

Tritan Color Vision Deficiency (MONDO:0008610): Comprehensive Disease Characteristics Report

Summary

Tritan Color Vision Deficiency (tritan CVD; MONDO:0008610; OMIM 190900) is a rare, congenital, autosomal dominant disorder of the blue-yellow (short-wavelength) axis of color vision. It is caused by heterozygous mutations in **OPN1SW**, the single autosomal gene on chromosome 7q32.1 that encodes the short-wavelength-sensitive (S) cone opsin (HGNC:1012; UniProt P03999). Because OPN1SW — unlike the tandemly arranged X-linked L/M opsin genes (OPN1LW/OPN1MW) — is a solitary autosomal gene, a single pathogenic allele is sufficient to disrupt S-cone function, giving the disorder its autosomal dominant inheritance pattern and roughly equal sex distribution. Pathogenic missense alleles (L56P, G79R, S214P, P264S, R283Q, T190I) are thought to cause S-opsin misfolding/dysfunction, while splice-disrupting variants act through haploinsufficiency, producing a reduced or absent S-cone signal and selective loss of blue-yellow discrimination.

Clinically, tritan CVD is **benign, stationary, and non-degenerative**. Affected individuals have normal visual acuity, a normal fundus, and normal protan/deutan (red-green) color discrimination; the defect is confined to the tritan (blue-yellow) vector and is detected by color-vision psychophysics such as the Farnsworth-Munsell 100-hue, D-15, Mollon-Reffin Minimal test, and computerized tests (Cambridge Colour Test, CAD). Congenital tritan is the **rarest of the congenital color vision deficiencies**, in sharp contrast to acquired tritan defects, which are the most common pattern of acquired color vision loss (seen in glaucoma, diabetic retinopathy, multiple sclerosis, and normal aging owing to the selective vulnerability of the S-cone/short-wavelength pathway). The disorder shows incomplete penetrance and markedly variable expressivity — one allele (T190I) produces an illuminance-dependent phenotype ranging from mild tritanomaly to full tritanopia within a single genotype.

There is **no disease-modifying therapy** for congenital tritan CVD. Management is entirely supportive (education, occupational counseling, color-filter/assistive aids) together with genetic counseling for autosomal dominant inheritance. Because the condition does not affect

survival, acuity, or cause ocular complications, the prognosis is excellent. The principal animal model — the *Opn1sw* knockout (*Opn1sw*^{Neo/Neo}) mouse — confirms that S-opsin-deficient cones remain viable for at least 1.5 years without degeneration, establishing that S-cones are a theoretically rescuable target. AAV-mediated cone-opsin gene augmentation has restored cone structure and function in related blue cone monochromacy models, providing translational proof-of-concept for a future S-opsin gene therapy, although no tritan-specific clinical trials exist.

1. Disease Information

Overview. Tritan Color Vision Deficiency is an inherited abnormality of the blue-yellow axis of color perception caused by dysfunction of the short-wavelength-sensitive (S) cone photoreceptors. The spectrum ranges from **tritanomaly** (reduced but present S-cone function; anomalous trichromacy on the tritan axis) to **tritanopia** (complete loss of S-cone function; dichromacy). It is sometimes described as "blue-yellow color blindness."

Key identifiers.

Resource	Identifier
MONDO	MONDO:0008610
OMIM	190900 (Tritanopia / Colorblindness, tritan)
Gene (HGNC)	OPN1SW, HGNC:1012
UniProt	P03999 (OPN1SW / Blue-sensitive opsin)
MeSH	Color Vision Defects / Tritanopia
ICD-10	H53.59 (Other color vision deficiencies)

Synonyms / alternative names: Tritanopia, Tritanomaly, Blue-yellow color blindness, Tritan defect, Colorblindness (tritan), S-cone color vision deficiency.

Information source type: Information is derived predominantly from **aggregated disease-level resources** (OMIM, Orphanet, HPO) and from small clinical pedigree / psychophysical case studies rather than from large EHR-based individual-patient cohorts. Because the congenital form is rare and benign, it is under-ascertained in the general population; much of the molecular evidence derives from a handful of families and from model organisms.

