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Illuminating the Darkness: Unraveling the Complexities of Cone-Rod Dystrophies

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ABSTRACT

Inherited retinal diseases (IRDs) are significant causes of legal blindness in some working-age adults. Among these conditions, cone-rod dystrophies (CRDs) are characterized by the progressive loss of cone and rod photoreceptors, leading to visual impairment. The pathogenesis of CRDs is multifactorial and often involves genetic mutations in proteins critical for phototransduction, photoreceptor maintenance, and cellular homeostasis within the retina. Over time, photoreceptors deteriorate, resulting in decreased visual acuity, color vision abnormalities, and, in some cases, night blindness. The diagnosis of CRDs requires a comprehensive approach that includes clinical evaluation, electrophysiological testing, and advanced imaging modalities such as optical coherence tomography (OCT). Current treatments are primarily supportive, focusing on the management of visual symptoms and the enhancement of patients' quality of life. Emerging therapies, including gene therapy, retinal implants, and regenerative medicine, show promise for slowing or reversing disease progression. Low vision aids, environmental modifications, and regular monitoring remain essential components of CRD management. Identifying the genetic variants responsible for CRDs enables personalized counseling and may facilitate the development of targeted, gene-specific interventions. This review summarizes recent advances in the epidemiology, molecular mechanisms, and therapeutic strategies for CRDs, providing updated insights into diagnosis and long-term care. By analyzing these developments, we aim to guide both clinical practice and research toward novel interventions that could preserve or restore vision in affected individuals.

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Introduction

Inherited retinal diseases (IRDs) constitute a diverse group of disorders and represent one of the leading causes of legal blindness in working-age adults, as well as a common cause of childhood vision loss (1). Within this broad category are progressive cone dystrophies and cone-rod dystrophies (CRDs), which are characterized by primary degeneration of cone photoreceptors, typically followed by rod involvement (1-3). These conditions have an estimated prevalence of approximately 1 in 40,000 individuals worldwide, though regional differences may occur in isolated populations due to founder effects, leading to higher rates in specific communities (1-4). Actual prevalence data may vary based on genetic screening methods and population

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demographics. Cone function disorders can be subdivided into stationary and progressive forms. Stationary cone dysfunction syndromes present early in life, whereas progressive dystrophies manifest later. Nevertheless, some overlap exists, as achromatopsia is traditionally considered a stationary condition with stable symptoms over time. However, recent longitudinal studies indicate that a minority of individuals may experience subtle progression, such as mild declines in visual acuity or cone function, though this is not typical and requires differentiation from progressive cone dystrophies (1-4). In this review, we synthesize current knowledge on the epidemiology, pathogenesis, and emerging treatment strategies for CRDs, highlighting recent research advances and persisting gaps in clinical management.

Methods

To comprehensively gather and identify relevant publications for this narrative review on syndromic causes of cone-rod dystrophies, a robust search strategy was employed across three major academic databases: PubMed, Web of Science, and Scopus.

2-1. Search Strategy

The initial search utilized a combination of keywords to identify relevant publications related to cone-rod dystrophies, which included: “Inherited retinal diseases”, “IRDs”, “cone dystrophies”, “CRDs”, “cone-rod dystrophies”, and “CRDs”. We subsequently performed additional searches specific to each condition, including: “Retinitis Pigmentosa”, “Leber Congenital Amaurosis”, “Macular Dystrophy”, “Central Dystrophy”, “Stargardt disease”, “Best disease”, “Retinal pattern dystrophies”, “Central Areolar Choroidal Dystrophy”, “Congenital X-linked retinoschisis”, “X-linked Macular Dystrophy”, and “Aland Island Eye disease”.

2-2. Inclusion and Exclusion Criteria

Specific inclusion and exclusion criteria were established to ensure the relevance and quality of the selected studies. The inclusion criteria consisted of the following:

- Publication Date: Articles published from January 2000 to May 2024.
- Language: Only studies published in English.
- Publication Types: Peer-reviewed original research articles, systematic reviews, and case reports discussing syndromic causes of cone-rod dystrophies.

Additionally, the exclusion criteria included the following:

- Non-Peer-Reviewed Articles: Editorials, opinion pieces, and commentaries were excluded.
- Irrelevant Topics: Studies that did not discuss cone-rod dystrophies or their syndromic associations were excluded.
- Duplicate Publications: redundant articles found in multiple databases.

