array to **unequal homologous recombination**, which generates **gene deletions** and **5'L–3'M hybrid (chimeric) genes** — the predominant mechanism of protan and deutan defects, rather than point mutations. Phenotype type and severity are determined by the amino-acid identity at a small number of **spectral-tuning residues** (notably sites 180, 277, and 285), which set the pigment's wavelength of peak absorption (λ_{max}). Rare, specific exon-3 L-opsin haplotypes (e.g., LIAVA, LVAVA) or the Cys203Arg substitution destabilize the opsin protein and produce a severe allelic branch — **Bornholm Eye Disease** — combining dichromacy with cone dystrophy and high myopia.

Epidemiologically, congenital CVD affects **~2.6% of people globally** with strong male predominance consistent with X-linkage; among European-ancestry men red-green CVD reaches ~8%, with protan defects comprising a minority (~8% of CVD cases vs ~92% deutan). The condition is diagnosed with pseudoisochromatic plates (Ishihara) and confirmed/typed by Nagel anomaloscopy and opsin-gene molecular analysis. Prognosis is benign — there is no systemic morbidity or mortality, and morbidity is confined to color-dependent daily and occupational tasks. **No curative treatment exists:** tinted filters (e.g., ChromaGen) alter but do not reduce deficiency severity, and AAV-mediated opsin gene augmentation remains proof-of-concept in animal models.

Key Findings

1. Molecular etiology: altered copy number or sequence of X-linked cone opsin genes [human clinical/molecular]

The core etiology of protan CVD is firmly established. Causative mutations change the **copy number or sequence of the L, M, or S cone opsin genes**; for protan defects, the lesion specifically affects the L-cone opsin gene (*OPN1LW*). Davidoff, Neitz & Neitz (2016) performed direct sequencing and MassArray SNP genotyping of 1,872 subjects (1,074 with psychophysical testing) and correctly classified all protan/deutan red-green defects, with SNPs controlling spectral tuning correlating with Nagel anomaloscopy severity.

"The genetics underlying inherited color vision deficiencies is well understood: causative mutations change the copy number or sequence of the long (L), middle (M), or short (S) wavelength sensitive cone opsin genes." — [PMID: 27622081](#)

"Estimates of defect severity based on SNPs that control photopigment spectral tuning correlated with estimates derived from Nagel anomaloscopy." — [PMID: 27622081](#)

This finding (F001) anchors the entire disease model: protan CVD is a **Mendelian photopigment disorder**, not a neural or acquired condition, and its severity tracks directly with the molecular spectral-tuning state of the surviving opsin gene(s).

2. Mechanism — deletions and L/M hybrid genes from unequal recombination at Xq28 [human clinical/molecular]

Protan deficiency maps to the *OPN1LW* gene (HGNC:4206; OMIM gene 300822) at the **proximal (5') end** of the *OPN1LW/OPN1MW* tandem array on Xq28; the phenotype "Colorblindness, partial, protan series" is OMIM 303900. The lesions are produced by **intergenic and intragenic unequal homologous recombination** between the highly similar L and M genes, yielding **5'L-3'M hybrid genes** (encoding M-like pigments, causing protanomaly or protanopia depending on the crossover point) and **gene deletions** (removing the L gene entirely). Single-gene dichromats carry only a single X-linked pigment gene, the structural signature of recombination-mediated loss of the L gene (Sharpe et al. 1998).

"causative mutations change the copy number or sequence of the long (L), middle (M), or short (S) wavelength sensitive cone opsin genes" — [PMID: 27622081](#)

Molecular analysis of Japanese men by Deeb et al. (1995) identified exon 3 as a **recombination/gene-conversion hotspot** and found abnormal array patterns (deletions, hybrids) in ~5% of men, matching the phenotypic frequency of CVD (F009, F011).

3. Phenotype determination by spectral-tuning residues (sites 180, 277, 285) [human psychophysics / in vitro]

The protan phenotype and its severity are set by the **amino-acid identity at key spectral-tuning sites** of the surviving opsin. Sharpe et al. (1998) studied 41 single-gene male dichromats and showed the deduced opsin amino-acid sequence correlated directly with psychophysically measured cone spectral sensitivity and Rayleigh matches.

