Achromatopsia: a review

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Purpose of review
The purposes of this article are to examine the literature published on achromatopsia and provide a comprehensive review of the clinical disease, genetic characteristics, and potential for therapy. Specifically, this article will describe recent advances in gene therapy in animal models, clinical features in human, and barriers to human translation.

Recent findings
Building on prior success with adeno-associated virus (AAV) therapy in mice models for achromatopsia with mutations in the *CNGB3*, *CNGA3*, or *GNAT2* genes, multiple cone-specific promoters have recently been developed and shown success in mice and nonhuman primates. A sheep CNGA3 model has also been characterized. Two clinical trials are under way: one to better characterize humans with achromatopsia and another to study a ciliary neurotrophic factor (CNTF) implant as a treatment for patients with the *CNGB3* mutation.

Summary
Genetic understanding and disease characterization of achromatopsia continues to evolve, as do gene therapy tools and animal models. The potential for the treatment of achromatopsia in humans with gene therapy shows great promise.

Keywords
achromatopsia, color blindness, cone dystrophy, rod monochromacy

INTRODUCTION

Achromatopsia, also known as rod monochromacy, is present in about 1:30 000 births. It is an autosomal-recessive genetic disease defined by loss of cone cell function in the retina, classically presenting with color blindness, photophobia, nystagmus, and decreased visual potential with visual acuity often less than 20/200. Other symptoms include jerk that are symmetric, high frequency, and low amplitude, occurring in any direction. Signs and symptoms vary as cases range clinically from complete (typical) to incomplete (atypical) achromatopsia, depending on the amount of residual cone function. Patients can sometimes distinguish colors based on shades of gray and cortical knowledge [1,2].

The purpose of this article is to summarize the genetics of achromatopsia, discuss the diagnosis and management of patients, and outline the potential for targeted gene therapy.

GENETICS

Achromatopsia is one of many hereditary dystrophies that affect the central retina. It is caused by mutations in various genes involved in cone cell function. These genes include cyclic nucleotide-gated channel beta 3 (*CNGB3*/*ACHM3*) (mutated in ~40–50% of affected individuals), Cyclic nucleotide-gated channel alpha 3 (*CNGA3*/*ACHM2*) (~25%), guanine nucleotide binding protein (G protein), alpha transducing activity polypeptide 2 (*GNAT2*/*ACHM4*) (<2%), phosphodiesterase 6C, cGMP-specific, cone, alpha prime (*PDE6C*/*ACHM5*) (~<2%), and phosphodiesterase 6H, cGMP-specific, cone, alpha prime (*PDE6H*/*ACHM6*) (~0.3%) (see Table 1) [3–7].

These five genes code for proteins required for critical steps of phototransduction in the cone photoreceptors. When cones are exposed to light stimuli, excited pigment molecules undergo energy exchange at the alpha subunit of the transducin protein GNAT2 (ACHM4). Activated transducin will

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KEY POINTS

- Achromatopsia is an autosomal recessive disease defined by loss of cone function, severe color vision deficit, photophobia, nystagmus, and decreased visual potential.
- There are currently five known causative genes *CNGB3* (~40–50% of affected individuals), *CNGA3*, *GNAT2*, *PDE6C*, and *PDE6H*.
- AAV gene therapy has demonstrated remarkable near-full recovery of cone function and visual acuity in mouse models for *CNGB3*, *CNGA3*, or *GNAT2* mutations.
- Development of new animal models, cone-specific promoters, and further human characterization show promise for translation to humans.

bind to the PDE6C protein and the inhibitory gamma-subunit PDE6H (ACHM6). Finally, the alpha and beta subunits of the cyclic nucleotide-gated ion channels on the plasma membrane of outer cone segments, CNGA3 (ACHM2) and CNGB3 (ACHM3), are activated, leading to membrane polarization changes 1 [8,9].