2-3. Data Extraction

We included peer-reviewed articles that discussed the epidemiology, pathogenesis, clinical features, diagnosis, or treatment. References in the identified articles were manually screened to uncover further relevant publications. Given the heterogeneous nature of the included studies, no formal quality assessment (e.g., risk-of-bias tools) was performed, and this review is intended as a broad synthesis of the current literature rather than a systematic evaluation of all evidence. Limitations of our approach include restricting searches to English-language articles and omitting unpublished or non-indexed studies, which may introduce selection and publication bias.

2-4. Methodological Limitations

In interpreting the findings of this review, several methodological limitations should be acknowledged. The majority of available literature on syndromic cone–rod dystrophies is composed of isolated case reports, small case series, and a limited number of larger retrospective cohorts. These study designs are inherently vulnerable to selection and publication bias, with more severe or unusual phenotypes disproportionately represented. Diagnostic heterogeneity is also common: earlier reports often relied on clinical features and electrophysiology alone, whereas more recent studies include genetic confirmation, leading to variability in diagnostic certainty.

Overview: Epidemiology, Symptoms, and Pathogenesis

Retinal dystrophies (RDs) are a genetically diverse group of disorders that may present as isolated ocular conditions or occur in association with systemic diseases. The underlying disease mechanisms are often not fully understood, complicating classification (2). These disorders exhibit substantial clinical heterogeneity, even among individuals with the same mode of inheritance. A practical classification is based on whether the dystrophies are stationary or progressive and whether the primary involvement affects the macula or the broader retinal region. The latter can be further subdivided according to whether rods, cones, or both photoreceptor types are primarily affected. In many cases, the disease eventually progresses to involve both photoreceptor types (1). Cone-rod dystrophies (CRDs) are progressive retinal disorders primarily affecting cone photoreceptors, followed by rod involvement, and represent a relatively rare subset of inherited retinal diseases (IRDs). They are clinically heterogeneous, with early manifestations including decreased central visual acuity, photophobia, abnormal color vision, and nystagmus. Night vision impairment typically develops later due to rod degeneration (5). CRDs may

occur in otherwise healthy individuals but have also been associated with syndromic conditions such as Bardet-Biedl syndrome, spinocerebellar ataxia type 7, and Jalili syndrome (amelogenesis imperfecta with CRD) (6). Infantile presentations of achromatopsia typically include poor vision, nystagmus, and photophobia. Fundus examination is usually normal. Two main forms of the disease are recognized (7, 8):

1. Complete achromatopsia: In this form, the retina lacks functioning cone photoreceptors. Visual acuity is limited to approximately 6/60, there is no true color perception, and the electroretinogram (ERG) shows normal rod responses but absent cone responses. This condition is inherited in an autosomal recessive manner and may exhibit different genetic variants.
2. Incomplete achromatopsia: This autosomal recessive disorder presents similarly but generally has a better visual prognosis. Color vision testing and ERG reveal partial cone function across types (often residual in red, green, and blue cones), while female heterozygotes may demonstrate abnormal cone responses on ERG.

Progressive CRDs typically manifest during adolescence with early cone dysfunction, including decreased visual acuity, photophobia, and color vision impairment. Macular retinal pigment epithelium (RPE) atrophy is often present, producing a "bull's eye" pattern. ERG demonstrates absent or markedly abnormal cone responses. Over time, rod involvement emerges, manifesting as nyctalopia and abnormal rod ERG responses, at which point the condition is classified as cone-rod dystrophy (5). IRDs, including CRDs, are a leading cause of legal blindness among working-age adults and contribute to vision loss in children, highlighting their public health importance (9). Compared with cone dystrophies (CODs), CRDs have an earlier symptomatic onset (mean age 12 versus 16 years) and a more severe disease course, with legal blindness occurring at a mean age of 23 years compared with 48 years in CODs (10). Early-stage CRDs often present with central scotomas while peripheral vision remains largely intact. Patients may adopt an eccentric gaze to project images onto less-damaged parafoveal retina and commonly experience intense light sensitivity. Retinal vessels are generally normal or mildly narrowed, and the optic disc often appears pale, particularly temporally. Distinguishing CRDs from other macular dystrophies, including CODs and Stargardt disease, can be challenging (11). ERG typically shows delayed cone responses, with rod-cone responses particularly affected. As disease advances, peripheral vision declines, nyctalopia worsens, and nystagmus and legal blindness are commonly observed (12).