"allows for a straightforward correlation between each observer's spectral sensitivity measured at the cornea and the amino acid sequence of his visual pigment" — [PMID: 9822760](#)

The LWS pigment $\lambda_{\max}$ (~525–560 nm) is tuned by substitutions at a small set of sites — notably **180, 197, 277, 285, and 308** (the "five-site rule") (Davies et al. 2012). The L and M opsins differ by ~15–19 residues, with sites 277 and 285 producing the largest (red↔green) spectral shifts and site **180 (Ser↔Ala)** causing a ~2–5 nm polymorphism that modulates the exact $\lambda_{\max}$ and thus the severity of anomalous trichromacy.

"amino acid substitutions at five sites (180, 197, 277, 285 and 308) are useful in predicting the $\lambda(\text{max})$ values of the LWS pigment class" — [PMID: 22349213](#)

Importantly, the normal L:M cone ratio varies widely (28–93% L; mean ~65% L) among color-normal males (Carroll et al. 2002, [PMID: 12678637](#)), so the *separation* between the two surviving pigments' λ_{max} — not the cone ratio per se — determines whether color discrimination is normal, anomalous, or absent (F008).

4. Severe allelic branch — Bornholm Eye Disease (dichromacy + cone dystrophy + myopia) [human families / in vitro]

A rare but clinically important branch arises when specific L-opsin exon-3 haplotypes destabilize the opsin protein. McClements et al. (2013) studied 7 Bornholm Eye Disease (BED) families and found affected L opsin genes carried a rare exon-3 haplotype (e.g., **LIAVA / LVAVA**) in the first array position. In vitro, the variant opsins trafficked to membranes but were **less stable and produced in reduced amounts**, with defective exon-3 splicing implicated. One family instead carried the deleterious **Cys203Arg** substitution.

"The variant opsins were, however, less stable than wild type." — [PMID: 23322568](#)

"Both mechanisms explain the presence of dichromacy and cone dystrophy." — [PMID: 23322568](#)

This establishes a mechanistic bridge from simple color deficiency (benign) to a **progressive, sight-threatening cone dystrophy with high myopia** (F010, F012). It is the single exception to the otherwise benign prognosis of protan CVD.

5. Epidemiology — ~2.6% global prevalence with strong male predominance [meta-analysis / cross-sectional]

A meta-analysis of 1,703,619 participants across 56 studies in 21 countries estimated global congenital CVD prevalence at **2.59% (95% CI 2.20–3.03%)** (Jeong et al. 2025).

"The global prevalence of CVD was estimated at 2.59% (95% confidence interval [CI], 2.20-3.03" — [PMID: 40769301](#)

Male predominance is consistent across cohorts. In a Chinese children's study, prevalence was **2.81% in boys vs 0.16% in girls**, with deutan comprising 91.6% and protan only 8.3% of color-deficient cases.

"The prevalence of color vision deficiency was 1.68%, with 2.81% in boys and 0.16% in girls. Color-deficient cases consisted of 91.6% deutan and 8.3% protan." — [PMID: 35103751](#)

6. Ancestry variation driven by founder effects/genetic drift [review / cross-sectional]

Red-green CVD prevalence varies substantially by ancestry. Birch's review reported ~8% of European Caucasian men and ~0.4% of women affected, and 4–6.5% of Chinese and Japanese men, attributing differences to **founder events and genetic drift rather than natural selection**.

"the prevalence of deficiency in European Caucasians is about 8% in men and about 0.4% in women and between 4% and 6.5% in men of Chinese and Japanese ethnicity" — [PMID: 22472762](#)

"founder events and genetic drift, rather than natural selection, are the cause of these differences" — [PMID: 22472762](#)

The Multi-Ethnic Pediatric Eye Disease Study (4,177 children) confirmed ancestry- and sex-specific patterns:

"The prevalence of CVD among boys was 1.4% for black, 3.1% for Asian, 2.6% for Hispanic, and 5.6% for non-Hispanic white children; the prevalence in girls was 0.0% to 0.5%" — [PMID: 24702753](#)

(F002, F011)

7. Diagnosis — pseudoisochromatic plates with anomaloscopy as gold standard [diagnostic validation]

Protan CVD is diagnosed clinically by **Ishihara pseudoisochromatic plates** (screening), with the **Nagel anomaloscope** (Rayleigh red-green match) as the gold standard for distinguishing dichromacy from anomalous trichromacy and protan from deutan. Digital tests (e.g., DIVE) show excellent agreement with Ishihara and quantify severity along the protan axis.