2. Etiology

Disease causal factors. Congenital tritan CVD is a **Mendelian genetic disorder** caused by heterozygous mutations in the **OPN1SW** gene (chromosome 7q32.1), which encodes the S-cone opsin. There is no infectious or environmental cause for the congenital form. (See Finding F001.)

Genetic risk factors. The causal variants are pathogenic alleles of OPN1SW. At least six recognized pathogenic missense substitutions are associated with tritan deficiency:

Variant	Note
L56P	Classic tritan allele
G79R	Classic tritan allele; also observed co-segregating in a PDE6C achromatopsia family
S214P	Classic tritan allele
P264S	Classic tritan allele
R283Q	Classic tritan allele
T190I	Illuminance-dependent phenotype (mild tritan → tritanope)

In addition, **splice-disrupting OPN1SW variants** cause tritan deficiency via haploinsufficiency (Finding F002). Because OPN1SW is a single autosomal gene (not part of a head-to-tail tandem array like the X-linked L/M opsins), a single mutant allele is sufficient to produce the phenotype — hence autosomal dominant inheritance.

Environmental / acquired risk factors. The *congenital* disorder has no environmental trigger. However, **acquired tritan defects** (phenotypically similar blue-yellow loss) are common and are driven by preferential short-wavelength-pathway vulnerability in glaucoma, primary angle

closure, diabetic retinopathy, macular telangiectasia type II, multiple sclerosis, HIV retinopathy, and normal aging (Finding F003). These are distinct in etiology from the Mendelian OPN1SW disorder but important for differential diagnosis.

Protective factors. No genetic or environmental protective factors are established for congenital tritan CVD. (Information not available.)

Gene-environment interactions. For the T190I allele, **retinal illuminance (an environmental/testing variable) interacts with genotype** to determine severity: the same genotype behaves as mild tritanomaly at higher illuminance but as full tritanopia at low illuminance (Finding F002). This is the clearest documented gene-environment (gene × light-level) interaction for this disorder.

3. Phenotypes

The defining phenotype is **selective impairment of blue-yellow (tritan-axis) color discrimination** with sparing of all other visual functions (Finding F005).

Phenotype	Type	Onset	Severity	Progression	Frequency	HPO term
Tritan (blue-yellow) discrimination loss	Clinical sign / lab abnormality	Congenital	Mild (tritanomaly) → severe (tritanopia); variable	Stationary	Defining feature (100%)	HP:0000552 (Tritanomaly)
Abnormal color vision	Clinical sign	Congenital	Variable	Stationary	100%	HP:0000551 / HP:0000496
Normal visual acuity	(Preserved)	—	—	—	Typical	—
Normal fundus	(Preserved)	—	—	—	Typical	—

Phenotype characteristics. Onset is congenital; severity is variable (mild tritanomaly to complete tritanopia), including within a single family and even illuminance-dependent for the T190I allele; progression is stable/stationary (non-degenerative). Red-green (protan/deutan) discrimination, visual acuity, and the retinal fundus are normal, which distinguishes tritan CVD from the progressive cone dystrophies that can begin with tritan-like defects.

Quality of life impact. Congenital tritan is typically mild and many individuals are undiagnosed. Color vision deficiency broadly causes documented difficulties in daily activities, education, career choice, and emotional well-being (Finding F005), but the tritan subtype is generally less disabling than red-green defects for everyday red-green-coded tasks. Impact is best characterized at the level of "color vision deficiency" generally rather than tritan-specifically.

Suggested HPO terms: HP:0000552 (Tritanomaly), HP:0000551 (Abnormality of color vision), HP:0000496 (Abnormality of color vision), and HP:0000496/HP:0000551 for abnormal color vision generally.

4. Genetic / Molecular Information

Causal gene. OPN1SW (opsin 1, short-wave-sensitive), chromosome **7q32.1**; HGNC:1012; UniProt P03999; OMIM gene/phenotype 190900. Encodes the S-cone opsin, a G-protein-coupled receptor (GPCR) of the visual-pigment family that, with 11-cis-retinal as chromophore, forms the short-wavelength-sensitive photopigment of S-cones (Finding F001).