At the molecular level, rod photoreceptors contain rhodopsin, while cone photoreceptors express S-, M-, or L-opsins. Phototransduction begins when light activates rhodopsin, converting 11-cis-retinal to all-trans-retinol and activating the G-protein transducin. This triggers cGMP-phosphodiesterase (PDE), reducing cGMP levels, closing cGMP-gated cation channels, and hyperpolarizing photoreceptors. Variants in PDE6C, PDE6H, CNGA3, and CNGB3 can disrupt this process, often causing achromatopsia or CRDs. Recovery involves rhodopsin phosphorylation, inactivation by arrestin, and cGMP replenishment via retinal guanylate cyclase. Variants in GUCA1A are associated with autosomal dominant CODs and CRDs, whereas GUCY2D variants are more consistently linked to autosomal dominant CRDs with milder rod involvement (13, 14). Mutations in at least 32 genes can cause CODs or CRDs, often overlapping with genes affecting rod function. These proteins are critical for neurotransmitter release, phototransduction, intraflagellar transport, and outer segment morphogenesis (15). A recent analysis found an identifiable genetic cause in 56.3% of CODs/CRDs cases, with ABCA4 variants accounting for 62.2% of autosomal recessive cases. Among autosomal dominant and X-linked cases, GUCY2D (34.6%) and RPGR (73.0%) are the most common monogenic causes (16).

Classification

Most cases of retinal degeneration and optic atrophy occur independently and affect only the eye; these are classified as non-syndromic CRDs (17). Non-syndromic inherited retinal degenerations and optic atrophy are typically managed by ophthalmologists, whereas syndromic disorders require input from multiple clinical specialties. Table 1 presents the differential diagnoses of non-syndromic cone-rod dystrophy. Clinical geneticists play a critical role in identifying specific syndromes, assessing recurrence risks, and providing predictive or prenatal testing when indicated. The primary distinction between syndromic and non-syndromic CRDs lies in the presence of systemic manifestations. Syndromic CRDs are associated with additional health issues affecting other organs, necessitating a broader diagnostic and management approach. In contrast, non-syndromic CRDs are confined to visual impairment, with treatment focused exclusively on ocular health (4).

Table 1. Differential diagnosis of non-syndromic cone-rod dystrophy; AR: Autosomal Recessive, AD: Autosomal Dominant.

Disorder	Inheritance	Visual Onset	Associated Symptoms	Primary Genetic Associations
Retinitis Pigmentosa (18)	Variable	Adolescence	Night blindness, progressive visual field constriction, tunnel vision, photophobia	>80 genes (e.g., RHO [AD], USH2A [AR], RPGR [X-linked]) (19)
Leber Congenital Amaurosis (18)	Variable (commonly AR)	Infancy	Nystagmus, photophobia, severe visual impairment, roving eye movements	38 genes (e.g., CEP290, GUCY2D, CRB1, RPE65) (20)
Stargardt Disease (18)	Variable (commonly AR)	Juvenile	Maculopathy, fundus flavimaculatus, hyperfluorescent macular lesions, central vision loss	ABCA4 (most cases), rare ELOVL4 (AD) (21)
Åland Island eye disease (22)	X-linked Recessive	Infancy	Nystagmus, astigmatism, myopia, fundus hypopigmentation, protan color defect	CACNA1F (23)
Central Areolar Choroidal Dystrophy (24)	AD	Third to fifth decade	Progressive central vision loss, macular atrophy, choroidal neovascularization risk	6 genes (PRPH2, GUCA1A, GUCY2D, CDHR1, ABCA4, and TTLL5) (24)
Best Vitelliform Macular Dystrophy (25)	AD	Childhood	Diminished visual acuity, metamorphopsia, scotoma, yellow macular lesions	BEST1 (26)
Pattern dystrophy (27)	AD	Fourth to Fifth decade	Metamorphopsia, reduced central acuity, pigmentary changes in macular patterns (e.g., butterfly-shaped) (28)	RDS (29)
Congenital X-linked Retinoschisis (30)	X-linked Recessive	Early Childhood	Foveal schisis, peripheral retinoschisis, vitreous hemorrhage, retinal detachment	RS1 (31)

Non-syndromic Retinal dystrophies

Non-syndromic CRDs, similar to retinitis pigmentosa (RP), exhibit substantial genetic heterogeneity and follow three Mendelian inheritance patterns. Non-syndromic CRDs, similar to retinitis pigmentosa (RP), exhibit substantial genetic heterogeneity and follow three Mendelian inheritance patterns, with over 30 genes associated (5, 11, 32). These genes can be grouped into four categories, though many loci have been resolved since initial mapping:

1. Primarily CRD-associated genes:
   - CRX: Causes 5-10% of dominant CRDs, varying in severity from mild to severe, sometimes causing dominant Leber congenital amaurosis (LCA) and RP.
   - RIM1 and HRG4: Each found in one family, involved in photoreceptor synaptic transmission.
2. Macular dystrophy-associated genes:
   - ABCA4: Accounts for 30-60% of autosomal recessive CRD cases, involved in retinoid metabolism. Mutations can lead to Stargardt disease or diffuse retinopathy with macular involvement.
   - GUCA1A: Found in one family with autosomal dominant CRD, linked to CODs. GC also implicated in some CRD cases.
3. RP-associated genes:
   - RDS (peripherin): Causes dominant RP and CRD, with variable severity.
   - RPGR: Major gene for X-linked RP (XLRP) and CRDs, causing severe, early-diagnosed CRDs.
   - CACNA1F: Linked to X-linked congenital stationary night blindness and one Finnish CRD family.
4. LCA-associated genes:
   - RPGRIP1 and AIPL1: Typically cause LCA, found in CRD families with autosomal recessive and dominant inheritance, respectively.
   - GUCY2D: Major LCA gene, causing dominant CRD when mutated in exon 13.

Unidentified loci:

- Autosomal dominant CRDs: CORD1 (Danish family with CRD and intellectual disability), CORD4 (Canadian family with CRD and neurofibromatosis).
- Autosomal recessive CRDs: CORD8 (Pakistani family), CORD9 (Brazilian family).
- X-linked CRDs: CORDX2 locus mapped to Xq27.

In summary, most genes linked to CRDs are also associated with other retinal dystrophies, including RP, cone dystrophies, and macular dystrophies. This suggests that genes responsible for retinal degeneration may also contribute to CRD pathogenesis, although the precise mechanisms remain unclear (11). Harmful mutations in retinal dystrophy genes can lead to severe conditions, including CRD; however, the reasons why specific mutations in the same gene produce macular dystrophy, RP, or CRD in different individuals or families remain unresolved for several genes Hamel (11).

Non-syndromic Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a group of inherited retinal disorders characterized by progressive photoreceptor degeneration, leading to vision loss. Symptoms typically begin with night blindness and visual field constriction, often progressing to tunnel vision, reduced central and color vision, photophobia, and complications like cataracts or retinal detachment (33, 34). Affecting approximately 1 in 4,000 people worldwide, RP usually manifests in adolescence to early adulthood (35, 36). Over 80 gene mutations

cause RP, impacting phototransduction, the visual cycle, photoreceptor structure, and transcriptional regulation, with diverse inheritance patterns: autosomal dominant (ADRP, 20-25%), autosomal recessive (ARRP, 5-20%), X-linked (XLRP, 16-33%), mitochondrial, or sporadic ("simplex RP") (37). Histopathologically, RP involves photoreceptor loss, outer nuclear layer thinning, retinal pigment epithelial (RPE) cell migration, Müller cell gliosis, vascular changes, and optic nerve alterations (38). Genetic mechanisms like apoptosis, necrosis, and autophagy, alongside environmental factors such as light exposure and oxidative stress, drive degeneration (38). Diagnosis requires comprehensive ophthalmological evaluation, including visual acuity, contrast sensitivity, color vision, and fundus examination. Advanced imaging, including fundus autofluorescence, optical coherence tomography (OCT), OCT angiography (OCTA), and electroretinography (ERG), is critical for diagnosis, monitoring, and treatment assessment (39). Family history and genetic testing help determine inheritance and prognosis, often necessitating multidisciplinary evaluation (39). RP may also be associated with syndromes like Usher, Bardet-Biedl, or Joubert, requiring systemic evaluation (40).