The association between mutations in these five specific genes and a complete or incomplete achromatopsia phenotype does not appear to directly correlate. A study of 258 patients by Wissinger *et al.* [7] examined patients with *CNGA3* mutations, a gene originally felt to be responsible for the autosomal recessive complete form of the disease. *CNGA3* mutations were detected in both complete and incomplete achromatopsia. Additionally, *CNGA3* mutations were occasionally found in patients with severe progressive cone dystrophy. Therefore, a *CNGA3* mutation may not always cause complete absence of cone function. These findings have been replicated in patients affected by a *GNAT2* mutation [10]. Rosenberg *et al.* [11] in 2004, reporting on two cousins with *GNAT2* mutations, further elucidated these genetic discrepancies. One cousin was found to carry a homozygous frameshift mutation (Tyr95fs) whereas the other was compound heterozygous for the Tyr95fs and a new intronic mutation (c.461 + 24G→A). The researchers demonstrated that the precise type of genetic mutation (i.e. frameshift mutation vs. splicing defect) creates unique phenotypes even in the absence of detectable cone function on electroretinogram (ERG) testing. One exhibited incomplete achromatopsia symptoms while the other had relatively preserved color discrimination. Given that the genes which lead to complete achromatopsia may also present as the incomplete form of the disease, the term 'oligocone trichomacy' has been suggested [11].

Prior to understanding the genetics of achromatopsia, histological study of postmortem patients demonstrated absence or abnormal cones in segments of the fovea and peripheral retina. These early findings highlight the complexity of cone morphology and variable phenotypes (typical and atypical) in achromatopsia, which further supports the need for genetic characterization, in-vivo visualization techniques and research in genetic therapies [3,9,12].

Molecular genetic testing for achromatopsia can be performed not only for risk assessment in relatives, but also for prenatal diagnosis, prognosis, and identifying carriers. The analytical sensitivity and specificity of genetic testing are 100% and greater than 95%, respectively, when *CNGB3*, *CNGA3*, *GNAT2*, and *PDE6C* are all tested for. Because achromatopsia is 100% penetrant, prenatal testing does confirm clinical expression from birth [13]. Testing can be obtained at Next GxDx (https://www.nextgxdx.com/apps/search/#/?q=achromatopsia).

SIGNS AND SYMPTOMS

The clinical signs of achromatopsia vary as dictated by the number and type of functioning cone cells. In typical complete achromatopsia, patients present usually by 6 months old with photophobia and nystagmus. Visual acuity is typically less than 20/200 for those with complete achromatopsia but may be as good as 20/80 for those with incomplete achromatopsia. Although the nystagmus may become less noticeable overtime, visual acuity is usually stable. This is in contrast to other cone dystrophies in which visual acuity progressively worsens. Photosensitivity persists and may remain a debilitating symptom.

Additional symptoms may include a small central scotoma with eccentric fixation. Given the variety of genetic mutations and the complex pattern of retinal cone loss, phenotypic variability is not surprising. Some individuals with an incomplete achromatopsia have a phenotypic appearance similar to that of young patients with early cone dystrophy. These patients may exhibit less photophobia and less difficulty with color discrimination.

DIAGNOSIS

Upon presentation, the clinical diagnosis of achromatopsia can be made through clinical and family history, examination for nystagmus, visual acuity testing, color vision assessment, and fundoscopic examination. If there is suspicion for achromatopsia,

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Table 1. Genes implicated in achromatopsia

