Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Unraveling the Tapestry of Syndromic Cone–Rod Dystrophies: Navigating the Complexities of Sight and Beyond

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ARTICLE INFO

Article type

Review article

Article history
Received: 23 Apr 2025
Accepted: 08 Feb 2026

Keywords
Syndromic Cone-Rod Dystrophies
Retinal Degeneration
Genetic Mutations,
Photoreceptor Degeneration
Systemic Manifestations

ABSTRACT

Syndromic cone-rod dystrophies (CRDs) represent a heterogeneous group of genetic retinal disorders characterized by the progressive degeneration of photoreceptors. These conditions, through their impact on both cone and rod cells, lead to significant visual impairment, manifesting as diminished central visual acuity, compromised color perception, and increased light sensitivity. In addition to the associated ocular symptoms, syndromic CRDs are frequently seen accompanied with systemic manifestations, including that of skeletal, metabolic, neurological, renal, and cardiac anomalies, which complicate diagnosis and management. The genetic basis of syndromic CRDs is complex, involving several mutations in multiple genes linked to a diverse array of syndromic conditions, such as that of Bardet-Biedl, Usher, Alström, Jalili, Refsum disease, Senior-Loken, Cohen syndrome, Jeune, Sensenbrenner, and Joubert syndrome. Non-genetic assessments, such as that of electroretinography, play vital roles in differentiating CRDs, in particular syndromic forms, from pure cone dystrophies an, as they tend to reveal functional deficits in both cone and rod photoreceptors. This review aims to clarify the distinct genetic origins and clinical characteristics for these disorders.

Please cite this paper as:
Nejad Shahrokh Abadi Z, Nejad Shahrokh Abadi Z, Azimzadeh M, Islampanah M, Mirtooni S, Hashemi N. Unraveling the Tapestry of Syndromic Cone–Rod Dystrophies: Navigating the Complexities of Sight and Beyond. *Reviews in Clinical Medicine*. 2026;13(1): 24-33

Introduction

Cone-Rod Dystrophies (CRDs) are a diverse set of genetic eye diseases characterized by severe vision loss due to the gradual deterioration of retinal photoreceptors. The results include a reduction in central visual clarity, compromised color perception, and heightened sensitivity to light. Contrary to diseases like Retinitis Pigmentosa that mainly impact rod photoreceptors, CRDs typically start earlier and show more severe deterioration of cone cells. The symptoms of these conditions can range greatly, sometimes becoming more complex with other systemic symptoms present (1, 2). The genetic cause of CRDs is intricate, usually including mutations in multiple genes. *ABCA4* mutations are linked to autosomal recessive Stargardt disease, a prevalent type of inherited retinal degeneration (2). Additional genes linked to CRDs are *RPGR*, which is located on the X chromosome, and *ATXN7*, a gene on autosomal dominant trait involved in *SCA7*. As mentioned, CRDs frequently appear in syndromic disorders, with ocular symptoms being linked to systemic issues involving skeletal, metabolic, neurological, and cardiac irregularities. Bardet-Biedl syndrome, involving complex mutations in multiple genes, is