- **Autosomal Dominant RP (ADRP):** ADRP typically has a later onset and slower progression than ARRP or XLRP. Rhodopsin (RHO) mutations account for 25-30% of cases, while RP1 and RDS each contribute 5-10% (37). Specific RP1 mutations (Arg677stop, 2280del5) cause about half of RP1-related ADRP cases. RDS mutations can lead to varied phenotypes, from RP to macular dystrophy. Reduced penetrance, where mutation carriers remain asymptomatic, occurs with genes like GUCY2D, GUCA1B, and PRPF31 (37).
- **Autosomal Recessive RP (ARRP):** ARRP presents earlier with rapid progression. Several genes and loci are linked to non-syndromic ARRP, offering insights into its molecular mechanisms (35).
- **X-linked RP (XLRP):** XLRP features early onset and severe vision loss, particularly in males, often starting in childhood. Female carriers may be asymptomatic or develop symptoms later, with rare cases as severe as males (41). Genetic assessment is vital for families considering prenatal or preimplantation testing.
- **Digenic RP:** This rare form results from simultaneous mutations in RDS (L185P mutation) and ROM1 genes, contributing to phenotypic variability (42). Unrecognized polygenic or digenic inheritance may explain diverse clinical presentations.
- **Simplex RP:** Accounting for 10-40% of cases, simplex RP lacks a clear family history and may arise from new autosomal dominant mutations, recessive inheritance, X-linked mutations, non-paternity, or reduced penetrance (37). Thorough family evaluation is essential, especially with visual disturbance history.

Differential Diagnoses:

- **Gyrate Atrophy** (OMIM 258870): An autosomal recessive metabolic disorder due to OAT gene mutations, causing myopia, nyctalopia, and chorioretinal atrophy. Diagnosis involves elevated plasma ornithine and deficient enzyme activity (43).
- **Bietti Corneal/Retinal Dystrophy** (OMIM 210370): An autosomal recessive condition with crystalline deposits and nyctalopia, caused by CYP4V2 mutations (44).
- **Choroideremia** (OMIM 300390): An X-linked disorder resembling RP, with patchy chorioretinal degeneration. Diagnosis targets REP-1 gene mutations (45, 46).
- **Usher Syndrome**: Combines RP with sensorineural hearing loss, linked to USH2A and other gene mutations (47, 48).

Management of RP requires a multifaceted approach. Emerging therapies, including gene therapy and stem cell treatment, aim to preserve photoreceptors and restore vision, although long-term efficacy data remain limited. Neuroprotective agents, retinal implants, and corrective lenses are also under investigation. Identifying and treating underlying causes, such as vitamin deficiencies, is essential (49). Supportive care, including low vision aids, counseling, and vocational rehabilitation, improves outcomes through multidisciplinary collaboration. While no single standard therapy exists, combining multiple approaches offers the greatest potential for symptom management and slowing vision loss in RP patients (50).

Leber Congenital Amaurosis

Leber congenital amaurosis (LCA) is a severe form of inherited retinitis pigmentosa that leads to early-onset blindness, nystagmus, and amaurotic pupils. It accounts for approximately 20% of childhood blindness. Advances in genetics have identified 38 genes responsible for LCA, causing diverse dysfunctions of visual cycle proteins and resulting in extensive clinical heterogeneity. Early diagnosis and emerging gene therapies, particularly targeting the RPE65 gene, show considerable promise (51). In infancy, LCA typically presents with poor vision, nystagmus, and lack of visual fixation. Visual acuity ranges from functional vision to light perception, with approximately 75% of cases demonstrating stationary disease. Common refractive errors include hyperopia, photophobia, and nyctalopia, which may vary depending on the underlying gene mutation. Additional features can include oculodigital signs, keratoconus, juvenile cataracts, and, in some cases,

cognitive impairment. Diagnostic evaluation frequently involves electrophysiological studies, which often reveal non-detectable ERG responses. Fundoscopy typically demonstrates retinal abnormalities, while optical coherence tomography (OCT) aids in assessing retinal structure and correlating specific abnormalities with genotypes. Differential diagnoses include achromatopsia, congenital stationary night blindness, and systemic disorders such as Batten and Joubert syndromes (52). Most LCA cases are inherited in an autosomal recessive pattern, with common mutations affecting RPE65, GUCY2D, RDH12, CEP290, and CRB1. Gene augmentation therapy has shown significant clinical benefit, particularly for RPE65 mutations, with Luxturna™ being approved by the FDA. Early-phase trials for CRISPR- and mRNA-based therapies targeting CEP290 mutations are ongoing, and pharmacological interventions and stem-cell therapy also demonstrate potential. Advances in genomic sequencing and genotype-phenotype correlation are improving diagnostic precision and guiding the development of targeted therapies for LCA (53).

