GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Achromatopsia

[*Rod Monochromatism, Total Color Blindness*]

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Initial Posting: June 24, 2004.
Last Update: October 23, 2006.

Summary

Disease 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 symptoms are similar to those of individuals with complete achromatopsia, but generally less severe. Hyperopia is common. 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 and vessel narrowing may be present in some affected individuals.

Diagnosis/testing. The diagnosis of achromatopsia is based on case history, color vision testing, electrophysiologic examination, and absent or only minor fundus changes. Mutations in *CNGA3*, *CNGB3*, and *GNAT2* are causative. Molecular genetic testing of *CNGA3* and *CNGB3* is clinically available.

Management. Treatment of achromatopsia may include dark or special filter glasses or red-tinted contact lenses to reduce photophobia and potentially improve visual acuity; low vision aids; and occupational aids. Surveillance includes ophthalmologic examination annually for

children and every two to three years for adults. To avoid additional light damage to the retina, it is recommended that individuals wear appropriate protective (dark) glasses in bright light.

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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygotes (carriers) are asymptomatic. Carrier testing for family members at risk for *CNGA3* or *CNGB3* mutations is available on a clinical basis once the mutations have been identified in the proband. Prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutations have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of achromatopsia is based on the presence of typical clinical findings:

- **Reduced visual acuity**
- **Pendular nystagmus**
- **Increased sensitivity to light**
- **Small central scotoma**
- **Eccentric fixation**
- **Reduced or complete loss of color discrimination**

The following also contribute to the diagnosis:

- **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 lightnesses) is characteristic 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.
- **Electrophysiology.** In the single-flash electroretinogram (ERG), the photopic response (including the 30-Hz flicker response) is absent or markedly diminished, while the scotopic response is normal or mildly abnormal.

- **Fundus appearance.** Many affected individuals have a normal-appearing fundus. Others 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 in the fovea can occur in older individuals.
- **Visual fields.** Small central scotomas can be demonstrated in some individuals by careful testing. However, unsteady fixation can make demonstration of a central scotoma difficult.
- **Family history** is consistent with autosomal recessive inheritance.
- **Psychophysical tests,** available in specialized centers but not necessary for diagnosis, include the following:
  - Absence of the Kohlrausch kink (cone-rod break) in the dark-adaptation curve in complete achromatopsia
  - Peaking of photopic luminosity or brightness measured as a function of spectral wavelength, whether by flicker photometry, incremental thresholds, or by side-by-side matching, at 507 nm (the peak wavelength of the rod or scotopic visual system) instead of at 555 nm (the peak wavelength of the cone or photopic visual system)

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. To date, mutations in the following three genes are known to be associated with autosomal recessive achromatopsia:

- ***CNGB3:***~50% of affected individuals [Kohl et al 2005]
- ***CNGA3:***25% of affected individuals [Wissinger et al 2001]
- ***GNAT2:***<2% of affected individuals [Aligianis et al 2002, Kohl et al 2002]

Other loci. An additional locus (ACHM1) has been assigned to chromosome 14 as a result of a single case of maternal uniparental isodisomy of chromosome 14 [Pentao et al 1992]. Neither the gene nor the frequency of the locus is known.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier testing

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** Targeted mutation analysis for the six most common mutations in *CNGB3* is available on a clinical basis. The 1-bp deletion, c.1148delC, accounts for about 70% of all mutant *CNGB3* alleles [Kohl et al 2005].
- **Sequence analysis.** Sequence analysis is available on a clinical basis.
- **Mutation scanning.** Mutation scanning is available for *CNGB3*.

Molecular genetic testing: Research. Molecular genetic testing for *GNAT2* is available on a research basis only.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Achromatopsia

Gene Symbol	% of Achromatopsia Caused by Mutations in the Gene	Test Method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
CNGB3	~50%	Targeted mutation analysis	Six most common *CNGB3* mutations [2]	40%-50%	Clinical Testing
		Mutation scanning	*CNGB3* sequence variants	75%-80% [3]	
CNGA3	~25%	Sequence analysis	*CNGA3* sequence variants	>95%	Clinical Testing
GNAT2	<2%	Mutation scanning or sequence analysis	*GNAT2* sequence variants	>95%	Research only

