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Achromatopsia

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Summary

Clinical characteristics

Achromatopsia is characterized by reduced visual acuity, pendular nystagmus, increased sensitivity to light (photophobia), a small central scotoma, eccentric fixation, and reduced or complete loss of color discrimination. All individuals with achromatopsia (achromats) have impaired color discrimination along all three axes of color vision corresponding to the three cone classes: the protan or long-wavelength-sensitive cone axis (red), the deutan or middle-wavelength-sensitive cone axis (green), and the tritan or short-wavelength-sensitive cone axis (blue). Most individuals have *complete achromatopsia*, with total lack of function of all three types of cones. Rarely, individuals have *incomplete achromatopsia*, in which one or more cone types may be partially functioning. The manifestations are similar to those of individuals with complete achromatopsia, but generally less severe.

Hyperopia is common in achromatopsia. Nystagmus develops during the first few weeks after birth followed by increased sensitivity to bright light. Best visual acuity varies with severity of the disease; it is 20/200 or less in complete achromatopsia and may be as high as 20/80 in incomplete achromatopsia. Visual acuity is usually stable over time; both nystagmus and sensitivity to bright light may improve slightly. Although the fundus is usually normal, macular changes (which may show early signs of progression) and vessel narrowing may be present in some affected individuals. Defects in the macula are visible on optical coherence tomography.

Diagnosis/testing

The diagnosis of achromatopsia is established in a proband through clinical and family history, examination for nystagmus, visual acuity testing, color vision assessment, and fundoscopic examination. If achromatopsia is suspected, additional testing may include optical coherence tomography, fundus autofluorescence, visual fields, and electroretinogram. Identification of biallelic pathogenic (or likely pathogenic) variants in *ATF6*, *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, or *PDE6H* confirms the clinical diagnosis.

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Management

Treatment of manifestations: Dark or special filter glasses or red-tinted contact lenses to reduce photophobia and potentially improve visual acuity; low vision aids; preferential classroom seating for children; occupational aids.

Surveillance: Ophthalmologic examination every six to 12 months for children and every two to three years for adults.

Genetic counseling

Achromatopsia is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the pathogenic variants have been identified in the family.

GeneReview Scope

Achromatopsia: Included Phenotypes [1]
• Complete achromatopsia (rod monochromatism, total color blindness) • Incomplete achromatopsia

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

Achromatopsia **should be suspected** in individuals with the following typical clinical findings, additional testing, and family history.

Clinical findings

- Pendular nystagmus
- Increased sensitivity to light (photophobia)
- Eccentric fixation
- Reduced visual acuity
- Reduced or complete lack of color discrimination
- Small central scotoma
- Fundus appearance: normal in many affected individuals, but can show subtle bilateral macular changes such as absence of the foveal reflex, pigment mottling, or narrowing of the retinal vessels. Frank atrophy of the retinal pigment epithelium (RPE) in the fovea can occur in older individuals.

Additional testing

Color vision tests. The color perception of individuals with achromatopsia (achromats) is unreliable; many achromats learn to associate certain colors with objects and to recognize some colors by discerning differences in brightness [Sharpe et al 1999]. In general, all achromats have anomalous (impaired) color discrimination along all three axes of color vision corresponding to the three cone classes: the protan or long-wavelength-sensitive cone axis (red), the deutan or middle-wavelength-sensitive cone axis (green), and the tritan or short-wavelength-sensitive cone axis (blue). The following results are found on standard testing for color vision:

- Generally, no specific axis of color confusion is found on the Farnsworth Munsell 100-hue test.

- An achromat axis (in which the constituent color chips are arranged according to their rod-perceived lightness) is characteristic for complete achromatopsia on both the saturated and desaturated versions of the Panel D-15 test.
- The most important and diagnostic test is red-green color discrimination with the Rayleigh anomaloscope equation. Although a complete achromat can always fully color-match the spectral yellow primary to any mixture of the spectral red and green primaries, a brightness match is only possible to red primary-dominated mixtures.

Visual field testing. Small central scotomas can be demonstrated in some individuals by careful testing. However, unsteady fixation can make demonstration of a central scotoma difficult.

Electroretinogram (ERG)

- **Full-field ERG.** The photopic response (including the 30-Hz flicker response) is absent or markedly diminished; the scotopic response is normal or mildly abnormal.
- **15-Hz flicker ERG.** A typical finding is absence of the cone-driven fast pathway response elicited by high flash intensities [Bijveld et al 2011].

Optical coherence tomography (OCT). A variable degree of foveal hypoplasia as well as disruption and/or loss of inner-/outer-segment junction of the photoreceptors and an attenuation of the RPE layer within the macular region can be observed at an early age [Genead et al 2011, Thomas et al 2011, Sundaram et al 2014, Lee et al 2015, Zobor et al 2017].