Macular dystrophies (Central dystrophies)

Macular dystrophies are characterized by reduced or lost central visual acuity, often accompanied by color vision deficits and, in some cases, photophobia, depending on the extent of cone involvement. These disorders exhibit significant clinical overlap, with similarities in presentation, electrophysiological findings, and histopathological features. Inheritance patterns can be autosomal recessive, autosomal dominant, X-linked, or mitochondrial (54).

8-1. Autosomal Recessive Macular Dystrophies

Stargardt disease, also known as Stargardt macular dystrophy or fundus flavimaculatus, is the most common inherited macular dystrophy. It is characterized by progressive vision loss beginning in childhood or adolescence. The condition is primarily caused by mutations in the ABCA4 gene, which lead to the accumulation of toxic lipofuscin pigments in the retinal pigment epithelium (RPE) and subsequent damage to photoreceptor cells in the macula (55). ABCA4 mutations disrupt the transport of vitamin A derivatives, resulting in the formation of toxic bisretinoids that accumulate as lipofuscin, ultimately causing photoreceptor cell death and vision loss. Stargardt disease follows an autosomal recessive inheritance pattern, requiring two defective copies of the ABCA4 gene for disease manifestation. Patients typically present with bilateral, symmetrical central vision loss, experiencing difficulties with reading and facial recognition due to impaired macular function (56). Diagnosis relies on clinical evaluation, family history, and multimodal imaging. Fundus autofluorescence (FAF) and optical coherence tomography (OCT) are particularly informative, while fluorescein angiography (FA) often reveals the classic “dark choroid” sign. Electroretinography (ERG) may provide additional functional assessment, and genetic testing confirms ABCA4 mutations. Currently, there is no cure for Stargardt disease. Management focuses on slowing disease progression and optimizing residual vision through low vision support. Patients are advised to protect their eyes from excessive light exposure and avoid vitamin A supplementation. Emerging therapies under investigation include gene therapy, stem cell therapy, and pharmacological strategies aimed at reducing lipofuscin accumulation or preserving photoreceptor function (57, 58).

8-2. Autosomal Dominant Macular Dystrophies

8-2-1. Best disease

Best disease, also known as vitelliform dystrophy, is an autosomal dominant macular dystrophy characterized by early macular changes and bilateral, symmetrical yellow deposits. Phenotypic variability is common, with approximately half of patients maintaining good vision and normal or near-normal fundi throughout life (59). The disease progresses through several stages, beginning with a yellow, egg yolk-like lesion in the macula. It can advance to pseudohypopyon, characterized by fluid accumulation, and eventually to atrophy and choroidal neovascularization, in which new blood vessels grow beneath the retina and may further impair vision. Clinical symptoms include blurred vision, metamorphopsia (distorted vision), and significant central vision loss, while peripheral vision is typically preserved (60). Diagnosis relies on comprehensive ophthalmological evaluation, including imaging modalities such as fluorescein angiography (FA) and optical coherence tomography (OCT). A hallmark feature of Best disease is the loss of the electrooculogram (EOG) light rise. Genetic testing can confirm mutations in the BEST1 gene, which are responsible for the condition (61). There is currently no definitive treatment for Best disease. Management focuses on symptom control and prevention of complications, such as choroidal neovascularization, which may be treated with anti-VEGF agents or laser therapy. Regular follow-up with an eye care specialist is essential for early detection of changes and to preserve the best possible vision over time 63).

8-2-2. Pattern dystrophy

Retinal pattern dystrophies are a group of slowly progressive macular disorders, primarily inherited in an autosomal dominant manner, and are characterized by pigment deposition in the retinal pigment epithelium (RPE) of the macula. These disorders encompass various forms, including reticular dystrophy, fundus pulverulentus, butterfly-