Pathogenic variants. - **Affected gene:** OPN1SW (HGNC:1012). - **Variant classification:** The classic missense alleles (L56P, G79R, S214P, P264S, R283Q, T190I) are pathogenic/likely pathogenic for autosomal dominant tritan deficiency per co-segregation and functional data. - **Variant type/class:** Predominantly **missense** substitutions; also **splice-site** variants acting through haploinsufficiency. - **Functional consequences:** Missense variants are inferred to cause **S-opsin misfolding / loss of function** (dominant through reduced functional S-opsin), while splice variants cause **haploinsufficiency** (Finding F002). The T190I allele produces a dosage/light-dependent partial loss of function. - **Allele frequency:** These are rare variants; precise gnomAD frequencies are not well established for the congenital tritan alleles (Information limited). - **Somatic vs germline:** Germline.

Modifier genes. No formal modifier genes are established. Co-occurrence of an OPN1SW G79R allele was proposed to modify the phenotype (complete vs incomplete achromatopsia) in a family also segregating a recessive PDE6C mutation, suggesting OPN1SW status can modulate cone phenotype in trans with other cone-gene lesions (a modifier-like effect;).

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Epigenetic information. No disease-specific epigenetic changes are documented for tritan CVD. Cone opsin expression is transcriptionally controlled by nuclear receptors TR β 2 (THRB), RXR γ , ROR β , ROR α , and the homeobox factor CRX (Finding F004), but these are developmental regulators, not established epigenetic disease mechanisms.

Chromosomal abnormalities. None for the single-gene OPN1SW disorder. Of note, a distinct autosomal dominant cone dystrophy with *early tritanopic* color defect maps to a 16q12 duplication affecting the IRXB/IRX5-IRX6 cluster ()

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— this is a separate progressive disease, not OPN1SW tritan CVD.

5. Environmental Information

- **Environmental factors:** None cause the congenital disorder. Acquired tritan-type defects arise secondarily to toxic, metabolic, and degenerative retinal/optic-nerve insults (see §2 and §3).
- **Lifestyle factors:** Not applicable to congenital tritan CVD.
- **Infectious agents:** Not applicable to the congenital genetic disorder. (HIV retinopathy can produce acquired cone dysfunction with downregulation of OPN1SW and other cone transcripts, but this is a secondary, acquired phenomenon, not congenital tritan CVD.)

6. Mechanism / Pathophysiology

Ordered causal chain

1. A heterozygous **OPN1SW mutation** (missense, e.g., L56P/G79R/S214P/P264S/R283Q/T190I, or a splice-site variant) is inherited in autosomal dominant fashion → **leads to** an abnormal or reduced-quantity S-cone opsin protein.
2. **Missense branch:** The amino-acid substitution **leads to** misfolding / impaired function of the S-opsin GPCR (inferred from GPCR structural biology; direct structural proof for each tritan allele is limited) → **results in** reduced functional short-wavelength photopigment in S-cones. **Splice branch:** The splice-disrupting variant **leads to** loss of one functional allele's product (haploinsufficiency) → **results in** reduced S-opsin quantity (Finding F002).
3. Reduced/abnormal S-opsin **results in** a diminished or absent S-cone photoreceptor light response (phototransduction signal) along the short-wavelength pathway.
4. Loss of the S-cone signal **leads to** impaired coding of the blue-yellow (koniocellular/S-cone-opponent) chromatic channel downstream.
5. This **results in** the clinical manifestation: selective loss of blue-yellow (tritan-axis) color discrimination, with preserved acuity, red-green discrimination, and normal fundus (Finding F005).
6. Because S-cones (unlike rods) remain viable without their opsin (demonstrated in the $Opn1sw^{Neo/Neo}$ mouse, Finding F004), the phenotype is **stationary and non-degenerative** — the chain does not progress to photoreceptor death or vision loss.

For the **T190I allele**, step 2 is partial and **illuminance-modulated**: at higher retinal illuminance enough functional S-opsin signal remains for mild tritanomaly, whereas at low illuminance the signal falls below threshold and the phenotype becomes full tritanopia (Finding F002).