1. Percent of all individuals of European descent with autosomal recessive achromatopsia in whom at least one mutation is identified
2. Common mutations: c.819-826del8, c.886-896del11insT, c.991-3T>G, p.E336X, c.1148delC, p.R403Q
3. Of 163 individuals with mutations in *CNGB3*, 105 (64%) were homozygous, 44 (42%) were compound heterozygotes, and in 14 (13%) only one mutation was identified [Kohl et al 2005]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

The order of molecular genetic testing is the following:

1. Targeted mutation analysis for the most common mutations in *CNGB3*
2. Sequence analysis of *CNGA3*
3. Mutation scanning of *CNGB3*

Genetically Related (Allelic) Disorders

CNGB3

- In a few individuals, progressive cone dystrophy has been associated with mutations in *CNGB3* [Michaelides et al 2004].
- Macular degeneration has been described in some individuals [Nishiguchi et al 2005].

CNGA3

- In a few individuals, progressive cone dystrophy has been associated with mutations in *CNGA3* [Wissinger et al 2001, Nishiguchi et al 2005]. However, the differentiation from achromatopsia can be difficult and the diagnosis of cone dystrophy can often only be established by the observation of disease progression (see Differential Diagnosis).

GNAT2

- A mild phenotype best characterized as oligocone trichromacy has been described [Rosenberg et al 2004].

Clinical Description

Natural History

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 loss 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.

Although the fundus is usually normal, macular changes and vessel narrowing may be present in some individuals.

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

Genotype-Phenotype Correlations

In the majority of individuals affected by autosomal recessive achromatopsia, mutations in one of the three reported genes result in the complete form of the disorder. In a few individuals, mutations in *CNGA3* [Jagle et al 2001, Wissinger et al 2001, Michaelides et al 2004, Trankner et al 2004] or *GNAT2* are associated with the milder phenotype of incomplete achromatopsia [Rosenberg et al 2004].

Nomenclature

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

Prevalence

Autosomal recessive achromatopsia is a rare disorder with an estimated prevalence of fewer than 1:30,000 [Francois 1961, Sharpe & Norby 1990, Sharpe et al 1999].

Parental consanguinity is common in certain geographical 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 mutation S435F in *CNGB3* [Sharpe et al 1999].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Achromatopsia is readily recognized by its characteristic features: severely reduced visual acuity, pendular nystagmus, increased sensitivity to light, and reduced or complete loss of color discrimination and other psychophysical and electroretinographic findings. The following retinopathies may be confused with achromatopsia:

Blue-cone monochromatism. Like achromatopsia, blue-cone monochromacy (also referred to as S-cone monochromacy or X-chromosome-linked achromatopsia) is characterized by severely reduced visual acuity, eccentric fixation, infantile nystagmus, no obvious fundus abnormalities, and poor or no color discrimination (for a review, see Sharpe et al 1999). However, unlike achromatopsia, the peak of the photopic luminosity function is near 440 nm (the peak sensitivity of the S cones), not 507 nm (the peak sensitivity of the rods); and cone ERG responses can be elicited by presenting blue flashes on a yellow background. This is because the S cones are functioning in addition to the rods. The dysfunction of the L (red) and M (green) cones is caused by loss and inactivating mutations in the X-linked opsin gene array or by loss of a critical region that regulates the expression of the red/green gene array (locus control region) (see Red-Green Color Vision Defects) [Nathans et al 1989, 1993]. A special four-color plate test [Berson et al 1983] or a two-color filter test [Zrenner et al 1988] can clinically distinguish blue-cone monochromats from achromats (rod monochromats).

Cone monochromatism (complete achromatopsia with normal visual acuity). Achromatopsia is less often confused with two other extremely rare forms of cone monochromatism, in which nystagmus and light aversion are not present and the visual acuity and the cone ERG are normal.

- L- or red-cone monochromacy, in which only the L cones may be functioning in addition to the rods
- M- or green-cone monochromacy, in which only the M cones may be functioning in addition to the rods (for a review, see Sharpe et al 1999). In both disorders, color discrimination may be lacking or unreliable.