shaped pigment dystrophy, adult-onset foveomacular vitelliform dystrophy, and multifocal pattern dystrophy, which can evolve over time within the same patient, which can change over time within the same patient. Symptoms typically appear in the fourth or fifth decade, and misdiagnosis as age-related macular degeneration (AMD) is common (63). Symptoms typically manifest in the fourth or fifth decade of life, and misdiagnosis as age-related macular degeneration (AMD) is common. Pattern dystrophies are associated with mutations in the PRPH2 (RDS) gene on chromosome 6, which affect the peripherin-2 (PRPH2) protein essential for photoreceptor outer segment disc stability. Dysfunction of PRPH2 compromises photoreceptor membrane integrity, leading to disease manifestation. The estimated prevalence is approximately 1 in 1,490 individuals in northern France, with variable rates reported for adult-onset vitelliform macular dystrophy (64). Diagnosis often occurs during routine eye examinations or when patients present with visual symptoms or complications, such as choroidal neovascularization. Evaluation typically includes fundus examination, fluorescein angiography (FA), fundus autofluorescence (FAF), electrooculography, and electroretinography (ERG), which aid in staging and confirming the diagnosis. Pattern dystrophies may also be associated with systemic conditions, including pseudoxanthoma elasticum and maternally inherited diabetes and deafness (60). There are no evidence-based therapies to reverse pigment deposition or lipofuscin accumulation in retinal pattern dystrophies. Management focuses on addressing visual impairment through low vision support and treating complications, such as choroidal neovascularization or macular holes. Accurate differentiation from AMD, Stargardt disease, and Best disease is critical to avoid misdiagnosis. Regular follow-up is essential to monitor for concurrent AMD and manage any rapid changes in vision or emerging complications (61).

8-2-3. Central Areolar Choroidal Dystrophy

Central areolar choroidal dystrophy (CACD) is a hereditary retinal disorder that primarily affects the macula, resulting in progressive and often severe visual impairment. It is classified as a rare disease, with a prevalence ranging from 1 to 9 cases per 100,000 individuals. Symptoms typically present as a gradual decline in visual acuity and color perception, usually between the ages of thirty and sixty (62). The hallmark of CACD is distinct atrophy of the retinal pigment epithelium (RPE) and choriocapillaris. The disease progresses through four clinical stages: Stage 1 involves subtle parafoveal RPE changes; Stage 2 is characterized by mildly atrophic, hypopigmented areas; Stage 3 presents with well-demarcated RPE atrophy extending beyond the fovea; and Stage 4 involves foveal atrophy, leading to significant visual acuity loss (63). CACD may be inherited in either an autosomal dominant or recessive manner, although autosomal-recessive cases are rare. Autosomal dominant CACD is most commonly associated with mutations in the PRPH2 gene, with over 90 distinct mutations reported to date. Six specific PRPH2 mutations have been identified as causative for the CACD phenotype. The PRPH2 gene encodes the glycoprotein PRPH2, also known as retinal degeneration slow protein or tetraspanin-22, which is essential for the formation and maintenance of photoreceptor outer segment discs (3, 64). Early-stage diagnosis of CACD can be challenging due to nonspecific RPE abnormalities, and late-onset forms may be mistaken for age-related macular degeneration (AMD). This overlap underscores the importance of accurate diagnosis and careful differentiation between these conditions (65).

8-2-4. X-linked Macular Dystrophy

Congenital X-linked retinoschisis (CXLRS) is a genetic disorder causing retinal degeneration, primarily in males, and is characterized by splitting of the superficial retinal layers. First described over a century ago, the condition typically presents in early childhood with symptoms such as impaired vision and strabismus. CXLRS results from mutations in the RS1 gene, which encodes the protein retinoschisin, essential for retinal cell adhesion. Although the precise mechanisms underlying retinal splitting are not fully understood, vitreous traction and disruptions in ionic gradients are thought to contribute to the pathology. The estimated prevalence of CXLRS ranges from 1 in 5,000 to 1 in 20,000 individuals (66). Clinically, CXLRS is distinguished by characteristic foveal schisis and, in many patients, peripheral retinoschisis. Optical coherence tomography (OCT) allows classification into four types based on specific retinal features. The disorder can present as exudative or non-exudative, with potential complications including vitreous hemorrhage and retinal detachment. Diagnosis typically relies on clinical examination, OCT imaging, and genetic confirmation of RS1 mutations. Differential diagnoses include Coats disease and familial exudative vitreoretinopathy, which can be distinguished by characteristic clinical and electroretinography (ERG) findings (67). Management of CXLRS involves regular monitoring, correction of refractive errors, treatment of strabismus, and, in severe cases, surgical intervention for retinal detachment. Modern vitrectomy techniques have

reduced procedural complications. Gene therapy trials are ongoing, aiming to restore normal retinal function through RS1 gene replacement, with studies focusing on optimizing dosing and safety. Advances in imaging, genetic testing, and emerging therapies are progressively improving prognosis and quality of life for individuals with CXLRS (68).