Mechanistic detail by category

- **Molecular pathways:** Visual phototransduction (GPCR/opsin → transducin → cGMP phosphodiesterase → CNG channel) specifically in the S-cone. The primary lesion is at the receptor (opsin) step. GO: phototransduction (GO:0007602), detection of light stimulus involved in visual perception (GO:0050908).
- **Cellular processes:** Reduced S-cone light response; notably **no apoptosis/degeneration** (cones survive). GO: visual perception (GO:0007601), photoreceptor cell maintenance.

- **Protein dysfunction:** S-opsin misfolding / loss of function (missense) or reduced quantity (haploinsufficiency). GO: photoreceptor outer segment (GO:0001750).
- **Metabolic changes:** None established; the chromophore is 11-cis-retinal (CHEBI:16066).
- **Immune involvement:** None.
- **Tissue damage mechanisms:** None in the congenital disorder (benign, stationary).
- **Biochemical abnormalities:** Defective short-wavelength photopigment function.
- **Molecular profiling:** In the mouse model, elimination of S-opsin mRNA relieves translational competition, **increasing M-opsin expression** in affected cones — a compensatory shift (Finding F004).

Cell type involved: S-cone photoreceptor (CL:0000573, retinal cone cell / short-wavelength-sensitive cone). **Biological process GO terms:** GO:0007602 (phototransduction), GO:0007601 (visual perception), GO:0050908 (detection of light stimulus in visual perception).

7. Anatomical Structures Affected

- **Organ level (primary):** Eye — specifically the **retina** (UBERON:0000966). Body system: visual/nervous system. No secondary organ involvement.
 - **Tissue/cell level:** **Neural retina** (UBERON:0003902); specific target cell population = **S-cone photoreceptors** (CL:0000573, cone retinal photoreceptor cell). Rods, L-cones, and M-cones are spared.
 - **Subcellular level:** The **photoreceptor outer segment** (GO:0001750), where opsin-based phototransduction occurs; the S-opsin is a membrane protein of the outer-segment disc membranes. In the mouse model, many S-opsin-null ventral cones **fail to form outer segments** (Finding F004).
 - **Localization:** Bilateral and symmetric (both eyes equally, as expected for a germline opsin gene defect). UBERON:0000966 (retina), UBERON:0001782 (retinal photoreceptor layer).
 - **Lateralization:** Bilateral, symmetric.
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8. Temporal Development

- **Onset:** Congenital (present from birth), though frequently detected only when color vision is formally tested in later childhood or adulthood. Onset pattern: non-progressive/congenital.
 - **Progression: Stationary** — stable and non-progressive over life. No disease stages. This is supported both clinically and by the animal model, in which S-opsin-null cones survive ≥ 1.5 years without degeneration (Finding F004).
 - **Disease course:** Chronic lifelong but benign and unchanging.
 - **Remission patterns:** Not applicable (stable congenital trait; no remission, no worsening).
 - **Critical periods:** Not applicable; because cones remain viable long-term, any hypothetical gene-replacement window would be broad (a favorable feature for future therapy).
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9. Inheritance and Population

Epidemiology. Congenital tritan CVD is the **rarest congenital color vision deficiency** (Finding F003). A 2025 systematic review/meta-analysis (1,703,619 participants; 56 studies; 21 countries) estimated the global prevalence of all congenital CVD at **2.59% (95% CI 2.20–3.03%)**, overwhelmingly red-green (deutan/protan); tritan is the smallest subtype. Classic textbook estimates place tritan prevalence on the order of ~ 1 in 10,000 or lower, but precise congenital tritan prevalence figures are uncertain owing to under-ascertainment.

Inheritance. Autosomal dominant (OPN1SW is a single autosomal gene on 7q32.1), with: - **Penetrance:** Incomplete. - **Expressivity:** Variable — ranging from mild tritanomaly to tritanopia, even illuminance-dependent for T190I (Finding F002). - **Genetic anticipation:** Not applicable (not a repeat-expansion disorder). - **Germline mosaicism / founder effects / consanguinity:** Not established as relevant; as an autosomal dominant single-gene trait, consanguinity is not a driver. - **Carrier frequency:** Not well defined (rare alleles).