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seen to be associated with obesity, polydactyly, and renal anomalies, in addition to neurodevelopmental delays (3). Alström syndrome, resulting in mutations in the *ALMS1* gene, presents with early-onset obesity, diabetes, and dilated cardiomyopathy (4, 5). Autosomal recessive inheritance of USH gene mutations lead to hearing loss in addition to progressive decline in visual acuity (6). Retinal dystrophy and optic nerve atrophy accompanied by megaloblastic anemia is seen in a number of patients with autosomal recessive mutations of the *SLC19A2* gene resulting in loss of function in a thiamine transporter (7, 8). The varied and diverse presentations seen as a result of these genetic mutations coupled with their unique and rare nature presentations complex challenges in diagnosis and management, and highlights the importance of multidisciplinary care (3). Management strategies for syndromic CRDs are primarily supportive, focusing on alleviating visual impairment and addressing systemic complications. Low-vision rehabilitation, the use of visual aids, and educational support are essential components of care for individuals with significant visual deficits (9). Furthermore, emerging therapies, such as gene replacement strategies, hold promise for treating CRDs, with ongoing clinical trials investigating their efficacy and safety (10). Non-genetic assessments, such as that of electroretinography, play vital roles in differentiating CRDs, in particular syndromic forms, from pure cone dystrophies an, as they tend to reveal functional deficits in both cone and rod photoreceptors (11). However, genetic analysis is primarily relied upon for diagnosing syndromic cone-rod dystrophies. Due to the infrequency of these disorders, numerous patients frequently undergo whole exome sequencing, a costly diagnostic technique. Hence, an accurate and up to date understanding of the distinct clinical traits linked to each one of these syndromes is crucial for clinicians to choose appropriate genetic testing for the specific mutated genes. This method not just simplifies the diagnosis procedure but also greatly improves the way patients are managed and followed up on (2, 9). Identification of these mutations through genetic testing is not only essential for diagnosing these disorders, but also offers potential treatment opportunities, such as emerging gene therapies (12, 13). In conclusion, syndromic cone-rod dystrophies represent a complex interplay of genetic, ocular, and systemic factors, necessitating a comprehensive approach to diagnosis and differentiation. Continued research into the genetic basis and clinical manifestations of these disorders will be crucial in advancing our knowledge and understanding of patients with syndromic CRDs. In this review, we present an exhaustive list of syndromic CRDs, along with their unique genetic and clinical characteristics.

Methods and Materials

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: “cone dystrophies”, “CODs (Cone Dystrophies)”, “CORD (Cone-Rod Dystrophies)”, “cone-rod dystrophies”, and “CRD (Cone-Rod Dystrophy)”. This initial search was followed by a focused review using specific keywords for each of the identified syndromic disorders associated with cone-rod dystrophies. These terms included: “neuronal ceroid lipofuscinosis”, “NCL”, “Batten disease”, “Bardet Biedl syndrome”, “Spinocerebellar ataxia type 7”, “SCA7”, “Jalili syndrome”, “Hypotrichosis with juvenile macular dystrophy”, “Thiamine-responsive megaloblastic anemia”, “TRMA”, “Usher syndrome”, “Refsum disease”, “Alstrom syndrome”, “Cohen syndrome”, “Senior-Loken syndrome”, “Jeune syndrome”, “Sensenbrenner syndrome”, and “Joubert syndrome”. These terms were also adapted to fit the specific syntax and requirements of each database.

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

This extracted data was organized based on the specific disorder and syndromic cause of CRDs. A summary of the relevant data was extracted and added as a table to further compare and contrast the syndromes. In addition to the database searches, the reference lists of all included studies were reviewed to identify any additional relevant publications that may not have been captured in the initial search.

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.

Syndromic Inherited Retinal Degeneration

Syndromic CRD is a type of inherited retinal disorder that not only causes visual impairment but also manifests with additional systemic symptoms affecting other parts of the body. Patients with syndromic CRD experience progressive degeneration of the cone and rod photoreceptors in the retina, leading to symptoms such as reduced visual acuity, loss of color vision, and peripheral vision deterioration (12). However, unlike non-syndromic CRD, syndromic CRD is characterized by the presence of other health issues, which can include hearing loss, kidney abnormalities, neurological deficits, or metabolic disturbances. These systemic symptoms are often the result of mutations in genes that have roles in various bodily systems, necessitating a comprehensive, multidisciplinary approach to diagnosis and treatment. Genetic testing is crucial for identifying specific mutations and guiding the management of both the ocular and extraocular manifestations of the condition (13).