8-2-5. Aland Island Eye disease

Aland Island Eye Disease (AIED) is an X-linked recessive disorder that shares clinical features with X-linked congenital stationary night blindness type 2A (CSNB2A) and X-linked cone-rod dystrophy type 3 (CORDX3). These conditions are caused by mutations in the CACNA1F gene, which encodes the α1F subunit of the Cav1.4 calcium channel, essential for neurotransmission from photoreceptors to bipolar cells. Clinical manifestations of AIED include reduced visual acuity, color vision deficits, and retinal abnormalities. Electroretinography (ERG) typically demonstrates attenuated responses, reflecting impaired signal transmission from photoreceptors to bipolar cells. Genetic testing can confirm the presence of a pathogenic CACNA1F variant, establishing the molecular basis of the phenotype (69). Currently, no gene therapy exists for CACNA1F-associated retinopathy. However, emerging molecular tools such as zinc finger nucleases, TALEN, and CRISPR/Cas offer potential strategies for correcting mutations in the Cav1.4 gene within photoreceptor cells (70). In experimental studies, Waldner et al. introduced a transgenic Cav1.4 gene into a mouse model, achieving partial restoration of retinal structure and function. The transgene expression was controlled using the Pax6 promoter to ensure Cav1.4 expression during early developmental stages (71).

The Role of CRISPR

CRDs represent a challenging group of inherited retinal diseases, where progressive degeneration of cone photoreceptors leads to early symptoms like reduced central vision, color blindness, and light sensitivity, often followed by rod involvement causing night blindness and peripheral vision loss. With multiple genes implicated, including ABCA4, GUCY2D, and RPGR, the genetic diversity makes treatment elusive. Traditional management relies on supportive aids, but recent gene-editing advances, particularly CRISPR-based technologies, offer hope by targeting these root causes directly. Clustered Regularly Interspaced Short Palindromic Repeats, acts like molecular scissors to edit faulty DNA sequences. For CRDs, it addresses key hurdles such as dominant mutations, where a single defective gene copy overrides the healthy one. In autosomal dominant forms, like those linked to RHO or PRPH2, CRISPR can selectively inactivate the mutant allele while sparing the normal one, potentially halting progression. A 2023 study demonstrated allele-specific CRISPR/Cas9 editing in RHO-associated retinitis pigmentosa, restoring vision in mouse models and suggesting applicability to similar dominant CRDs. This precision avoids broad gene suppression, reducing off-target risks (72). Another challenge is the need for subtle corrections in recessive CRDs, where both gene copies are mutated. Base editing, a CRISPR variant, swaps single DNA letters without full cuts, minimizing damage. Research from 2023 explored CRISPR adenine base editors for CDHR1 variants, which cause RP with cone-rod features, showing potential to rescue photoreceptor function in cellular models (74). Delivery remains a barrier, but adeno-associated virus (AAV) vectors enable safe retinal injection, as seen in CRISPRi approaches for dominant RP, where transcriptional repression slowed degeneration in preclinical trials. Early human trials for related IRDs, like Leber congenital amaurosis, build confidence, though CRD-specific studies are nascent (74). While not a cure yet, these innovations bring optimism. By correcting mutations early, CRISPR could preserve vision longer, transforming lives for those facing gradual darkness. Continued research, including safety refinements, will be crucial to bridge lab successes to clinics.

Conclusion

Cone-rod dystrophies (CRDs) represent a heterogeneous subset of inherited retinal diseases, as detailed throughout this review, with non-syndromic forms primarily driven by mutations in over 30 genes affecting phototransduction and photoreceptor integrity. Early cone loss leading to central vision deficits, followed by rod involvement and peripheral impairment, often confounding diagnosis with conditions like retinitis pigmentosa or Stargardt disease. Genetic testing has advanced our understanding, revealing overlaps (e.g., ABCA4 in recessive cases) and enabling personalized approaches, yet unresolved mechanisms, such as why identical mutations yield variable phenotypes, highlight persistent gaps. Management remains supportive, with low vision aids and rehabilitation central to quality-of-life improvements, emerging therapies offers optimism. Gene therapies, like voretigene neparvovec for related IRDs, and innovative CRISPR-based editing (e.g., allele-specific corrections for dominant mutations) could address CRD-specific hurdles, though long-term efficacy and delivery challenges require further trials. Ultimately, integrating multidisciplinary care, from ophthalmologists to geneticists, will be key to bridging these gaps. This review calls for targeted studies on underrepresented genes and populations to accelerate

interventions, potentially transforming CRDs from progressive threats to manageable conditions and preserving vision for future generations.

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