Population demographics. - **Sex ratio:** Approximately **1:1** (autosomal), in contrast to the strong male predominance of X-linked red-green CVD. - **Affected populations / geographic distribution:** No strong ethnic or geographic enrichment is established for congenital tritan CVD. (Information limited.)

10. Diagnostics

Clinical/psychophysical color-vision tests (primary diagnostic modality). Diagnosis rests on demonstrating a selective tritan-axis defect (Finding F005):

Test	Role in tritan diagnosis
Farnsworth-Munsell 100-hue	Blue-yellow confusion axis errors
Farnsworth D-15 / Lanthony D-15	Tritan confusion axis crossings
Hardy-Rand-Rittler (HRR) plates	Includes tritan plates
Mollon-Reffin Minimal test	Sensitive color-discrimination test for tritan axis
Cambridge Colour Test (CCT)	Computerized; quantifies tritan vector threshold
Colour Assessment and Diagnosis (CAD)	Quantifies tritan vector; high sensitivity/specificity
Anomaloscope (Moreland equation)	Tritan/blue-green matching

Electrophysiology: S-cone-specific ERG can demonstrate selective S-cone dysfunction; standard full-field ERG and acuity are otherwise normal, helping distinguish stationary tritan CVD from cone dystrophies.

Genetic testing: Single-gene **OPN1SW sequencing** (including splice-site analysis) confirms the molecular diagnosis; WES/WGS or inherited-retinal-disease gene panels including OPN1SW are appropriate in atypical cases. Genetic testing distinguishes benign stationary OPN1SW tritan CVD from progressive cone dystrophies that present with early tritan defects (e.g., the 16q12/IRXB duplication disorder).

Imaging: Fundus examination and OCT are **normal** in congenital tritan CVD — a key discriminator from acquired tritan defects and cone dystrophies.

Differential diagnosis: - Acquired tritan defects (glaucoma, primary angle closure, diabetic retinopathy, macular telangiectasia type II, multiple sclerosis, HIV retinopathy, aging) — these have an underlying ocular/systemic cause and often additional findings. - Autosomal dominant cone dystrophy with early tritanopia (16q12/IRXB duplication) — progressive, with acuity loss. - Enhanced S-cone syndrome, blue cone monochromacy, achromatopsia — distinguished by ERG, acuity, and genetics.

Screening: No population newborn or carrier screening program exists; detection is opportunistic via color-vision testing (e.g., occupational/educational screening).

11. Outcome / Prognosis

- **Survival/mortality:** Not affected. Congenital tritan CVD does not influence life expectancy or mortality (Finding F006).
- **Morbidity/function:** Minimal; visual acuity and ocular health are preserved. The main impact is on color-dependent tasks and occupational suitability; congenital tritan is generally milder than red-green CVD.
- **Quality of life:** Color vision deficiency broadly affects daily activities, education, career choice, and emotional well-being (Finding F005), but tritan-specific QoL burden is modest and many cases are undiagnosed.
- **Disease course / complications:** None — stationary and non-degenerative; no ocular complications.
- **Prognostic factors/biomarkers:** Not applicable; the condition is stable regardless of genotype (although genotype determines baseline severity, e.g., T190I vs classic alleles).

Overall prognosis is **excellent** (benign, lifelong, stable).

12. Treatment

There is no approved disease-modifying therapy for congenital tritan CVD (Finding F006). Management is:

- **Supportive/rehabilitative:** Patient education, occupational counseling (relevant where color discrimination is safety-critical), and **color-filter/assistive aids** (e.g., tinted lenses, digital color-identification tools). NCIT: supportive care, visual rehabilitation.
- **Genetic counseling:** For autosomal dominant inheritance (50% transmission risk; incomplete penetrance and variable expressivity should be conveyed).
- **Pharmacotherapy / surgery / immunotherapy:** None applicable.
- **Experimental/advanced therapeutics (future):** **AAV-mediated cone-opsin gene augmentation** has achieved robust rescue of cone structure and function in related disorders (blue cone monochromacy mouse models, e.g., C203R/C198R all-cone models), demonstrating that opsin cDNA delivery can restore cone function (Finding F006). Combined with the finding that S-opsin-null cones remain viable for ≥ 1.5 years (Finding

F004), this makes S-cones a theoretically rescuable target. However, **no tritan-specific clinical trials exist**, and given the benign stationary nature of the disease, the clinical imperative for gene therapy is low compared with blinding cone disorders.