Neuronal Ceroid Lipofuscinosis

Batten disease is a group of neurodegenerative lysosomal storage disorders resulting from mutations in one of at least 13 ceroid lipofuscinosis neuronal (CLN) genes (14). The disease typically begins early in life, with defects in intracellular trafficking and lysosomal function causing neural dysfunction, neuroinflammation, neurodegeneration, and premature death. The etiology of most Batten disease subtypes remains poorly understood, complicating the development of effective treatments. Owing to this lack of knowledge, gene replacement strategies, particularly those based on adeno-associated virus (AAV) vectors, are promising (9). CLN7 Batten disease, also known as variant late infantile neuronal ceroid lipofuscinosis type 7 (vLINCL7), is an ultra-rare form of Batten disease caused by biallelic mutations in the *MFSD8* (CLN7) gene, which encodes a putative lysosomal transporter of unknown function (10). The disease pathology includes lysosomal storage material enriched in subunit C of mitochondrial ATP synthase, neuroinflammation, and neurodegeneration in various central nervous system regions, such as the cerebral cortex, cerebellum, and retina (10, 15). Affected individuals present early in life with severe neurological symptoms, including visual deficits, motor problems, and frequent seizures (10, 14, 15). Visual impairments include rod-cone dystrophy followed by late loss of bipolar cells (10, 14, 15). CLN types 2 and 3 (autosomal recessive), respectively known as late infantile and juvenile subtypes, are also associated with varying degrees of cone-rod dystrophy and retinal involvement (14, 16-18). These patients may also experience seizures in addition cognitive and motor regression (14, 16-18). CLN2 is caused by mutations in the *TPP1* gene, which encodes the enzyme tripeptidyl peptidase I (19-21). This enzyme is crucial for lysosomal function, and its deficiency leads to the accumulation of ceroid lipofuscin in neuron (19-21). The most well-known mutation associated with NCL3 is a large deletion involving exons 7-16 of the CLN3 gene, which accounts for a significant proportion of cases (18).

Bardet–Biedl syndrome

Bardet–Biedl syndrome (BBS) is a rare inherited disorder that exemplifies non-motile ciliopathies and is characterized by mutations in genes affecting the base of the cilium. This syndrome shares clinical features with other ciliopathies and presents with a wide array of symptoms, including retinal degeneration, learning disabilities, and obesity. The prevalence of BBS varies geographically and is often higher in communities with consanguineous marriages (22). BBS is diagnosed through specific criteria requiring primary and secondary clinical features. Early signs include polydactyly and obesity, with major symptoms such as retinal dystrophy and kidney abnormalities appearing later. Common features also include cognitive impairment, speech delay, developmental delays, and various physical anomalies. The syndrome is genetically complex, involving mutations in multiple genes, with BBS1 to BBS18 being the most common, and its genetic prevalence varies among populations owing to founder effects (23). Managing BBS requires a multidisciplinary approach, with comprehensive

medical assessments and treatments tailored to specific symptoms. Interventions include low-vision aids, corrective surgeries, renal function screening, and obesity management through diet and exercise. Potential treatments such as gene therapy that target specific organs, such as the eyes, are under investigation, raising hopes for more effective future therapies (3).

Spinocerebellar Ataxia 7

Spinocerebellar ataxia type 7 (SCA7) is a genetic disorder characterized by a wide range of symptoms that can vary depending on the age of onset. It can manifest as progressive cerebellar ataxia and cone–rod retinal dystrophy in adolescents or adults or as infantile or early childhood onset with multi-organ failure and a rapid disease course. Anticipation, where symptoms worsen and appear earlier in successive generations, is a notable feature of SCA7. Diagnosis is made through genetic testing to identify abnormal CAG trinucleotide repeat expansions in the *ATXN7* gene (24). SCA7 follows an autosomal dominant inheritance pattern, with a 50% chance of passing on the abnormal CAG repeat expansion to offspring. Genetic testing allows for prenatal diagnosis and preimplantation genetic testing, and family members should undergo evaluation and counseling for family planning. Predictive testing is available for at-risk relatives, but it is not recommended for minors. Overall, SCA7 management involves comprehensive genetic counseling and testing strategies to guide reproductive decisions and provide support to affected individuals and their families (25). Management of SCA7 focuses on supportive care, as there is currently no known treatment to slow down or halt disease progression. Supportive treatment involves a multidisciplinary approach, including physical and occupational therapy, pharmacological interventions, speech and language therapy, feeding therapy, and the use of low vision aids for individuals with visual impairment. Regular follow-up with a multidisciplinary care team is recommended. It is important for individuals with SCA7 to avoid excessive alcohol intake and follow dietary recommendations to minimize cerebellar impairment and manage symptoms (24).