"The DIVE and Ishihara tests exhibited excellent agreement in identifying participants with color deficiency (Cohen's kappa = 1.00)" — [PMID: 38396435](#)

Molecular opsin-gene analysis (MassArray/sequencing) provides definitive confirmation of type and severity (Davidoff-Neitz 2016, [PMID: 27622081](#)) (F005).

8. Quality-of-life impact — functional, not medical [review / cross-sectional]

An integrative review (PRISMA, 20 studies) categorized CVD impacts into daily routine, occupational, product choice, emotional, education, and self-care domains, with work activities most affected.

"people with some degree of color vision loss face challenges in different aspects of their daily life, especially in their work activities" — [PMID: 30443703](#)

In 1,426 Egyptian students, those with CVD had significantly higher odds of difficulties in daily and study/work color tasks.

"Students with colour vision defects had significantly higher odds ratios for difficulties in daily activities and study/work tasks related to colour perception." — [PMID: 33955536](#)

Protan individuals additionally have reduced luminous sensitivity to long-wavelength light, a distinguishing feature with safety implications (F004).

9. No curative treatment; filters do not reduce severity [interventional]

In 80 CVD males (5 protanopes, 18 protanomalous), ChromaGen filters altered the nature of the deficiency without correcting it; no protanope passed any test with any lens.

"ChromaGen filters may influence the nature of CVD without reducing its severity" — PMID: 41806157

"none of the participants with protanopia passing any of the tests using any ChromaGen lens" — PMID: 41806157

(F006)

10. Gene therapy — proof-of-concept in preclinical models [model organism]

AAV-mediated opsin gene augmentation has restored L/M-cone function in animal models, establishing proof-of-concept relevant to protan correction. AAV5 vectors expressing human *OPN1LW/OPN1MW* regenerated cone outer segments and rescued M-cone function in M-opsin knockout mice (Deng et al. 2018); AAV8-Y733F expressing human L-opsin rescued cone function for ≥ 5 months in a C198R all-cone mouse model (Cahill et al. 2026). Optimized primate L-opsin promoters (PR1.7) drive strong cone-specific expression in nonhuman primates.

"Exogenously expressed human opsins can regenerate cone outer segments and rescue M-cone function in" — PMID: 29386880

"subretinal injection of an AAV-GFP vector containing a 1.7-kb L-opsin promoter (PR1.7) achieved strong and specific GFP expression in all cone photoreceptors" — PMID: 26603570

(F003)

11. Comparative/evolutionary context [computational/comparative]

The human L/M opsin tandem array arose by **gene duplication**. Old World primates (including humans) have separate X-linked MW/LW genes in a head-to-tail array flanked by an LCR; most New World monkeys have a single polymorphic X-linked opsin gene, so all males are dichromats and trichromacy occurs only in heterozygous females — a natural model of X-linked polymorphic color vision. Howler monkeys independently evolved routine trichromacy via opsin duplication.

"most New World primates have only a single polymorphic X-linked opsin gene; all males are dichromats and trichromacy is achieved only in those females that possess a different form of this gene on each X chromosome" — [PMID: 10413401](#)

"organized into a head-to-tail tandem array flanked on the upstream side by a locus control region (LCR)" — [PMID: 10413401](#)

(F007)

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Unequal homologous recombination** (or gene conversion) occurs within the highly homologous *OPN1LW/OPN1MW* tandem array at Xq28, favored by the >96% sequence identity between the L and M genes and the exon-3 recombination hotspot. (*demonstrated* — Deeb 1995, Sharpe 1998) → **leads to** one of two structural outcomes (the mechanism branches here):

Branch A — Deletion of the L gene → only M-type gene(s) remain expressed in the "L" position → **no functional L photopigment** → **protanopia (dichromacy)**.