Cone dystrophies. In cone dystrophy, cone function is normal at birth. Typical symptoms appear later. These include reduced visual acuity, photophobia, increased sensitivity to glare, and abnormal color vision [Goodman et al 1963, Berson et al 1968, Small & Gehrs 1996, Holopigan et al 2004]. The age of onset of vision loss may be as early as childhood or as late as the sixties. Differentiating between achromatopsia and cone dystrophy can be difficult, particularly in individuals with onset in early childhood; the best clinical discriminator is disease progression, which occurs in cone dystrophy and not typically in individuals with achromatopsia. In contrast with achromatopsia, dark-adapted rod thresholds are typically elevated by approximately 0.5 log unit in cone dystrophy [Berson et al 1968].

Hereditary red-green color vision defects are manifest in early infancy, mostly in males; the condition is not accompanied by ophthalmologic or other associated clinical abnormalities. Most individuals with protanomalous and deuteranomalous color vision defects (i.e., anomalous trichromats) have no problems in naming colors; some males with mildly defective red-green color vision may not be aware of it until they are tested. Among Caucasians, 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.

Clinical chart tests widely used to detect red-green color vision defects include Ishihara plates and the American Optical HRR pseudoisochromatic plates. Definitive classification of

protanopia, deuteranopia, protanomaly, and deuteranomaly requires use of the anomaloscope, which involves color matching.

The two genes associated with red-green color vision defects are OPN1LW (opsin 1 long wave), encoding the L (red) pigment and OPN1MW (opsin 1 middle wave), encoding the M (green) pigment. Inheritance is X-linked.

Tritan and yellow-blue defects. Often referred to as yellow-blue disorders, although the color confusion is typically between blues and greens, tritan defects affect the S (blue) cones. In congenital cases, they arise from mutations in the gene encoding the S-cone opsin, located on chromosome 7. They often remain undetected because of their rarity, frequent incomplete manifestation, and the limited nature of the color confusion (blues and greens). Other non-congenital cases of yellow-blue deficits, which are similar in some ways to tritan defects, may result from aging or disorders of the choroid, the pigment epithelium, the retina, or the optic nerve. They are usually progressive and have other related signs, such as associated visual acuity defects (see Sharpe et al 1999).

Cerebral achromatopsia. Cerebral achromatopisa or dyschromatopsia, which is associated with severe or total color vision deficits, can arise adventitiously after brain fever, cortical trauma, or cerebral infarction, especially involving lesions to the ventral occipital cortex [Bouvier & Engel 2006].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Standard clinical ophthalmologic evaluation and testing
- Electrophysiologic examination
- Color vision evaluation
- Testing dark adaptometry

Treatment of Manifestations

Dark or special filter glasses or red-tinted contact lenses reduce photophobia and may improve visual acuity [Park & Sunness 2004].

Low vision aids include high-powered magnifiers for reading. Children with achromatopsia should have preferential seating in the front of the class to benefit maximally from their magnifying devices.

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

Surveillance

- Ophthalmologic examination every six to 12 months in children to monitor changes in refraction and to achieve the best possible visual acuity
- Ophthalmologic examination 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.

Therapies Under Investigation

Search ClinicalTrials.gov for access to 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with achromatopsia are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for family members at risk for *CNGA3* or *CNGB3* mutations is available on a clinical basis once the mutations have been identified in the proband.

Carrier testing using molecular genetic techniques for *GNAT2* is not offered because it is not clinically available.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant

in situations in which molecular genetic testing is available on a research basis only or the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of achromatopsia are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Achromatopsia

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
ACHM1	Unknown	Chr.14	Unknown
ACHM2	*CNGA3*	2q11	Cyclic nucleotide-gated cation channel alpha 3
ACHM3	*CNGB3*	8q21-q22	Cyclic nucleotide-gated cation channel beta 3
ACHM4	*GNAT2*	1p13	Guanine nucleotide-binding protein G(t), alpha-2 subunit

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Achromatopsia

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
603096	ACHROMATOPSIA 1
605080	CYCLIC NUCLEOTIDE-GATED CHANNEL, BETA-3; CNGB3

Table C. Genomic Databases for Achromatopsia

Locus Name	Gene Symbol	Entrez Gene	HGMD
ACHM1	Unknown	603096	
ACHM2	*CNGA3*	1261 (MIM No. 600053)	CNGA3
ACHM3	*CNGB3*	54714 (MIM No. 605080)	CNGB3
ACHM4	*GNAT2*	2780 (MIM No. 139340)	GNAT2