Jalili syndrome

Jalili syndrome is a recessively inherited condition characterized by CRD and amelogenesis imperfecta (AI) and was first reported in 1988. It has since been identified in several families and linked to the CNNM4 gene on chromosome 2q11. Mutations in *CNNM4*, including missense, termination, deletion, and insertion mutations, have been found in all seven families studied (25-26). The syndrome involves the progressive loss of cone photoreceptors in the retina, leading to visual impairments, and is associated with abnormalities in tooth development. The discovery of the role of CNNM4 in Jalili syndrome provides new insights into the connections among metal transport, visual function, and biomineralization (25, 27). Compared with retinal degeneration, abnormal tooth biomineralization, specifically amelogenesis imperfecta (AI) and dentinogenesis imperfecta (DI), has a limited genetic understanding (28). AI is associated with mutations in enamel-matrix proteins and enzymes controlling enamel processing, whereas DI is linked to a single gene. Both AI and DI can be part of syndromes involving multiple tissues and organs (29, 30). Jalili syndrome results in consistent dental and ocular phenotypes across affected families. The enamel of the teeth is grossly abnormal, prone to posteruptive failure, and reflects hypomineralization (27). Taurodontism, an abnormality in tooth morphology involving dentine, is also present. Visual impairment is evident from infancy or early childhood, with progressive loss of vision, nystagmus, photophobia, and impaired color vision (26-28, 30). Genetic analyses confirmed the existence of a genetically homogeneous syndrome linked to chromosome 2q11. Mutations in the CNNM4 gene were identified as the likely cause of Jalili syndrome, and the tooth phenotype showed characteristics of hypo-maturation AI (31).

Hypotrichosis with juvenile macular dystrophy

Hypotrichosis with juvenile macular dystrophy is a rare autosomal recessive disease characterized by hypotrichosis and progressive macular degeneration, leading to blindness in the first three decades of life. It is associated with mutations in the cadherin 3 gene, resulting in the abnormal expression of P-cadherin. The *CDH3* gene encodes P-cadherin, a cell adhesion molecule crucial for normal hair follicle and retinal pigment epithelial cell development (32). The absence of functional P-cadherin disrupts cell–cell adhesion and leads to the characteristic symptoms of HJMD. While the severity of symptoms can vary among individuals, all patients with HJMD experience retinal degeneration and limited hair growth throughout their lives

Thiamine-responsive megaloblastic anemia

Thiamine-responsive megaloblastic anemia (TRMA) is an autosomal recessive disease in which active thiamine uptake into cells is disrupted (33-35). The molecular basis underlying the disorder has been related to mutations in the *SLC19A2* gene on chromosome 1q23.3, which encodes a functional

thiamine transporter (33-35). The protein is predicted to have 12 transmembrane domains. TRMA is characterized by sensorineural deafness, diabetes mellitus, megaloblastic anemia, and cardiomyopathy (although not common). Optic nerve atrophy and retinal dystrophy have been reported in a small number of patients (7, 8).