Fundus autofluorescence imaging shows missing or variable formation of foveal hypofluorescence or a larger lesion with a surrounding hyperautofluorescent ring and a central region of absent autofluorescence corresponding to the lesion area seen on OCT [Greenberg et al 2014, Kohl et al 2015].

Adaptive optics imaging shows remnant cone structure; however, the number and spatial distribution of the foveal cones are highly variable – the foveal cone mosaic ranges from a contiguously packed mosaic to a sparsely arranged collection of cones [Langlo et al 2016].

Family history is consistent with autosomal recessive inheritance.

Establishing the Diagnosis

The clinical diagnosis of achromatopsia **is established** in a proband with typical findings on clinical examination, additional testing, and family history (see Suggestive Findings). Identification of biallelic pathogenic (or likely pathogenic) variants in one of the six genes listed in Table 1 establishes the molecular diagnosis.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) in one of the six genes listed in Table 1 does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **targeted analysis** for the common *CNGB3* variant c.1148delC, use of a **multigene panel**, or **comprehensive genomic testing** (typically **exome sequencing**):

- **Targeted analysis** for the most common pathogenic variant c.1148delC in *CNGB3* can be performed first in European populations or populations of European descent in the US, Canada, Australia, and New Zealand (see Molecular Genetics, *CNGB3*, **Pathogenic variants**).

- **A multigene panel** that includes *ATF6*, *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, *PDE6H*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene[s] are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** can also be used.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Achromatopsia

Gene [1]	Proportion of Achromatopsia Attributed to Pathogenic Variants in Gene [2] (Population)	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ATF6	1.5%	15/15 [6]	None reported [7]
CNGA3	5%-33% (European) 84% (Israeli & Palestinian) [8] 80% (Chinese) [9]	~100% [10]	None reported [7]
CNGB3	60% (European) 16% (Israeli & Palestinian) [11]	~95% [12]	7 distinct deletions in 7 families; 3 duplications in 10 families [13]
GNAT2	1.8%	~99%	3 families [14]
PDE6C	2.5% [15]	All reported [16]	None reported [7]
PDE6H	0.1%	See footnote 17.	None reported [7]

Table 1. continued from previous page.

Gene [1]	Proportion of Achromatopsia Attributed to Pathogenic Variants in Gene [2] (Population)	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown	10%-25% [18]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Mayer et al [2017] unless otherwise noted
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Ansar et al [2015], Kohl et al [2015], Xu et al [2015], Carss et al [2017], Skorczyk-Werner et al [2017]
7. Larger deletions, insertions, or duplications have either not been reported or are confined to single reports or families [Rosenberg et al 2004]. Consequently, the prevalence and detection rate for such pathogenic variants cannot be estimated.
8. Zelinger et al [2015]
9. Kohl et al [1998], Wissinger et al [2001], Kohl et al [2005], Liang et al [2015], Zelinger et al [2015]
10. Kohl et al [1998], Wissinger et al [2001], Johnson et al [2004], Tränkner et al [2004], Nishiguchi et al [2005], Varsányi et al [2005], Ahuja et al [2008], Koeppen et al [2008], Reuter et al [2008], Koeppen et al [2010], Thiadens et al [2010], Genead et al [2011], Vincent et al [2011]
11. Kohl et al [2000], Kohl et al [2005], Thiadens et al [2009b], Zelinger et al [2015]
12. Of 163 individuals with pathogenic variants in *CNGB3*, 105 (64%) were homozygotes for c.1148delC, 44 (27%) were compound heterozygotes, and in 14 (9%) only one pathogenic variant was identified [Mayer et al 2017].
13. Kohl et al [2015], Mayer et al [2017]
14. Rosenberg et al [2004]; S Kohl, unpublished data
15. Chang et al [2009], Thiadens et al [2009a], Grau et al [2011], Huang et al [2013]
16. Aligianis et al [2002], Kohl et al [2002], Michaelides et al [2003], Piña et al [2004], Rosenberg et al [2004], Ouechtati et al [2011], Langlo et al [2016], Bryant et al [2017], Carss et al [2017], Taylor et al [2017], Ueno et al [2017]
17. A single nonsense variant has been reported in three families [Kohl et al 2012, Pedurupillay et al 2016].
18. Kohl et al [2005], Thiadens et al [2009b]

Clinical Characteristics

Clinical Description

Achromatopsia is characterized by reduced visual acuity, pendular nystagmus, increased sensitivity to light (photophobia), a small central scotoma (which is often difficult to demonstrate), eccentric fixation, and reduced or complete lack of color discrimination. Hyperopia is common. Nystagmus develops during the first few weeks after birth and is followed by increased sensitivity to bright light.

Best visual acuity varies with severity of the disease; it is 20/200 or less in complete achromatopsia and may be as high as 20/80 in incomplete achromatopsia. Visual acuity is usually stable over time, but both nystagmus and sensitivity to bright light may improve slightly. The fundus is usually normal, but macular changes and vessel narrowing may be present in some individuals, and optical coherence tomography (OCT) reveals macular changes that can progress with time [Thomas et al 2012].