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

CNGA3, *CNGB3*, and *GNAT2* 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 at the guanosine binding site of the transducin alpha subunit (GNAT2) and its subsequent release from the inhibitory beta/gamma subunits. The activated GTP transducin then binds and activates a phosphodiesterase, which hydrolyzes cGMP and effectively reduces its intracellular concentration. This results in the closure of the hetero-oligomeric cGMP-gated cation channels (CNGA3/CNGB3) and, subsequently, membrane hyperpolarization [Muller & Kaupp 1998]. Transducin thus mediates one of the first steps of the phototransduction cascade, while the cGMP-gated channel represents the final component of the same process.

Functional analysis by heterologous expression of mutant CNG channels has shown that in many cases channel function is strongly impaired or completely absent (see *CNGA3* Abnormal gene product, *CNGB3* Abnormal gene product).

In addition, animal models may help to clarify the underlying pathogenic mechanisms. The analysis of the homologous *CNGA3* knockout mouse model shows complete absence of physiologically measurable 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 down-regulate various proteins of the phototransduction cascade. An apoptotic cell death is induced; however, loss of *CNGA3* does not seem to affect the transcription of other cone-specific genes. Cone degeneration in the *CNGA3* knockout animals, evident from the second postnatal week on, proceeds significantly faster in the ventral than in the dorsal part of the retina. In addition, *CNGA3* appears to be essential for normal postnatal migration of cone somata [Biel et al 1999, Michalakis et al 2005].

Two canine models for *CNGB3* have been identified. It has been shown that autosomal recessive canine cone degeneration (cd) in the Alaskan malamute and the German shorthaired pointer breeds is caused by mutations in the canine *CNGB3* gene [Sidjanin et al 2002]. In the naturally-occurring Alaskan malamute, cone-degenerate pups develop dayblindness and photophobia. Symptoms are present only in bright light; vision in dim light is normal. Affected dogs remain ophthalmoscopically normal throughout life. Cone function, detectable on electroretinogram in very young cd-affected pups, begins to fail at a few weeks' age and is undetectable in mature cd-affected dogs [Aguirre & Rubin 1975]. Adult cd-affected retinas lack all cones. Cones degenerate by extrusion of the nucleus into the inner segment and later displacement of the cone nuclei in the interphotoreceptor space [Aguirre & Rubin 1974, Gropp et al 1996]. Genetic analysis has shown that in the Alaskan malamute the disease is caused by deletion of the complete gene, while in the German shorthaired pointers, the disease is caused by a missense mutation c.784G>A, resulting in the amino acid substitution p.D262N (Genbank accession no. AF490511) [Aguirre & Rubin 1974].

CNGA3

Normal allelic variants: The *CNGA3* gene consists of eight coding exons [Wissinger et al 1997, Wissinger et al 2001]. Only a few polymorphisms and rare variants are observed; most occur within non-coding regions or do not result in an amino acid substitution.

Pathologic allelic variants: More than 70 different mutations have been reported [Kohl et al 1998, Wissinger et al 2001, Johnson et al 2004, Trankner et al 2004, Nishiguchi et al 2005, Varsanyi et al 2005]. The vast majority of mutations are missense. Only a few nonsense mutations, insertions, and deletions have been observed.

Normal gene product: The polypeptide is 694 amino acids long and has a size of 78.8 kd [Wissinger et al 1997]. An alternatively spliced exon that extends the open reading frame by an additional 55 amino acids has been reported [Wissinger et al 2001]. *CNGA3* encodes for cyclic nucleotide-gated cation channel alpha 3 [the alpha subunit of the cone photoreceptor cGMP-gated cation channel (CNG)]. In vitro expression experiments have shown that alpha subunits on CNG channels alone are able to form functional homo-oligomeric channels, yet their biophysical properties differ from those of heteromeric native CNG channels consisting of two alpha and two beta subunits.