Usher syndrome

Usher syndrome is a rare genetic disorder that causes the loss of both hearing and vision. It is the leading cause of deaf-blindness worldwide. The syndrome is divided into three main types (*USH1*, *USH2*, and *USH3*) and is inherited in an autosomal recessive pattern. Mutations in different genes contribute to each type of Usher syndrome (6). Symptoms and severity can vary among individuals with Usher syndrome, but common features include hearing loss, retinitis pigmentosa (a degenerative retinal disorder), and balance problems. Early diagnosis is crucial for implementing appropriate interventions. Cochlear implants can help with hearing loss, whereas rehabilitation strategies focusing on alternative communication methods, sensory stimulation, and balance training can assist with vision loss (6). While there is currently no cure for Usher syndrome, recent advancements in gene therapy show promise for treating specific genetic mutations associated with this condition. Clinical trials using viral vectors and antisense oligonucleotides have shown positive results in correcting genetic defects. Additionally, CRISPR-Cas9 technology has potential for correcting gene mutations in vitro. Rehabilitation efforts remain important for improving the quality of life of individuals with Usher syndrome, with a focus on hearing rehabilitation and adaptive strategies for vision loss (36).

Alström syndrome

Alström syndrome is a rare genetic disorder caused by a mutation in the *ALMS1* gene, resulting in dysfunctional cilia and affecting multiple organ systems. Diagnosing Alström syndrome can be challenging because of the variability in symptoms and delayed presentation (4). Common complications include growth issues, early-onset diabetes mellitus, obesity, dilated cardiomyopathy, vision loss, hearing impairment, renal disease, hepatic abnormalities, and respiratory complications, which can significantly cause organ damage, reduce lifespan, and impact the overall quality of life of affected individuals. Regular monitoring through blood tests, echocardiography, and other evaluations is necessary to detect and manage these complications. Early diagnosis and appropriate management of complications are crucial for improving outcomes and quality of life in individuals with Alström syndrome (5). The prognosis of Alström syndrome can vary depending on the severity and range of complications. A reduced lifespan is a common outcome, with most affected individuals not living beyond the age of 50. Unfortunately, there are currently no specific treatments available to cure or prevent the complications of Alström syndrome (37). Management primarily focuses on symptom alleviation, regular monitoring of organ function, and supportive care (38).

Refsum disease

Refsum disease is a rare autosomal recessive genetic disorder (*PHYH* and *PEX7*) that impacts peroxisome function and is caused by a deficiency in the enzyme phytanoyl-CoA hydroxylase, leading to the accumulation of phytanic acid. This accumulation results in neurological and sensory symptoms such as night blindness, anosmia, peripheral neuropathy, ataxia, and hearing/cardiac issues (39). Diagnosis is a challenging issue because of the gradual onset and symptom progression, necessitating dietary restriction of phytanic acid and supportive therapies managed through interprofessional collaboration. Over 90% of Refsum disease cases are due to mutations in the PHYH gene, with a small percentage resulting from PEX7 gene defects. The disease is exceptionally rare, with a prevalence of less than 1 in 1,000,000 individuals in the white US population. Symptoms typically begin before age 20, although onset can range from 7 months to 50 years. Deficiency in phytanoyl-CoA hydroxylase hinders the breakdown of phytanic acid, causing its accumulation and resulting in a variety of clinical manifestations affecting multiple organ systems (39, 40). The management of Refsum disease focuses on the strict dietary restriction of phytanic acid and the avoidance of foods such as meat, dairy, and certain fish to limit intake to less than 10 mg daily. Acute removal of phytanic acid can be achieved through plasmapheresis or lipid apheresis, although long-term management relies on dietary control. Genetic counseling is crucial for educating patients and their families about inheritance patterns and family planning. Adhering to the dietary regimen can alleviate many symptoms, although vision and hearing loss may persist (41).