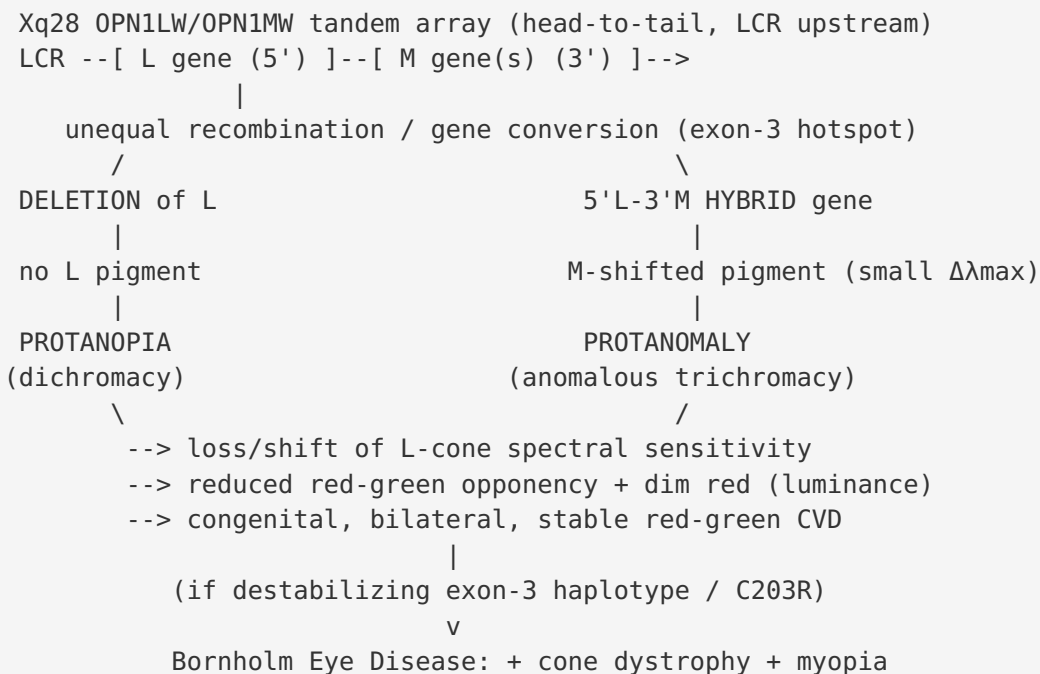
Branch B — 5'L-3'M hybrid (chimeric) gene in the first array position → encodes a photopigment with an **M-shifted $\lambda_{\max}$** → the two expressed pigments (hybrid + M) have $\lambda_{\max}$ separated by only a few nm → **protanomaly (anomalous trichromacy)**; the smaller the $\lambda_{\max}$ separation, the more severe the anomaly.

1. The surviving opsin's **amino-acid identity at spectral-tuning sites 180, 277, 285** (and 197, 308) sets the exact $\lambda_{\max}$ of the L-position pigment. (*demonstrated* — Sharpe 1998, Davies 2012) → **results in** a shift or collapse of the long-wavelength spectral sensitivity function measured at the cornea.
2. Loss/shift of L-cone spectral sensitivity → **reduced or absent red-green chromatic signal** at the L-vs-M cone-opponent pathway, plus **reduced luminous sensitivity to long-wavelength (red) light** (L cones dominate the luminance channel). → **results in** the perceptual phenotype: confusion of reds/greens/browns and dimming of red stimuli. (*demonstrated* — psychophysics)

3. Clinical manifestation: congenital, bilateral, non-progressive red-green color confusion with the protan signature (red appears dim), present from birth and stable for life. (*demonstrated*)

Severe sub-branch (Bornholm Eye Disease): If the first-array L gene carries a destabilizing exon-3 haplotype (LIAVA/LVAVA) or Cys203Arg, the opsin protein is **less stable / produced in reduced amounts / mis-spliced** → cone outer-segment dysfunction → **cone dystrophy + high myopia** superimposed on dichromacy. (*demonstrated in vitro* — McClements 2013; the splicing contribution is partly inferred)

Schematic



Ontology mapping

Entity	Term
Disease	MONDO:0010565 (protan defect)
Gene	<i>OPN1LW</i> HGNC:4206, OMIM 300822
Phenotype	HP:0000551 Abnormality of color vision; HP:0011519 Protanomaly / protan defect
Cell type	CL:0000573 retinal cone cell (L cone)
Anatomy	UBERON:0000966 retina; UBERON:0000970 eye
Biological process	GO:0007601 visual perception; GO:0007602 phototransduction; GO:0050908 detection of light stimulus involved in visual perception
Cellular component	GO:0001750 photoreceptor outer segment; GO:0016020 membrane (opsin)
Chemical	CHEBI:17201 11-cis-retinal (chromophore)