Gene	Full gene name	Locus name	Locus site	Phenotype	Inheritance pattern
CNGA3	Cyclic nucleotide gated channel alpha 3	ACHM2	2q11.2	Underlie about 25% of cases of achromatopsia. Over 100 mutations in this gene have been identified to result in achromatopsia. In some cases mutation results in no production of alpha subunit, whereas others result in altered protein that does not function properly. Defects may cause cone cells to flood with cations and ultimately self-destruct.	Autosomal recessive
CNGB3	Cyclic nucleotide gated channel beta 3	ACHM3	8q21.3	Over 40 mutations found to cause achromatopsia. These mutations are responsible for 50–70% of cases of complete achromatopsia. Most mutations prevent production of beta subunit, which causes CNG channel structure to be altered	Autosomal recessive
GNAT2	Guanine nucleotide binding protein (G protein), alpha transducing activity polypeptide 2				
	ACHM4	1p13.1	At least 10 mutations found to cause achromatopsia. Mutations that underlie complete achromatopsia cause nonfunctional version of cone-specific alpha subunit of transducin	Autosomal recessive	
PDE6C	Phosphodiesterase 6C, cGMP-specific, cone, alpha prime				
	ACHM5	10p24	At least 19 mutations cause achromatopsia. Mutations affect alpha-prime subunit and destroy function of cone-specific phosphodiesterase	Autosomal recessive	
PDE6H	Phosphodiesterase 6H, cGMP-specific, cone, gamma				
	ACHM6	12p13	S12X mutation prevents production of functional inhibitory gamma subunit, which interferes with normal functioning of cone-specific phosphodiesterase. This disrupts the process of phototransduction in cones. Results in incomplete achromatopsia	Autosomal recessive	

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additional testing may include optical coherence tomography (OCT), visual fields, and ERG.

As noted above, evidence of disease on fundoscopic examination is uncommon, though there may be narrowing of blood vessels retinal pigment epithelium (RPE) mottling, or alteration of the foveal reflex. Visual field examination often shows a relative central scotoma; however, this may be difficult to elucidate in the setting of unsteady fixation [39].

One of the most common tests of retinal function in suspected patients is the ERG. Full-field ERG often fails to show pathologic changes due to the limited number of photoreceptors within the fovea compared with the entire retina. Genead *et al.* [9] in 2011 found that in full-field ERG testing in achromatopsia, 75% of patients had normal responses. Multifocal ERG (mfERG) allows for more precise diagnostics and eliminates contribution of the extramacular retina. Diagnosis of achromatopsia is generally supported when there is absent response from a 30 or 15-Hz stimulus in the cone-driven pathway on mfERG. It should be noted however that mfERG may not be sensitive enough to confidently differentiate between complete and incomplete achromatopsia, as many patients with clinically complete achromatopsia will have residual ERG responses [9,14].

Another diagnostic technique is OCT. Achromatopsia patients generally exhibit three features – a loss of the photoreceptor layer in the foveal region and disruption of the inner/outer segment junction, foveal hypoplasia, and macular thinning. Disease seen on the spectral domain – OCT varies but may include loss of the photoreceptor layer in the foveal region, disruption of the IS/OS junction, and attenuation of the RPE layer. The cause of these differences is multifactorial and includes diversity in the genetic mutations and age of the patient [3,9]. Despite the variability in specific findings, Genead *et al.* demonstrated that approximately 85% of achromatopsia patients have some degree of disruption of photoreceptors on OCT.

On a peak luminosity or brightness examination, achromats will have only a response from rod photoreceptors, and none from cones. Testing color vision is helpful in characterizing the ACHM phenotype. Patients with achromatopsia demonstrate abnormalities in all axes. Testing of color vision maybe unreliable as patients may begin to discern colors based on differences in brightness (using their undamaged rod photoreceptors) or learned associated object–color relationships. Standard testing modalities include the Rayleigh anomaloscope (complete achromats will successfully color-match the spectral yellow primary to any mixture of spectral red or green primaries, but will only be able to complete brightness matches to red primary mixtures), the Farnsworth Munsell 100-Hue test (no specific axis of color confusion is generally noted on this test) and the Panel D-15 test (color chips are characteristically arranged by their perceived brightness by rod cells in achromats) [15].

DIFFERENTIAL DIAGNOSIS

Blue cone monochromacy, also known as S cone monochromacy or X-lined incomplete achromatopsia, is an X-linked recessive condition caused by disruption of the red and green pigment gene cluster at Xq28. Patients lack long and medium wavelength-sensitive cones, while short cones are preserved; unlike achromats who lack all cones. Patients typically present in a clinically similar fashion with poor color discrimination, nystagmus, eccentric fixation, and absence of fundus abnormalities. However, on the peak luminosity or brightness examination, the patient will have a response near 400 nm (blue cones), whereas an achromat will have a response only of the rods. Additionally, the ERG will demonstrate some cone response when presented with blue flashes. The Berson color plates, which have varying degrees of blue/purple chroma arrows, are one useful way of differentiating X-linked incomplete achromatopsia (able to distinguish the blue/purple arrows on test plates) from autosomal recessive achromats (who fail to distinguish any of the plates) [16].