Most individuals have **complete achromatopsia**, in which the symptoms can be explained by a total lack of function of all three types of cone (i.e., photopic) photoreceptors of the eye, with all visual functions being mediated by the rod (i.e., scotopic) photoreceptors.

Rarely, individuals have **incomplete achromatopsia**, in which one or more cone types may be partially functioning along with the rods. The symptoms are similar to those of individuals with complete achromatopsia

but generally less severe [Sharpe et al 1999]. Color discrimination ranges from well preserved to severely impaired; photophobia is usually absent; visual acuity is better preserved than in complete achromatopsia.

Phenotype Correlations by Gene

Complete achromatopsia. The majority of individuals with biallelic pathogenic variants in *ATF6*, *CNGA3*, *CNGB3*, *GNAT2*, and *PDE6C* have complete achromatopsia with similar clinical features. A significant genotype-phenotype correlation cannot be observed; however, individuals with *ATF6*-associated achromatopsia usually have a poorly formed or absent foveal pit.

Incomplete achromatopsia

- Certain *CNGA3* and *GNAT2* pathogenic variants are associated with a very mild phenotype of incomplete achromatopsia and oligo-cone trichromacy [Rosenberg et al 2004, Vincent et al 2011].
- Pathogenic variants in *PDE6H* lead to the incomplete form of achromatopsia [Kohl et al 2012].
- Cone-rod dystrophy and macular dystrophy have been reported for pathogenic variants in *ATF6* [Carss et al 2017, Skorczyk-Werner et al 2017].

Nomenclature

The **complete** form of achromatopsia is also referred to as rod monochromacy (monochromatism), complete (or total) color blindness (OMIM 216900), day blindness (hemeralopia), or "Pingelapese blindness." Clinically, it is known as typical, complete achromatopsia or complete achromatopsia with reduced visual acuity.

The **incomplete** form of achromatopsia is also known clinically as atypical, incomplete achromatopsia or incomplete achromatopsia with reduced visual acuity.

Prevalence

Achromatopsia is a rare disorder with an estimated prevalence of fewer than 1:30,000 [Sharpe et al 1999].

Parental consanguinity is common in certain geographic regions. On the island of Pingelap in the eastern Caroline Islands in Micronesia, the prevalence of achromatopsia is between 4% and 10%, secondary to the founder variant p.Ser435Phe in *CNGB3* [Sharpe et al 1999].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *PDE6H*.

Allelic disorders observed in the other five achromatopsia-associated genes are discussed in Tables 2a and 2b.

Table 2a. Allelic Disorders to Consider in the Differential Diagnosis of Achromatopsia

Gene	Disorder(s) [1]	MOI	References
CNGA3	Progressive cone dystrophy	AR	Wissinger et al [2001], Nishiguchi et al [2005]
CNGB3			Michaelides et al [2004], Thiadens et al [2010]
GNAT2			Piña et al [2004]
PDE6C			Thiadens et al [2009a], Huang et al [2013]
ATF6	Cone-rod dystrophy; macular dystrophy	AR	Carss et al [2017], Skorczyk-Werner et al [2017]

1. Often only distinguishable from achromatopsia by evidence of disease progression over time
AR = autosomal recessive ; MOI = mode of inheritance

Table 2b. Allelic Disorders (Not in the Differential Diagnosis of Achromatopsia)

Gene	Disorder	Reference
CNGB3	Macular degeneration	Nishiguchi et al [2005]
GNAT2	Oligo-cone trichromacy	Rosenberg et al [2004]

Differential Diagnosis

Achromatopsia is readily recognized by its characteristic features (see Suggestive Findings). Conditions to consider in the differential diagnosis are congenital nystagmus (as nystagmus is usually one of the first manifestations) and cerebral achromatopsia or dyschromatopsia, which is associated with severe or total color vision deficits and can arise adventitiously after brain fever, cortical trauma, or cerebral infarction, especially involving lesions to the ventral occipital cortex [Bouvier & Engel 2006].

Inherited retinal dystrophies that may be confused with achromatopsia are summarized in Table 3.