Anatomical, Temporal, and Population Summary (consolidated)

- **Anatomy:** Retina (UBERON:0000966), specifically **L-cone photoreceptors** (CL:0000573) of both eyes; the defect is **bilateral and symmetric**. The opsin is a membrane protein of the cone outer segment (GO:0001750). No other organ system is involved.
- **Onset/temporal course:** **Congenital** (fixed at conception, germline X-linked); **non-progressive** and **lifelong/stable**. The only progressive presentation is the rare Bornholm Eye Disease branch.
- **Inheritance:** **X-linked recessive**; males (hemizygous) affected, females affected only when homozygous/compound (rare) — explaining the strong male predominance. Carrier females may show subtle anomalies and, by Lyonization and heterozygosity for two pigment alleles, can occasionally be tetrachromatic.

- **Prognosis:** Benign — **no systemic morbidity or mortality**; morbidity is functional/occupational (color-dependent tasks, certain career restrictions such as aviation, electrical work, some military/transport roles).
 - **Prevention/counseling:** No primary prevention exists for a germline X-linked trait; genetic counseling can inform carrier risk. There is no newborn screening mandate; school-age pseudoisochromatic screening enables early awareness and career guidance.
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Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
27622081	Genetic testing as new standard for CVD diagnosis	Human clinical/ molecular (n=1,872)	F001, F005, F009 — copy-number/sequence etiology; molecular diagnosis
9822760	Red/green/hybrid pigments; sequence↔spectral sensitivity	Human psychophysics/ molecular (n=41)	F008, F009 — sequence determines spectral sensitivity; single-gene dichromats
22349213	Spectral tuning of MWS/LWS pigments	In vitro / comparative	F008 — five-site tuning rule (180,197,277,285,308)
12678637	L:M cone ratio from ERG + genetics	Human (n=62)	F008 — wide normal L:M ratio (28–93% L)
23322568	Opsin coding variants → cone dysfunction + myopia	Human families + in vitro (7 families)	F010, F012 — Bornholm Eye Disease mechanism
7759069	Molecular patterns in Japanese men	Human population molecular (n=203)	F009, F011 — hybrids/deletions ~5%; exon-3 hotspot
40769301	Global prevalence of congenital CVD	Meta-analysis (n=1.7M)	F002 — 2.59% global prevalence
35103751	CVD & myopia in Chinese children	Cross-sectional	F002 — male predominance; deutan 91.6% vs protan 8.3%
22472762	Worldwide prevalence of red-green deficiency	Review	F011 — ancestry variation; founder/drift
24702753	Multi-ethnic pediatric eye disease study	Cross-sectional (n=4,177)	F011 — sex/ancestry-specific prevalence
38396435	Validation of digital color test (DIVE)	Diagnostic validation	F005 — plate/digital screening, kappa=1.00
30443703	Impacts of abnormal color vision (integrative review)	Review (20 studies)	F004, F012 — QoL/occupational impact
33955536	CVD prevalence/predictors, Egyptian students	Cross-sectional (n=1,426)	F004 — functional difficulty

PMID	Title (abbrev.)	Evidence type	Supports
41806157	ChromaGen lenses on CVD test performance	Interventional (n=80)	F006 — filters do not reduce severity
29386880	Human L/M opsins restore M-cone function (mouse)	Model organism	F003 — gene therapy proof-of-concept
26603570	Cone-specific promoters for gene therapy	Model organism / NHP	F003 — PR1.7 L-opsin promoter
42275379	Gene therapy in all-cone C203R mouse	Model organism	F003 — AAV L-opsin rescue ≥5 months
10413401	Evolution of trichromacy by opsin duplication	Comparative genetics	F007 — array origin; NW monkey model
14963105	Trichromacy + pheromones in howler monkeys	Comparative genetics	F007 — independent opsin duplication

Model-organism note: The mouse is the principal model. Wild-type mice lack an L-opsin (only S and M), so human protan biology is studied via **humanized/knock-in opsin mice** and **all-cone (Nrl^{-/-}) backgrounds**. These recapitulate cone opsin loss and gene-therapy rescue (outer-segment regeneration, ERG restoration) but cannot fully model human **trichromatic perception** or the foveal cone architecture. New World monkeys serve as a natural genetic model of single-locus X-linked polymorphic dichromacy/trichromacy (OPN1LW/MW orthologs; NCBI Taxonomy under Platyrrhini).