Cohen syndrome

Cohen syndrome is a rare, autosomal recessive disorder caused by mutations in the *VPS13B* (COH1) gene on chromosome 8q22.2. The VPS13B protein plays a crucial role in vesicle-mediated transport, Golgi complex maintenance, and protein glycosylation. First, it was described in the 1970s and is characterized by a variety of clinical features (42). During the perinatal period, patients often have

decreased fetal activity, low birth weight and length, and hypotonia, which can cause feeding and respiratory difficulties and possibly a high-pitched cry. As they grow, patients may develop short stature, truncal obesity or abnormal fat distribution, and significant motor and language delays, with intellectual disability ranging from mild to profound (43). Characteristic craniofacial features, including microcephaly, downslanting palpebral fissures, hypertelorism, a short philtrum, and prominent upper incisors, can increase the risk of a difficult airway. In addition to developmental and physical abnormalities, patients with Cohen syndrome often have a cheerful disposition, friendly personality, and high-pitched voice. Cohen syndrome is characterized by progressive deterioration of vision starting in early childhood, with high myopia often requiring corrective lenses by age 2 and significant visual impairment by age 40. Other common ophthalmic features include retinal pigmentation changes, strabismus, and the potential for glaucoma. In addition, patients typically present with leukopenia and severe congenital neutropenia that can be managed with growth factor treatment (43). Feeding difficulties, hypotonia, musculoskeletal abnormalities such as joint laxity, and neurological features such as motor incoordination are also commonly observed. Cardiac issues such as decreased ventricular function, valvular defects, and metabolic abnormalities such as insulin resistance can develop. While there is no treatment to halt progressive vision and retinal degeneration, early intervention for visual defects and multidisciplinary management of various systemic manifestations are important (44). While more than 20 different pathogenic variants have been identified in patients with the classic Cohen syndrome phenotype, patients who only have a "Cohen-like" presentation without the full clinical criteria do not have detectable VPS13B mutations (45). The diagnosis of Cohen syndrome is challenging due to phenotypic variability, with no consensus on definitive diagnostic criteria. However, the presence of developmental delay, microcephaly, hypotonia, retinal dystrophy, and neutropenia are considered strong clinical indicators for Cohen syndrome across different ethnicities (46).

Senior-Loken syndrome

SLS is an autosomal recessive disorder with an incidence of approximately 1 in 100,000 people. It is caused by mutations in various *NPHP* genes, which lead to a ciliary dysfunction disorder. It is characterized by the combination of juvenile nephronophthisis, a type of cystic kidney disease, and retinal degeneration that leads to blindness and end-stage renal disease (46). The renal abnormalities in SLS typically begin with polyuria and progress over time to end-stage renal disease, whereas retinal degeneration can manifest as conditions such as retinitis pigmentosa, Leber congenital amaurosis, and tapetoretinal degeneration (47). Patients presenting with retinal disease should undergo evaluation of renal function, and those suspected of having nephronopathy require regular monitoring of kidney and liver function, as well as ophthalmological examinations, to prevent or delay the development of end-stage renal disease and improve quality of life (48, 49).

Jeune syndrome

Jeune syndrome is a rare autosomal recessive disorder, involving several different genes, characterized by skeletal dysplasia, including a narrow thorax, micromelia, and other pelvic and limb abnormalities. The classic features of Jeune syndrome include dwarfism, short ribs and limbs, and characteristic radiographic changes in the ribs and pelvis (50). The narrow thoracic cage leads to lung hypoplasia and respiratory failure, which causes mortality in 60–70% of cases in infancy. Survivors may also develop chronic renal failure due to associated cystic kidney disease. The severity of clinical and radiological manifestations can vary, likely due to genetic heterogeneity (51). Prenatal ultrasound can detect narrow thorax, short limbs, and other skeletal abnormalities associated with Jeune syndrome. Other diagnostic features include polyhydramnios and diminished fetal respiratory movements. Differentiating Jeune syndrome from other skeletal dysplasias, such as Ellis-van Creveld syndrome and achondroplasia, is important for accurate diagnosis and management of this rare, potentially lethal condition (52).