Table 3. Inherited Retinal Dystrophies to Consider in the Differential Diagnosis of Achromatopsia

Disorder	Gene(s)	MOI	Overlapping Clinical Features	Distinguishing Clinical Features	Comments
Blue-cone monochromatism [1] (OMIM 303700)	*OPN1LW*; *OPN1MW* [2]	XL [3]	• Severely ↓ visual acuity • Eccentric fixation • ± Infantile nystagmus • No obvious fundus abnormalities • Poor or no color discrimination [4]	In blue-cone monochromatism: • Peak of photopic luminosity function is near 440 nm (the peak sensitivity of the S cones), not 507 nm (the peak sensitivity of the rods). • Mostly males are affected.	• A special 4-color plate test or a 2-color filter test can clinically distinguish blue-cone monochromats from achromats (rod monochromats). • Cone ERG responses can be elicited by presenting blue flashes on a yellow background (because the S cones are functioning in addition to the rods).
Hereditary red-green color vision defects (OMIM 303800, 303900)	*OPN1LW*, *OPN1MW*	XL	Color vision defects [5]	In hereditary red-green color vision defects: • Absence of ophthalmologic or other associated clinical abnormalities • Most individuals w/protanomalous & deuteranomalous color vision defects (i.e., anomalous trichromats) have no major problems in naming colors. • Mostly males are affected.	• Clinical chart tests widely used to detect red-green color vision defects include Ishihara plates & the American Optical HRR pseudoisochromatic plates. • Definitive classification of color vision defects known as protanopia, deuteranopia, protanomaly, & deuteranomaly requires use of anomaloscope, which involves color matching.

Table 3. continued from previous page.

Disorder	Gene(s)	MOI	Overlapping Clinical Features	Distinguishing Clinical Features	Comments
Tritan and yellow-blue defects (OMIM 190900)	*OPN1SW*	AD	Color confusion	In tritan & yellow-blue defects: color confusion is limited to blues & greens. [6]	Other non-congenital yellow-blue deficits (similar in some ways to tritan defects) may result from aging or disorders of choroid, pigment epithelium, retina, or optic nerve (e.g., optic atrophy type 1; OMIM 165500); they are usually progressive & have other related signs; e.g. associated visual acuity defects. [7]
Cone / cone-rod dystrophies [8]	*ABCA4*, *AIPL1*, *CABP4*, *CNNM4*, *CDHR1*, *GUCY2D*, *KCNV2*, *RAB28*, *RPGRIP1*	AD, AR	• Cone function may be normal at birth. • Typical symptoms (↓ visual acuity, photophobia, ↑ sensitivity to glare, abnormal color vision) appear later. [9] • Age of onset of vision loss may be as early as childhood or as late as 7th decade. • Dark-adapted rod thresholds may be elevated. [10]	Disease progression occurs in cone dystrophy & typically not in achromatopsia.	• Differentiating between achromatopsia & cone dystrophy can be difficult, particularly in individuals w/early-childhood onset. • Best clinical discriminator is disease progression.
Leber congenital amaurosis (LCA)	*AIPL1* *CABP4* *CEP290* *GUCY2D* *RPGRIP1*	AR	• Infantile nystagmus • Photophobia • Severely reduced visual acuity • No obvious fundus abnormalities • Poor or no color discrimination	Night blindness & progression occur in LCA.	In very young individuals
Bradyopsia; delayed cone adaptation	*RGS9*		• Prolonged electroretinal response suppression leading to difficulties adjusting to changes in luminance • Normal to subnormal visual acuity • Photophobia		

Table 3. continued from previous page.

Disorder	Gene(s)	MOI	Overlapping Clinical Features	Distinguishing Clinical Features	Comments
Alström syndrome [11]	*ALMS1*	AR	• Infantile nystagmus • Photophobia • Severely reduced visual acuity • Poor or no color discrimination	Possible additional findings in Alström syndrome: cardiomyopathy, kidney failure, obesity, sensorineural hearing loss, diabetes	In young individuals

AD = autosomal dominant; AR = autosomal recessive; ERG = electroretinogram; MOI = mode of inheritance; XL = X-linked
1. Blue-cone monochromacy may also be referred to as S-cone monochromacy or X-chromosome-linked achromatopsia.
2. The dysfunction of the L (red) and M (green) cones is caused by pathogenic variants leading to the loss of the X-linked red (*OPN1LW*) and green (*OPN1MW*) opsin gene array, hybrid gene formation and/or inactivating variants, or by deletions affecting the locus control region, a critical region that regulates the expression of the red/green (*OPN1LW/OPN1MW*) gene array.
3. Blue-cone monochromacy affects mostly males.
4. Sharpe et al [1999]
5. Some males with mildly defective red-green color vision may not be aware of it until they are tested. Among individuals of northern European origin, about 8% of males and 0.5% of females have red-green color vision defects; these defects are less frequent among males of African (3%-4%) or Asian (3%) origin.
6. Often referred to as yellow-blue disorders, although the color confusion is typically between blues & greens, tritan defects affect the S (blue) cones.
7. Sharpe et al [1999]
8. See Glöckle et al [2014], Weisschuh et al [2016], Carss et al [2017] for genes identified in patients misdiagnosed as having achromatopsia.
9. Holopigian et al [2004]
10. Aboshiha et al [2014]
11. Nasser et al [2018]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with achromatopsia, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Standard clinical ophthalmologic evaluation and testing with attention to visual acuity and use of spectacles and/or contact lenses to achieve the best possible corrected visual acuity
- Color vision evaluation
- Consultation with a clinical geneticist and/or genetic counselor as treatment could be possible in the near future (See Therapies Under Investigation.)