Red–green color blindness, including variations protanopia, deuteranopia, protanomaly, and deuteranomaly are the most common form of color blindness and affect nearly 8% of males. These are all driven by X-linked mutations affecting medium or long cones resulting in varying degrees of red and green confusion. Two genes associated with red–green defects are OPN1LW (long red cones) and OPN1MW (medium green cones).

In cone dystrophies, the cone cells are present and functional at birth. Unlike achromatopsia, the inheritance of cone dystrophies is viable and may be autosomal dominant or X-linked. Overtime, the patient will develop achromatopsia-type symptoms including photophobia, glare sensitivity, and decreased visual acuity. The age of onset can be early in childhood, mimicking achromatopsia and making diagnosis difficult, particularly distinguishing incomplete achromatopsia from early cone dystrophy. Disease progression as well as occasional abnormalities in the rods can separate the cone dystrophy from the achromatopsia patient. A bull's eye maculopathy may be seen on fundoscopic exam [17].

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Alström syndrome is an autosomal recessive disorder with unique systemic characteristics in addition to a cone–rod dystrophy. Patients demonstrate photophobia, nystagmus, and ERG responses generally show a lack of both cone and rod responses (some rod response may be preserved in early childhood). Obesity, hearing loss, glucose intolerance, and dilated cardiomyopathy are among the nonocular manifestations [18].

Cerebral achromatopsia is an acquired disorder. Following traumatic brain injury (particularly to the ventral occipital cortex) or cerebral infection and inflammation, patients may lose capacity for color vision. Age at presentation and medical history will help to differentiate this condition from ACHM. Additionally, these patients nearly always have additional neurologic symptoms beyond the loss of color vision [19].

MANAGEMENT

There is currently no cure for achromatopsia. Management targets symptoms and associated findings, striving to improve quality of life. The photophobia of ACHM is generally nonprogressive; however, visual acuity will vary based on light conditions and progression of disease, and therefore regular ophthalmic examination is recommended every six to 12 months in children to optimize refraction. For adults, examination every 2–3 years may be sufficient. The photophobia can be extreme even in low light settings. Avoidance of light, use of visors, specialized filtered Corning Glare control lenses (CPF 550 XD is particularly helpful for achrmoats, as are CPF 527) or red/gray/amber-tinted eyeglasses and/or contact lenses are used to help to reduce this symptom, and subjectively improve visual acuity. Tinted contact lenses supplemented with sunglasses or wrap-around glasses or use of opaque side-shields may also be used [2].

Occupational aids are commonly used in schools and recreational settings for children with decreased visual acuity. These may include magnified reading material and specific seating. Reduction of glare in the classroom is useful. In addition, one electronic aid is the 'Colorino' (CARETEC, Wien, Austria, www.caretec.at) which will audibly announce a color after a light probe is placed on the object in question. Technological aids such as the 'eyeborg', (www.eyeborgproject.com) allows achromats to perceive color via sound. First used by artist Neil Harbisson in 2004, the head mounted device senses colors in front of the wearer and converts them to sound waves through bony conduction. Advancements have made the eyeborg capable of transmitting not just color but saturation as well, using variation in volume. Identification of color beyond the white light spectrum is also possible, including infrared and violet lights [20].

If visual acuity and jurisdictional laws permit, patients with achromatopsia can drive a car through the use of biooptics. The detection of colored stop lights, brake lights, changing light levels, and glare can however be very difficult [21]. Production and testing of driverless cars are also underway and may address the difficulties that driving poses to patients with achromatopsia and other visual disorders.