Pharmacogenomics / personalized medicine: Not applicable currently; any future approach would be genotype-guided (OPN1SW cDNA augmentation).

13. Prevention

- **Primary prevention:** Not applicable — a germline genetic trait cannot be prevented. Preconception/prenatal **genetic counseling** can inform reproductive decisions.
- **Secondary prevention:** Early detection via color-vision screening (educational/occupational) allows appropriate guidance, but there is no treatment to initiate.
- **Tertiary prevention:** Supportive measures (assistive aids, occupational accommodation) to minimize functional impact.
- **Genetic screening/counseling:** Cascade genetic testing within families and genetic counseling for the autosomal dominant pattern are the main preventive tools. Carrier/newborn screening programs are not established for this benign condition.
- **Immunization/public health/environmental interventions:** Not applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologous gene:** The mouse ortholog is **Opn1sw** (NCBI Gene; *Mus musculus*, NCBI:txid10090). S-opsin orthologs exist broadly across vertebrates; cone opsin expression is conserved and transcriptionally regulated by THRB (TR β 2), RXR γ , ROR β , ROR α , and CRX (Finding F004).
- **Natural disease in other species:** No well-characterized naturally occurring OPN1SW tritan-equivalent disease is cataloged as a major veterinary entity; S-opsin biology is primarily studied in engineered mouse models rather than spontaneous animal disease (Information limited for OMIA natural-disease entries).
- **Comparative biology:** Mouse S-opsin-null cones survive long-term and show compensatory M-opsin upregulation (Finding F004), illustrating conserved cone-survival mechanisms and

translational competition between opsins. S-opsin also contributes to violet-light-dependent refractive development in mice ($Opn1sw^{-/-}$ mice are more myopic and lack the violet-light hyperopic shift) — a species-specific role not directly part of the human color-vision phenotype.

- **Zoonotic potential:** Not applicable (non-infectious genetic trait).