Treatment of Manifestations

Dark or special filter glasses or red-tinted contact lenses reduce photophobia and may improve visual acuity.

Low vision aids include high-powered magnifiers for reading as well as digital/electronic devices.

Children with achromatopsia should have preferential seating in the classroom (i.e., in the front to benefit maximally from magnifying devices and away from windows to reduce the effects of glare on vision).

Extensive information about learning and occupational aids is available from the Achromatopsia Network (www.achromat.info).

Surveillance

Ophthalmologic examination is indicated:

- Every six to 12 months in children to monitor changes in refraction in order to achieve the best possible corrected visual acuity;
- Every two to three years in adults.

Agents/Circumstances to Avoid

To avoid additional light damage to the retina, it is recommended that individuals wear appropriate protective (dark) glasses in bright light.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

In July 2012 a Phase I/II clinical trial (NCT01846052) investigating the therapeutic effects and safety of an intraocular implant releasing ciliary neurotrophic factor (CNTF) in individuals with *CNGB3*-related achromatopsia was started. No objectively measurable enhancement of cone function was found by assessments of visual acuity, mesopic increment sensitivity threshold, photopic electroretinogram, or color hue discrimination. Subjectively, individuals reported beneficial changes of visual function in the treated eyes, including reduced light sensitivity and aversion to bright light, but slowed adaptation to darkness, consistent with CNTF action on rod photoreceptors [Zein et al 2014].

Several interventional Phase I/II clinical safety and efficacy trials for gene replacement therapy using viral AAV vectors for *CNGA3*-related achromatopsia (NCT02610582, NCT02935517) and *CNGB3*-related achromatopsia (NCT02599922, NCT03278873, NCT03001310) are currently running and recruiting patients.

In addition, clinical observational trials have been or are recruiting individuals for clinical assessment to establish the natural history of achromatopsia (NCT02435940, NCT01846052).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Achromatopsia is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one achromatopsia-related pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with achromatopsia are obligate heterozygotes (carriers) for an achromatopsia-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an achromatopsia-related pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the achromatopsia-related pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the achromatopsia-related pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for achromatopsia are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Achroma Corp**

  Phone: 724-841-4052

  Email: bvissari@achromacorp.org

  www.achromacorp.org

- **Achromatopsie Selbsthilfeverein e.V.**

  Germany

Email: info@achromatopsie.org
www.achromatopsie.org

- **Associazione Acromati Italiani Onlus**
  Italy
  Email: info@acromatopsia.it
  www.acromatopsia.it
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **National Library of Medicine Genetics Home Reference**
  Color vision deficiency

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Achromatopsia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATF6	1q23.3	Cyclic AMP-dependent transcription factor ATF-6 alpha	ATF6 @ LOVD	ATF6	ATF6
CNGA3	2q11.2	Cyclic nucleotide-gated cation channel alpha-3	CNGA3 @ LOVD	CNGA3	CNGA3
CNGB3	8q21.3	Cyclic nucleotide-gated cation channel beta-3	CNGB3 @ LOVD	CNGB3	CNGB3
GNAT2	1p13.3	Guanine nucleotide-binding protein G(t) subunit alpha-2		GNAT2	GNAT2
PDE6C	10q23.33	Cone cGMP-specific 3',5'-cyclic phosphodiesterase subunit alpha'	PDE6C @ LOVD	PDE6C	PDE6C
PDE6H	12p12.3	Retinal cone rhodopsin-sensitive cGMP 3',5'-cyclic phosphodiesterase subunit gamma	PDE6H @ LOVD	PDE6H	PDE6H

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Achromatopsia (View All in OMIM)

139340	GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-TRANSDUCING ACTIVITY POLYPEPTIDE 2; GNAT2
216900	ACHROMATOPSIA 2; ACHM2
262300	ACHROMATOPSIA 3; ACHM3
600053	CYCLIC NUCLEOTIDE-GATED CHANNEL, ALPHA-3; CNGA3
600827	PHOSPHODIESTERASE 6C; PDE6C

Table B. continued from previous page.

601190	PHOSPHODIESTERASE 6H; PDE6H
605080	CYCLIC NUCLEOTIDE-GATED CHANNEL, BETA-3; CNGB3
605537	ACTIVATING TRANSCRIPTION FACTOR 6; ATF6
610024	RETINAL CONE DYSTROPHY 3A; RCD3A
613093	CONE DYSTROPHY 4; COD4
613856	ACHROMATOPSIA 4; ACHM4
616517	ACHROMATOPSIA 7; ACHM7

Molecular Pathogenesis

CNGB3, *CNGA3*, *PDE6C*, *GNAT2*, and *PDE6H* are all expressed in the cone photoreceptor and are crucial for cone phototransduction:

- Light-excited cone visual pigment molecules induce the exchange of GDP to GTP on the transducin alpha subunit (**GNAT2**) and its release from the inhibitory beta/gamma subunits.
- The activated GTP-transducin then binds and activates the alpha' subunit of the retinal cone photoreceptor phosphodiesterase (**PDE6C**) by retracting the inhibitory gamma subunit (**PDE6H**).
- Retinal cone photoreceptor PDE6C hydrolyzes cGMP, reducing its intracellular concentration and causing closure of the heterotetrameric cGMP-gated cation channels (**CNGA3** and **CNGB3**) and, subsequently, membrane hyperpolarization [Lamb & Pugh 2006].