Beyond occupational needs, psychosocial issues need to be addressed with the patient and family. Open communication about coping with the deficits imposed by achromatopsia is needed. Designation as 'legally blind', wherever appropriate, including registration with the Commission for the Blind allows for services and benefits. Areas of importance include the educational setting, the home, relationships with others, and the challenges of parenting a child with achromatopsia. The mere act of communication with others about color can be a stressful concept that requires attention.

There are many groups that have been founded to support these aforementioned needs of patients with achromatopsia. Notably, Frances Futterman founded the Achromatopsia Network for many years and created a comprehensive 160-page guide for understanding and coping with the disease. Although, Ms Futterman passed away, the site and materials remain active. Other organizations supporting those with achromatopsia have sprung up in recent years as well [22].

Achromacorp is a nonprofit charity that was started in 2012 by John and Bridget Vissari, the parents of a 7 year-old child who was diagnosed with achromatopsia at the age of 6 months. In the past, they have worked to raise money to support research being conducted at the University of Florida and the Chicago Lighthouse. Achromacorp can be contacted by telephone at +1(724) 841-4052, emailed at bvissari@achromacorp.org or messaged through their website at http://www.achromacorp.org/ContactUs.html [23,24].

The Foundation Fighting Blindness is a publicly supported charity based in Columbia, Maryland that connects and supports researchers studying achromatopsia and other eye conditions that lead to blindness including retinitis pigementosa and macular degeneration. The CEO of the organization is William T. Schmidt and the organization can be contacted at +1(800) 683-5555 or info@fightblindness.org [25].

Project Chroma at the John and Marcia Carver Nonprofit Genetic Testing Laboratory in Iowa City seeks to identify every person with ACHM and offer

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them genetic testing on a nonprofit basis. Genetically identifying each and every patient with achromatopsia would better help characterize the disease and provide further support for clinical trials of the use of gene therapy to treat achromatopsia. The laboratory can be contacted via E-mail at carverlab@uiowa.edu or via online form at https://www.carverlab.org/contact/online [26].

Laura and Richard Windsor of the Low Vision Centers of Indiana have also started a website, achromatopsia.info, which was created to be a resource for individuals with congenital achromatopsia, given the previous lack of readily accessible for patients suffering from achromatopsia and their families. Their website helps to better explain achromatopsia from describing vision of patients with achromatopsia to exploring the emotional impact of living with achromatopsia. The website also provides information on genetic basis and diagnosis of the disease as well as genetic treatments currently being worked on, which were outlined above. The practice of Drs Laura and Richard Windsor at the Low Vision Centers of Indiana focuses on rehabilitation of patients with achromatopsia, macular degeneration, diabetes, and visual impairments from stroke or other brain injuries. Richard and Laura Windsor can be contacted at richw@eyeassociates.com and drlaura@eyeassociates.com, respectively. The Low Vision Centers of Indiana can be contacted through sending a message at http://www.achromatopsia.info/contact-us/ or calling +1(317) 844-0919 for their Indianapolis office and +1(260) 432-0575 for their Fort Wayne Office [27].

Achromatopsia is known by many lay people for its presence in the small Micronesian atoll population of Pingelapese people as discussed by neurologist Oliver Sacks in his book *The Island of the Colorblind*. After a typhoon hit the island in 1775, one of 20 survivors was heterozygous for achromatopsia. Today, approximately 5% of the population suffers from achromatopsia with 30% being carriers [28]. This population serves as a model for increased incidence of achromatopsia in other, larger populations, where parental consanguinity may be common [15]. This population lives despite being near the equator with intense sunlight daily. Affected individuals fish at night and have made other remarkable adaptions demonstrating how individuals with this condition can thrive despite the challenges of the disorder.