Sensenbrenner syndrome

Sensenbrenner syndrome, also known as cranioectodermal dysplasia, is a rare disorder characterized by distinctive craniofacial features, metaphyseal dysplasia, ectodermal anomalies, connective tissue abnormalities, and chronic organ dysfunction. Advances in genetic testing have revealed four molecular subtypes (CED1-4) associated with ciliary dysfunction (53). An analysis of 39 patients, including two new cases, highlighted common features, such as a high anterior hairline, forehead bossing, dolichocephaly, brachydactyly, and ectodermal anomalies, along with respiratory complications and mild cardiac defects (54). The syndrome shows phenotypic and genetic heterogeneity, aiding improved genotype–phenotype correlations and management guidelines.

Common symptoms include sagittal craniosynostosis, a narrow thorax, short long bones, joint laxity, hair and tooth abnormalities, and renal disease (54). Eye abnormalities affect visual acuity and the posterior segment, often requiring specialized testing. Retinal dystrophy is linked to *WDR19* mutations (55). Sensenbrenner syndrome overlaps with ATD-JS and other ciliopathies but has unique cranial and dental features. Renal, liver, and eye abnormalities are prevalent, with significant variability. Brain imaging typically reveals fluid-filled spaces without major defects. Early diagnosis and high mortality rates, particularly due to respiratory and renal issues, are common, with some patients surviving into their twenties. Renal and liver diseases are major contributors to morbidity and mortality (54).

Joubert syndrome

Joubert syndrome (JS) is a rare autosomal recessive genetic disorder characterized by cerebellar vermis hypoplasia and the distinctive "molar tooth sign" on brain MRI (56). This syndrome involves a variety of symptoms, including hypotonia with lateral ataxia, intellectual disability, oculomotor apraxia, retinal dystrophy, and abnormalities in the respiratory, renal, hepatic, and skeletal systems. These pleiotropic features are typical of disorders involving primary cilium dysfunction, resulting in significant overlap with other ciliopathies, such as nephronophthisis, Meckel syndrome, and Bardet–Biedl syndrome. Diagnosis often includes neurology, genetics, or pediatric clinics, which are based on MRI findings, clinical symptoms, and genetic testing (57). JS is inherited predominantly in an autosomal recessive manner, with mutations identified in more than 35 genes, including *INPP5E*, *TMEM216*, *AHI1*, *NPHP1*, and *CEP290*. Diagnostic accuracy is enhanced by next-generation sequencing (NGS), which can identify causative mutations in a significant percentage of cases. Genetic counseling is essential for families to understand inheritance patterns, recurrence risks, and reproductive options. JS can be classified into several subtypes on the basis of specific symptoms, including retinal diseases, renal diseases, hepatic diseases, and other specific features, such as oral-facial-digital anomalies or Jeune asphyxiating dystrophy (58, 59). Current treatments focus on managing symptoms and complications, with potential therapies including drugs to manage cystic renal diseases, gene therapy to correct specific mutations, and interventions to address co-occurring morbidities such as retinal, renal, and liver diseases. Despite the lack of a cure for the cerebellar malformations underlying JS, these treatments aim to improve the quality of life of patients. Future research should identify additional JS-causing genes and metabolic pathways, ultimately aiming to optimize treatment options and improve outcomes for individuals with JS (60).

Knowledge Gaps

Despite significant advances in the molecular characterization of syndromic cone–rod dystrophies, important knowledge gaps persist. For many syndromes, including Jalili syndrome and thiamine-responsive megaloblastic anemia, the number of genetically confirmed cases remains small, limiting the precision of natural history models and hindering the development of evidence-based management guidelines (27, 30). Phenotypic variability within single genotypes, such as the diverse ocular manifestations reported in CNNM4-related Jalili syndrome, suggests that modifier genes, epigenetic influences, or environmental exposures may play a significant role (61, 62). However, these mechanisms are poorly understood. In neurodegenerative syndromes such as the neuronal ceroid lipofuscinoses, the relative contribution of retinal versus central nervous system pathology to visual decline remains a matter of debate, complicating the design of targeted therapies (61, 62). Furthermore, while gene therapy and enzyme replacement strategies are emerging for select conditions, their long-term safety, durability of effect, and accessibility outside of specialized centres remain uncertain (61, 62). These unresolved issues highlight the need for coordinated international registries, standardized outcome measures, and mechanistic studies to advance the field.