Transducin thus mediates the first step, the phosphodiesterase the intermediate, and the cGMP-gated channel represents the final step in the phototransduction cascade.

In contrast, the most recently identified ACHM-related gene, *ATF6*, encodes a ubiquitously expressed transmembrane transcription factor known for its function in the ATF6 unfolded protein response pathway [Walter & Ron 2011, Wang & Kaufman 2012, Kohl et al 2015]. How and why pathogenic variants in this ubiquitously expressed gene result solely in cone dysfunction is to date unknown.

ATF6

Gene structure. *ATF* consists of 16 coding exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Thirteen different pathogenic variants have been reported in 15 families [Ansar et al 2015, Kohl et al 2015, Xu et al 2015, Carss et al 2017, Skorczyk-Werner et al 2017]. Nine of the 13 are nonsense variants, splice site variants, small insertions, and deletions. Only four missense variants have been reported.

Six individuals (from 2 unrelated families of Irish/British descent) who are homozygous for c.970C>T have been identified; the families were shown to have a common haplotype of 0.7 Mb suggestive of a founder variant [Kohl et al 2015]. Another pathogenic variant, c.1533+1G>C, was observed recurrently in four French Canadian families, also suggesting a founder variant in this population [Kohl et al 2015, Xu et al 2015].

Table 4. *ATF6* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.970C>T	p.Arg324Cys	NM_007348.3 NP_031374.2

Table 4. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1533+1G>C	See footnote 1.	NM_007348.3

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Two cDNAs were identified, one with partial intron retention and one with exon skipping [Kohl et al 2015].

Normal gene product. *ATF6* encodes a 670-amino-acid, ubiquitously expressed 90-kd ER stress-regulated transmembrane transcription factor known for its function in one of three unfolded protein response pathways (i.e., ATF6 pathway). It is required for ER stress response and transcriptional induction from ER stress-response elements (ERSEs). On induction of ER stress, the cytosolic ~400-residue N-terminal portion of ATF6 (N-ATF6) is released. N-ATF6 possesses the transcriptional activation domain, the bZIP domain, the DNA-binding domain, and nuclear localization signals. It translocates to the nucleus, where it interacts with several other proteins to form an ERSE-binding complex that is responsible for the induction of ER stress genes (ERSGs) [Walter & Ron 2011, Wang & Kaufman 2012].

Abnormal gene product. Most pathogenic missense variants result in loss of protein function. One missense variant, p.Arg324Cys, localizes to the basic region of the bZIP domain, affecting an arginine residue that is conserved not only among transcription factors of the ATF family but also in those of the AP-1 family, severely impairing ATF6 transcriptional activity [Kohl et al 2015]. The p.Arg324Cys variant was functionally characterized in detail and shown to impair transcriptional activity [Kohl et al 2015, Chiang et al 2017].

Other missense changes have been studied and divided into class I, 2, or 3:

- Class 1. Disease-associated *ATF6* missense variants that result in impaired ER-to-Golgi trafficking and diminished regulated intramembrane proteolysis and transcriptional activity
- Class 2. Disease-associated *ATF6* missense variants that retain the entire ATF6 cytosolic domain with fully intact transcriptional activity and constitutive induction of downstream target genes, even in the absence of ER stress
- Class 3. ATF6 missense variants with complete loss of transcriptional activity because of absent or defective bZIP domains

Primary fibroblasts from patients with class 1 or class 3 *ATF6* pathogenic variants show increased cell death in response to ER stress [Chiang et al 2017].

Of note, the *Atf6* knockout mouse model does not recapitulate the human achromatopsia phenotype [Kohl et al 2015].

CNGA3

Gene structure. *CNGA3* consists of eight coding exons [Wissinger et al 2001]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 150 different pathogenic variants have been associated with ACHM [Kohl et al 1998, Wissinger et al 2001, Johnson et al 2004, Tränkner et al 2004, Nishiguchi et al 2005, Varsányi et al 2005, Ahuja et al 2008, Koeppen et al 2008, Reuter et al 2008, Koeppen et al 2010, Thiadens et al 2010, Genead et al 2011, Vincent et al 2011]. The vast majority of pathogenic variants are missense (~80%). Only a few nonsense variants, insertions, and deletions have been observed.