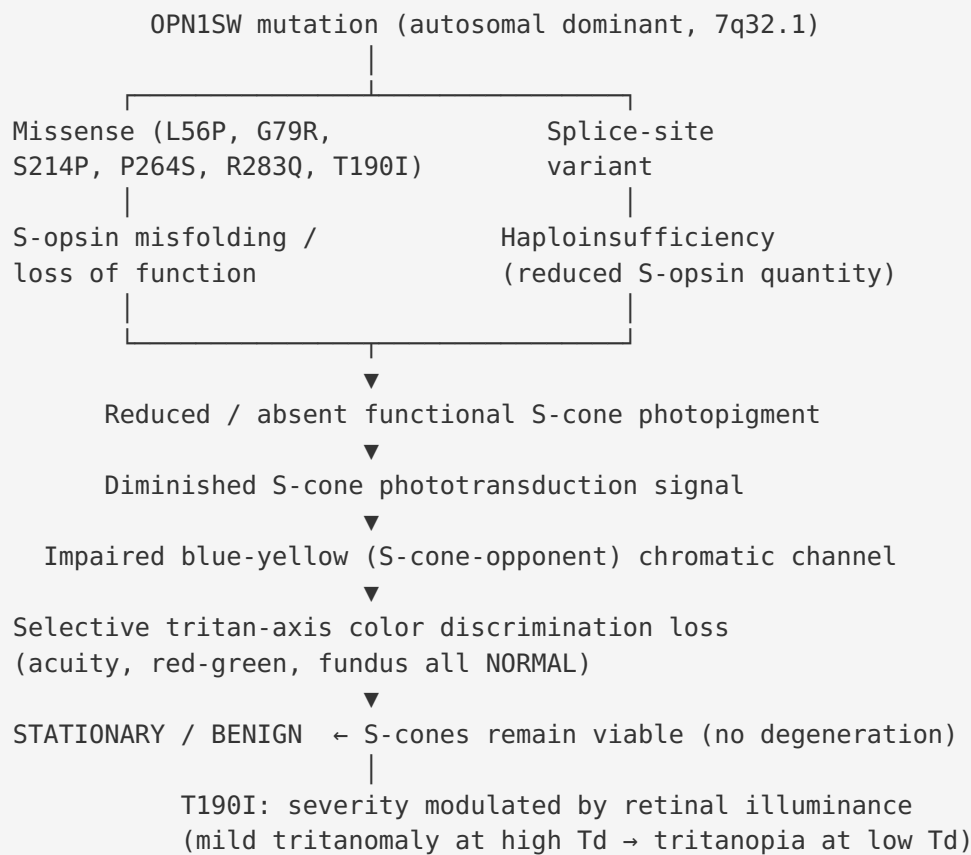
15. Model Organisms

Principal model: the $Opn1sw^{Neo/Neo}$ (S-opsin knockout) mouse (Finding F004).

Feature	Detail
Model type	Mammalian genetic knockout (mouse, <i>Mus musculus</i>)
Construct	Neomycin cassette inserted between exons 3–4 of <i>Opn1sw</i>
Phenotype recapitulation	Loss of S-cone (S-opsin) function; stationary, non-degenerative — models the key human feature that S-cone defect does not kill cones
Key findings	Cones remain viable ≥ 1.5 years (vs rod death by 2.5 months in $Rho^{-/-}$); many ventral cones fail to form outer segments; functional cones phototransduce normally and show increased M-opsin (compensatory, via relief of translational competition)
Limitations	Mice are dichromats with a dorsal-ventral opsin gradient, lack a human-like fovea and trichromatic color vision; models S-opsin <i>loss</i> (haploinsufficiency-like) better than dominant missense misfolding
Related models	$Opn1sw^{-/-}$ (refractive/violet-light studies); all-cone BCM gene-therapy models (C203R/C198R) used to demonstrate cone-opsin AAV rescue
Databases	MGI, IMPC, IMSR

Mouse studies underpin two central conclusions: (1) **S-cones survive without their opsin** (stationary phenotype, broad therapeutic window), and (2) **cone-opsin cDNA delivery restores cone function** (proof-of-concept for gene augmentation).

Mechanistic Model / Interpretation



Upstream vs downstream: The initiating lesion is the OPN1SW mutation (upstream); the most downstream event is the perceptual blue-yellow discrimination deficit. The critical "brake" on the chain is that S-cone survival is independent of S-opsin — so the disease never progresses to cell death, unlike rod opsin loss. **Cell type:** S-cone photoreceptor (CL:0000573). **Process:** phototransduction (GO:0007602) / visual perception (GO:0007601). **Anatomy:** retina (UBERON:0000966), photoreceptor outer segment (GO:0001750). **Chemical:** 11-cis-retinal chromophore (CHEBI:16066).

Evidence Base

PMID	Title (abbrev.)	Supports
23022137	<i>Substitution of isoleucine for threonine at position 190 of S-opsin...</i>	OPN1SW causal gene; five classic missense alleles; T190I illuminance-dependent phenotype (F001, F002)
32400513	<i>Tritan CVD may be associated with an OPN1SW splicing defect and haploinsufficiency</i>	Splicing/haploinsufficiency mechanism (F002)
42346125	<i>Cone Opsins and Inherited Retinal Disease</i>	Tritan CVD is a cone-opsin gene disorder (F001)
40769301	<i>Global Prevalence of Congenital Color Vision Deficiency, 1932–2022</i>	Global CVD prevalence 2.59%; tritan rarest subtype (F003)
41317340	<i>Digital Color Vision Testing... in Multiple Sclerosis</i>	Tritan most common acquired defect (39.9%) (F003)
21219924	<i>A mouse M-opsin monochromat: increased M-opsin when S-opsin knocked out</i>	Opn1sw KO cones viable ≥ 1.5 yr; compensatory M-opsin (F004, F006)
30443703	<i>The impacts of abnormal color vision on people's life</i>	QoL/occupational impact of CVD (F005)
15094734	<i>Blue cone monochromatism: phenotype/genotype...</i>	Supports Mollon-Reffin minimal color-discrimination testing (F005)
38060327	<i>Structural and functional rescue of cones... C203R</i>	Cone-opsin AAV augmentation restores cone function (F006)
25605338	<i>Congenital Achromatopsia... PDE6C</i>	OPN1SW G79R tritan allele co-segregating; modifier-like effect
33891002	<i>Duplication on 16q12 (IRXB)... AD cone dystrophy with early tritanopia</i>	Differential diagnosis: distinct progressive tritan disorder