Future Perspectives

Looking ahead, several priorities emerge for research and clinical practice. First, there is a pressing need for multicentre, prospective natural history studies that capture both ocular and systemic trajectories using harmonized protocols. Such studies would provide the foundation for reliable genotype–phenotype correlations and for defining clinically meaningful trial endpoints. Second, the integration of genomic sequencing into routine diagnostics should be accompanied by functional studies, including the use of patient-derived retinal organoids and animal models, to elucidate disease mechanisms and identify potential therapeutic targets. Third, future interventional trials must go beyond proof-of-concept to evaluate long-term efficacy, safety, and cost-effectiveness of gene- and cell-based therapies, ensuring that visual outcomes are assessed alongside systemic manifestations (62, 63). Equally important is the strengthening of multidisciplinary care pathways: expanding access to genetic counselling, low-vision rehabilitation, and coordinated specialty services should be recognized as a core research and

policy goal. Finally, ensuring equitable global access to molecular diagnostics and emerging therapies remains an overarching challenge; international collaboration, policy advocacy, and patient-led initiatives will be essential to translate scientific advances into meaningful benefits for all affected individuals (62, 63).

Management and Multidisciplinary Care

Management of syndromic cone–rod dystrophies remains largely supportive, yet optimal care requires a comprehensive and multidisciplinary approach. Early referral for low-vision services is essential, enabling the timely introduction of rehabilitation strategies such as orientation and mobility training, use of optical and electronic magnification devices, optimization of contrast and lighting, and incorporation of assistive digital technologies. Occupational and educational interventions are critical for maintaining independence and facilitating social and academic participation, particularly in pediatric populations. A coordinated inherited retinal disease clinic model, integrating ophthalmologists, clinical geneticists, genetic counsellors, audiologists, nephrologists, endocrinologists, and allied health professionals, has been shown to enhance diagnostic accuracy, streamline access to molecular testing, and provide holistic support (64). Genetic counselling is a cornerstone of care, offering families guidance on inheritance patterns, recurrence risk, reproductive options including preimplantation genetic diagnosis, and information about eligibility for emerging clinical trials and gene-targeted therapies (64). Disease-specific interventions, where available, should be incorporated, for example, dietary phytanic acid restriction in Refsum disease or cardiometabolic surveillance in Alström syndrome (64). This multidisciplinary approach not only addresses ocular morbidity but also ensures systemic manifestations are appropriately managed, ultimately improving long-term quality of life (64).

Conclusion

CRDs are a diverse group of inherited retinal disorders that are accompanied by additional systemic abnormalities. These conditions arise from mutations in genes that impact not only the retina but also other organ systems. The pathogenesis of syndromic CRDs involves genetic mutations that disrupt the normal function of photoreceptors and other cells, leading to progressive degeneration and a range of systemic issues. The diagnosis of syndromic CRDs requires a multidisciplinary approach involving detailed patient histories, clinical evaluations, and advanced genetic testing to identify the specific mutations responsible. Treatment is typically symptomatic and supportive, aiming to manage both ocular and systemic manifestations. For retinal symptoms, options may include visual aids, low vision rehabilitation, and emerging therapies such as gene therapy. Systemic symptoms are managed by relevant specialists. The overall goal is to improve the quality of life of patients through comprehensive care and targeted interventions.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Authors' contributions

All authors contributed equally in the drafting and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript.

Acknowledgements

None.

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