Normal gene product. *CNGA3* encodes the cyclic nucleotide-gated cation channel alpha 3 (the alpha subunit of the cone photoreceptor cGMP-gated cation channel [CNG]). CNGA3 has 694 amino acids and a predicted

weight of 78.8 kd. An alternatively spliced exon that extends the open reading frame by an additional 55 amino acids has been reported [Wissinger et al 2001]. Alpha subunits on CNG channels are able to form functional homo-oligomeric channels, yet their biophysical properties differ from those of heteromeric native CNG channels consisting of three alpha subunits and one beta subunit.

Abnormal gene product. Functional analysis has shown that in many cases channel function is strongly impaired or completely absent. The pathogenic missense variants mostly affect amino acid residues that are highly conserved among the members of the CNG channel family, and cluster at structural and functional domains including the cGMP-binding domain [Wissinger et al 2001, Faillace et al 2004, Patel et al 2005, Koeppen et al 2008, Reuter et al 2008].

Some pathogenic variants in the pore region and the cGMP binding domain are associated with incomplete achromatopsia. These abnormal proteins can form functional channels, but with grossly altered properties, including altered affinity for cGMP and/or cAMP, and changes in the gating properties of the cone CNG channels, like Ca^{2+} blockage and permeation [Tränkner et al 2004, Liu & Varnum 2005, Reuter et al 2008, Koeppen et al 2010].

Animal models have helped to clarify the underlying pathogenic mechanisms:

- **Mouse.** *Cnga3*$^{(-/-)}$ mice show absence of cone function, a decrease in the number of cones in the retina, and morphologic abnormalities of the remaining cones. *Cnga3*$^{(-/-)}$ cones fail to transport opsin into the outer segment and downregulate various proteins of the phototransduction cascade. Apoptotic cell death is induced; however, loss of *Cnga3* does not appear to affect the transcription of other cone-specific genes [Biel et al 1999, Michalakis et al 2005]. Gene therapy has been successfully tested in these mouse models and shown to restore cone-mediated vision [Michalakis et al 2012].
- **Sheep.** Lambs with congenital day blindness are homozygous for the pathogenic nonsense variant FN377574:c.706C>T (p.Arg236Ter) in the ovine *CNGA3* and serve as animal models for studying human achromatopsia and evaluating gene therapeutic approaches [Reicher et al 2010, Banin et al 2015].

CNGB3

Gene structure. *CNGB3* consists of 18 coding exons [Kohl et al 2000]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 125 different pathogenic variants have been reported [Kohl et al 2000, Sundin et al 2000, Rojas et al 2002, Johnson et al 2004, Michaelides et al 2004, Okada et al 2004, Kohl et al 2005, Nishiguchi et al 2005, Varsányi et al 2005, Khan et al 2007, Wiszniewski et al 2007, Thiadens et al 2009b, Azam et al 2010, Mayer et al 2017]. The vast majority are pathogenic nonsense variants, frameshift deletions and insertions, and putative splice site variants. Only a few pathogenic missense variants (~10%) have been observed.

One, resulting in the p.Ser435Phe mutated protein, causes "Pingelapese blindness" in achromats originating from the island of Pingelap in Micronesia [Kohl et al 2000, Sundin et al 2000].

The recurrent single base-pair deletion c.1148delC is the most common pathogenic variant underlying achromatopsia worldwide, accounting for approximately 70% of all *CNGB3* disease-causing alleles and approximately 40% of all achromatopsia-associated alleles. The c.1148delC deletion results from a founder effect [Wiszniewski et al 2007].

Table 5. *CNGB3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1148delC	p.Thr383IlefsTer13	NM_019098.3 NP_061971.3
c.1304C>T	p.Ser435Phe	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *CNGB3* encodes for cyclic nucleotide-gated cation channel beta 3 (the beta subunit of the cone photoreceptor cGMP-gated cation channel). CNGB3 is 809 amino acids long. The beta subunits are not able to form functional homo-oligomeric channels; they are therefore thought to be modulatory subunits. Functional cone CNG channels consist of three alpha subunits and one beta subunit.

Abnormal gene product. Functional analysis has shown that in many cases channel function is strongly impaired or completely absent [Peng et al 2003, Okada et al 2004, Bright et al 2005]. However, certain disease-associated *CNGB3* variants in the subunit are apparent gain-of-function variants [Okada et al 2004, Bright et al 2005]. Expression of human wild type *CNGA3* and mutated *CNGB3* containing the Pingelapese blindness-associated p.Ser435Phe variant generated functional heteromeric channels that exhibited an increase in apparent affinity for both cAMP and cGMP and changes in the pore properties of the channel compared with wild type heteromeric channels.