Abnormal gene product: The missense mutations mostly affect amino acid residues highly conserved among the members of the cyclic nucleotide-gated channel family and cluster at structural and functional domains including the cGMP-binding domain [Wissinger et al 2001]. In vitro expression experiments have shown that most mutations lead to a complete lack of channel activity. Full-length mutant proteins are synthesized but retained in the endoplasmic reticulum; cellular trafficking is therefore impaired [authors, unpublished data; Faillace et al 2004; Patel et al 2005].

However, some mutations have been shown to be associated with incomplete achromatopsia (i.e., residual but disturbed cone function). Psychophysical and electroretinographic analyses in these individuals demonstrate that the light sensitivity of the cone system is lowered and the signal transfer from cones to secondary neurons is perturbed [Trankner et al 2004]. Heterologous expression reveals that *CNGA3*-encoded polypeptides carrying certain point mutations especially in the pore region and the cGMP binding domain 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. Surprisingly, coexpression of some of these mutant channels with wild type CNGB3 subunits, rescue the channel function to some extent [Trankner et al 2004, Liu & Varnum 2005].

CNGB3

Normal allelic variants: The *CNGB3* gene consists of 18 coding exons [Kohl et al 2000]. Only a few polymorphisms and rare variants are observed; most occur within non-coding regions or do not result in an amino acid substitution.

Pathologic allelic variants: More than 40 different mutations 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]. The vast majority are nonsense mutations, frame-shift deletions and insertions, and putative splice site mutations. Only a few missense mutations have been observed. One, the S435F mutation, causes "Pingelapese blindness" in achromats originating from the island of Pingelap in Micronesia [Hussels & Morton 1972, Sacks 1997, Kohl et al 2000, Sundin et al 2000]. A recurrent single base-pair deletion, c.1148delC (p.T383fsX), is the most common mutation underlying achromatopsia worldwide, accounting for approximately 70% of all *CNGB3* disease-causing alleles and approximately 40% of all achromatopsia-associated alleles.

Normal gene product: The polypeptide is 809 amino acids long. *CNGB3* encodes for cyclic nucleotide-gated cation channel beta 3 (the beta subunit of the cone photoreceptor cGMP-gated cation channel). In vitro expression experiments have shown that beta subunits alone are not able to form functional homo-oligomeric channels; they are therefore thought to be modulatory subunits. Functional cone CNG channels consist of two alpha and two beta subunits.

Abnormal gene product: Most *CNGB3*-encoded mutant proteins are thought to be null alleles. However, heterologous coexpression of human polypeptide subunits encoded by a normal

CNGA3 gene and a mutated *CNGB3* gene containing the Pingelapese blindness-associated mutation S435F in the S6 transmembrane domain 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. The same holds true for certain other disease-associated mutations in the subunit encoded by *CNGB3*, rendering these gain-of-function mutations [Okada et al 2004, Bright et al 2005].

In contrast, coexpression of a presumptive null mutation, p.T383fsX (c.1148delC), the most common mutation associated with achromatopsia, produced channels with properties indistinguishable from homomeric CNGA3 channels, rendering it a null allele [Peng et al 2003, Okada et al 2004, Bright et al 2005].

GNAT2

Normal allelic variants: The *GNAT2* gene consists of eight coding exons [Morris & Fong 1993]. Only a few polymorphisms and rare variants are observed; most occur within non-coding regions or do not result in an amino acid substitution.

Pathologic allelic variants: Eight different disease-associated nonsense mutations, frame-shift deletions, or insertions, segregating in seven independent families, have been described [Aligianis et al 2002, Kohl et al 2002, Michaelides et al 2003, Rosenberg et al 2004].

Normal gene product: The polypeptide is 354 amino acids long [Lerea et al 1989]. *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.

Abnormal gene product: All observed mutations in the *GNAT2* gene result in polypeptides lacking considerable proportions of the genuine carboxy terminus that is thought to interact with the photopigment [Cai et al 2001].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The Low Vision Gateway
Achromatopsia

National Eye Institute
Low Vision

National Library of Medicine Genetics Home Reference
Color vision deficiency

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Deeb SS. Molecular genetics of colour vision deficiencies. Clin Exp Optom. 2004;87:224–9. [PubMed: 15312026]

Chapter Notes

Revision History

- 23 October 2006 (me) Comprehensive update posted to live Web site
- 24 June 2004 (me) Review posted to live Web site
- 17 February 2004 (sk, bw) Original submission