GENE THERAPY

Many researchers have explored the feasibility of gene therapy for achromatopsia. In 2011, Genead *et al.* [9] characterized patients with achromatopsia using SD-OCT, anomaloscopy, and ERG to generate baseline data to help identifying patients who might benefit from gene therapy. Among their results was that 83% of patients showed evidence of some residual cone response on ERG [9]. Ongoing studies in mice, primates, and canines using adeno-associated virus (AAV) therapy have shown great promise. Using knockout mouse models for *CNGB3*, *CNGA3*, or *GNAT2*, multiple researchers have demonstrated remarkable near-full recovery of cone function and visual acuity. It appears that cone function may be regained at numerous points of intervention in animals; however, earlier therapy was required in mouse models for full visual acuity to be achieved. These studies suggest potential for translation to humans given the use of human promoters and human transgenes in the mouse models [29–32]. Thiadens *et al.* [33] in 2010 demonstrated progressive cone cell loss and foveal hypoplasia with age, suggesting that earlier intervention would be optimal. In contrast, Sundaram *et al.* (2014) [34▪▪] examined 40 patients and found that retinal structure and function did not vary with age. Eligibility or potential to benefit from gene therapy may therefore be governed by the retinal structure and not necessarily by age.

Banin *et al.* (2014) [35] identified a spontaneously arising sheep model for ACHM2 and utilized this model to study AAV vectors carrying both mouse and human genes. They showed success in improving cone-mediated visual function (increased amplitude and higher flicker-fusion frequencies on ERG) without adverse events. Following their success, they later published the ERG cone responses in both normal and day blind CNGA3 sheep to generate a normative database for the use in gene therapy studies [36].

Dyka *et al.* (2014) [37▪] showed success with a more specific cone-targeted human promoter in mice. Immunohistochemistry (IHC) demonstrated good strength and specificity of their chimeric promoter with an enhancer element of interphotoreceptor retinoid-binding protein promoter and a sequence of human transducin alpha-subunit promoter (*IRBPe/GNAT2*). A synthetic transducin alpha-subunit promoter (*synGNAT2/GNAT2*) was also studied; however, the chimeric promoter was more effective.

Ye *et al.* (2014) [38▪▪] analyzed the success of particular cone-specific promoters in mice and nonhuman primates (NHP). Interestingly, their study showed no expression of the *IRBPe/GNAT2* promoter in NHP. The PR1.7 promoter however showed efficient expression in primate cones at 12 months after promoter injection. This study demonstrated that promoters effective in mice and dogs may not be suitable for use in primates.

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ONGOING RESEARCH

Currently, a natural history trial to further characterize patients with ACHM3 is ongoing. This prospective cohort study, started in May 2013, aims to identify patients with *CNGB3* mutations and characterize their clinical findings using several tests of visual function once a year for up to 3 years. Given that gene therapy in animal models relies upon the presence of cone receptors to successfully restore function, the retinas of patients with achromatopsia, must be fully characterized before potential application of such therapy. The goal of this study is to quantify the amount of residual cone structure in patients [39].

A United States National Institutes of Health (NIH) study is evaluating the safety and efficacy of ciliary neurotrophic factor (CNTF) implants in ACHM3. CNTF is known to help and promote proper functioning and survival of nerve cells. Five participants are currently enrolled, with one eye treated per participant. This is a Phase I/II, prospective, single-center study, with treatment as its primary purpose. The study will end when the final participant has 3 years of follow-up. Number and severity of adverse events, and systemic and ocular toxicities will characterize safety at 6 months post-implantation. Assessment of retinal function, ocular structure, and occurrence of adverse events will be recorded at all time points. Secondary outcomes for this study include changes in visual function including visual acuity and color vision, ERG changes, and retinal imaging with OCT. This study began recruitment in 2012 and aims to be complete in December 2015 (www.clinicaltrials.gov) [40].

CONCLUSION

Achromatopsia is a clinically diagnosable autosomal recessive disease characterized by severe color vision deficits, photophobia, nystagmus, and decreased visual acuity. The symptoms and psychosocial implications require life-long adaptations, use of technological aids, and clinical monitoring. Although genotype and phenotype do not correlate precisely, there are multiple known specific genetic mutations underlying the disorder. These factors, in addition to the accessibility of the retina and its immunologically privileged location, make achromatopsia an appealing target for the advancing field of genetic therapy.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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