Animal models have helped to clarify the underlying pathogenic mechanisms. Two naturally occurring *CNGB3*-null canine models, Alaskan malamute and German shorthaired pointer, have been identified [Sidjanin et al 2002]. In the Alaskan malamute, cone-degenerate pups develop day blindness and photophobia. Cone function, detectable on electroretinogram in very young affected pups, begins to fail at a few weeks' age and is undetectable in mature affected dogs. Adult affected retinas lack all cones. The first gene therapy studies in these animals showed restoration of cone-mediated vision, but the success was dependent on the age of intervention [Komáromy et al 2010].

GNAT2

Gene structure. *GNAT2* consists of eight coding exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Sixteen different disease-associated variants (nonsense variant, deletions and/or insertions, one large deletion of exon 4, and a variant c.461+24G>A activating a cryptic splice site and resulting in frameshift and PTC) have been described to date [Aligianis et al 2002, Kohl et al 2002, Michaelides et al 2003, Piña et al 2004, Rosenberg et al 2004, Ouechtati et al 2011, Langlo et al 2016, Bryant et al 2017, Carss et al 2017, Taylor et al 2017, Ueno et al 2017].

Table 6. *GNAT2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.461+24G>A	--	NM_001377295.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *GNAT2* encodes for guanine nucleotide-binding protein G(t), alpha-2 subunit (the cone-specific alpha subunit of transducin), a heterotrimeric G protein that couples to the cone photopigments. The protein is 354 amino acids long.

Abnormal gene product. The majority of pathogenic variants result in loss of protein function [Cai et al 2001]. The c.461+24G>A variant results in leaky aberrant splicing, resulting in a milder phenotype described as incomplete achromatopsia or oligo-cone trichromacy [Rosenberg et al 2004].

Animal models have helped to clarify the underlying pathogenic mechanisms.

An achromatopsia mouse model is homozygous for the murine *Gnat2* pathogenic variant NM_008141.3:c.598G>A (p.Asp200Asn) in exon 6 (also referred to as the *cpfl3* variant*)* [Chang et al 2006]. Homozygous mice have poor cone-mediated responses on electroretinogram (ERG) at three weeks that become undetectable by nine months. Microscopy of the retina reveals progressive vacuolization of the photoreceptor outer segments. Immunocytochemistry with cone-specific markers shows progressive loss of labeling for Gnat2 protein, but the cone outer segments in the oldest mice examined remain intact [Chang et al 2006].

PDE6C

Gene structure. *PDE6C* consists of 22 coding exons [Piriev et al 1995]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 50 different pathogenic variants in *PDE6C* have been described; they include missense variants, nonsense variants, small indels, and variants affecting splicing [Chang et al 2009, Thiadens et al 2009b, Grau et al 2011, Huang et al 2013, Weisschuh et al 2018].

Normal gene product. *PDE6C* encodes PDE6C, the phosphodiesterase 6C, cGMP-specific, cone, alpha-prime. This alpha' subunit of the cone-specific phosphodiesterase consists of 858 amino acids.

Abnormal gene product. Disease-associated variants result in markedly reduced to completely absent PDE6C enzymatic activity [Chang et al 2009, Grau et al 2011].

Animal models have helped to clarify the underlying pathogenic mechanisms. The cone photoreceptor function loss 1 (*cpfl1*) mouse mutant is a model for *Pde6c*-related achromatopsia [Chang et al 2009], which has a 116-bp insertion between exons 4 and 5 (NM_001170959.1:c.864_865ins116) and an additional 1-bp deletion in exon 7 (NM_001170959.1:c.1042delT) in *cis* (on the same allele). The phenotype can be easily typed by ERG as early as age three weeks. Histology of *cpfl1* mouse retinae revealed grossly normal morphology and layering. However, as early as age three weeks, there was vacuolization of a small subset of cells in the photoreceptor layer with subsequent rapid, progressive depletion of cone photoreceptors. Loss of cones progresses, such that very few were detected in retinal sections of five-month-old animals [Chang et al 2009].

PDE6H

Gene structure. *PDE6H* consists of only three coding exons [Shimizu-Matsumoto et al 1996]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Originally the single homozygous pathogenic nonsense variant c.35C>G in *PDE6H* was described in three affected individuals from two independent families originating from Belgium and the Netherlands [Kohl et al 2012]. Recently, two Pakistani brothers were shown to be homozygous for the same pathogenic variant [Pedurupillay et al 2016].

Table 7. *PDE6H* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.35C>G	p.Ser12Ter	NM_006205.2 NP_006196.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *PDE6H* encodes phosphodiesterase 6H, cGMP-specific, cone, gamma; PDE6H, the inhibitory gamma subunit of the cone photoreceptor phosphodiesterase. PDE6H consists of only 83 amino acids.

Abnormal gene production. The sole *PDE6H* nonsense variant is predicted to result in complete loss of function of PDE6H either by degradation of the mRNA by nonsense-mediated decay or the truncation of the protein [Kohl et al 2012].

Of note, the *Pde6h* knockout mouse model does not recapitulate the human achromatopsia phenotype [Brennenstuhl et al 2015].

Chapter Notes

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