Verbatim supporting quotes: - F001/F002: *"Five mutations in the S-cone-opsin gene (OPN1SW) that give rise to different single amino-acid substitutions (L56P, G79R, S214P, P264S, R283Q) are known to be associated with tritan color-vision deficiency."* and *"Individuals with the T190I S-*

opsin mutation behaved as mild tritans at 12.3-92.3Td, but as tritanopes at 1.2-9.2Td..."

([P 23022137](#))

- F002: *"Here we present evidence implicating disrupted RNA splicing as a potential cause of inherited tritan color vision."*

([P 32400513](#))

- F003: *"The global prevalence of CVD was estimated at 2.59%"*

([P 40769301](#));

"tritan deficiencies being the most common pure type (39.9%)"

([P 41317340](#))

- F004: *"cones of the Opn1sw(Neo/Neo) mouse remain viable for at least 1.5 yrs, even though many ventral cones do not form outer segments"*

([P 21219924](#))

- F006: *"gene augmentation targeting cones specifically yielded robust rescue of cone function and structure"*

([P 38060327](#))

Limitations and Knowledge Gaps

1. **Small molecular evidence base.** The pathogenic OPN1SW missense alleles derive from a limited number of families; functional/structural proof of misfolding for each specific allele is inferred rather than individually demonstrated.
2. **Imprecise epidemiology.** Congenital tritan prevalence is poorly quantified because the condition is benign and under-ascertained; most CVD prevalence data are dominated by red-green defects.
3. **Penetrance/expressivity not quantified.** Incomplete penetrance and variable expressivity are recognized but lack precise estimates; only T190I has a characterized illuminance-dependence.
4. **No allele frequency data.** gnomAD-level frequencies for the tritan alleles are not well established.

5. **Model limitations.** The mouse is dichromatic and fovealess; it models S-opsin loss (haploinsufficiency-like) more directly than dominant missense misfolding, and cannot reproduce human blue-yellow percepts.
 6. **No tritan-specific therapy data.** Gene-therapy evidence is extrapolated from blue cone monochromacy models, not from tritan CVD itself.
 7. **Differential-diagnosis overlap.** Acquired tritan defects and progressive tritanopic cone dystrophies (e.g., 16q12/IRXB) phenocopy early findings; genotype + fundus/ERG are needed to separate them.
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Proposed Follow-up Experiments / Actions

1. **Functional characterization of each OPN1SW allele** (heterologous expression, spectral tuning, folding/trafficking assays, AlphaFold-guided structural modeling) to convert "inferred misfolding" into demonstrated mechanism and refine ACMG classification.
 2. **Population genomics:** query gnomAD/large biobanks for OPN1SW tritan alleles to estimate true allele frequencies, penetrance, and any founder effects.
 3. **Deep phenotyping cohort** using standardized tritan-vector quantification (CAD/CCT) plus S-cone ERG and AO imaging to map genotype–severity relationships and test illuminance-dependence beyond T190I.
 4. **Knock-in mouse models** carrying human missense alleles (e.g., P264S, T190I) to distinguish misfolding/dominant-negative from haploinsufficiency mechanisms in vivo.
 5. **Proof-of-concept S-opsin gene augmentation** in an *Opn1sw*-deficient model (building on BCM AAV success and demonstrated long-term S-cone viability) to establish whether S-cone function is restorable — primarily of mechanistic interest given the benign clinical course.
 6. **Natural-history / QoL study** specifically in congenital tritan individuals to quantify (currently assumed modest) functional and occupational impact separately from red-green CVD.
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Evidence source types represented: human clinical/psychophysical and pedigree studies (OPN1SW variants, prevalence, QoL); model-organism (Opn1sw knockout mouse, BCM gene-therapy models); computational/structural (inferred GPCR misfolding). Information explicitly flagged as "not available / not applicable" where the literature does not support a claim for this specific disease.

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