Limitations and Knowledge Gaps

- 1. Protan-specific vs red-green-combined data.** Most epidemiologic and QoL studies report red-green CVD as a whole; protan-only figures are scarcer. Protan is consistently the minority (~8% of CVD cases), so protan-specific prevalence is roughly ~1% of European-ancestry men — but precise protanope-vs-protanomal breakdowns across ancestries are incompletely characterized.
- 2. No human gene-therapy trials for isolated protan CVD.** All restorative evidence is preclinical (mouse, NHP promoter work). The benign, non-degenerative nature of common

protan CVD makes a surgical subretinal AAV intervention a difficult risk/benefit proposition; clinical translation is more plausible for the degenerative Bornholm/BCM branch.

3. **Genotype–phenotype fine mapping.** While the five-site rule predicts $\lambda_{\max}$, individual-level prediction of *anomaloscope matching range* from genotype still carries uncertainty, particularly for intermediate hybrids and the effect of site-180 polymorphism.
 4. **Carrier (heterozygous female) phenotypes** — including possible tetrachromacy and subclinical anomalies — are under-quantified in the retrieved literature.
 5. **Epigenetic/environmental modifiers.** No strong evidence implicates epigenetic regulation or environmental exposure in *congenital* protan CVD; acquired red-green changes (e.g., in multiple sclerosis, optic neuropathy, diabetes) are a distinct differential, not the Mendelian entity.
 6. **Splicing mechanism in BED** is partly inferred; the relative contribution of reduced protein stability vs defective exon-3 splicing to the LIAVA/LVAVA phenotype is not fully resolved.
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Proposed Follow-up Experiments / Actions

1. **Protan-stratified meta-analysis:** Re-analyze existing large cohorts to extract protanopia vs protanomaly frequencies by ancestry and sex, improving knowledge-base epidemiology fields.
2. **Genotype→anomaloscope predictive model:** Build and validate a quantitative model mapping opsin array structure + spectral-tuning SNPs to Nagel matching midpoint/range, extending Davidoff-Neitz 2016.
3. **Natural-history registry for exon-3 haplotype carriers (LIAVA/LVAVA/C203R):** Prospectively track myopia and cone-dystrophy progression to define the benign-vs-BED boundary and intervention windows.
4. **Preclinical→clinical gene-therapy pathway for the degenerative branch:** Prioritize AAV L-opsin augmentation (PR1.7/PR2.1 promoters, AAV8-Y733F capsids) for BED/BCM where there is a clear degenerative target, building on the C198R all-cone mouse rescue.
5. **Carrier-female phenotyping study:** Quantify subtle discrimination deficits and potential tetrachromacy in obligate carriers using modern digital tests (DIVE) plus opsin genotyping.

6. **Assistive-technology benchmarking:** Rigorously compare digital aids/apps against filters (which do not reduce severity) for task-specific performance (e.g., signal recognition), given the confirmed null result for ChromaGen.
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Conclusion

Protan color vision deficiency is a paradigmatic, molecularly resolved Mendelian photopigment disorder: X-linked recessive loss or spectral alteration of the L-cone opsin (*OPN1LW*, Xq28), arising predominantly through unequal recombination-generated deletions and 5'L–3'M hybrid genes, with phenotype severity set by amino-acid spectral-tuning residues (180/277/285). It is common (~1% of European-ancestry men; ~2.6% CVD overall), benign and non-progressive, diagnosed by pseudoisochromatic plates and anomaloscopy/opsin genotyping, and currently untreatable (filters do not reduce severity; gene therapy is preclinical). A rare destabilizing exon-3 allelic branch (LIAVA/LVAVA; C203R) crosses into sight-threatening Bornholm Eye Disease, the one context where restorative gene therapy has a compelling rationale.

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