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Ocular Albinism, X-Linked – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Nettleship-Falls Ocular Albinism, OA1, Ocular Albinism Type 1, XLOA

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

X-linked ocular albinism (XLOA) is a disorder of melanosome biogenesis leading to minor cutaneous and adnexal manifestations and congenital and persistent visual impairment in affected males. XLOA is characterized by infantile nystagmus, reduced visual acuity, hypopigmentation of the iris pigment epithelium and the ocular fundus, and foveal hypoplasia. Significant refractive errors, reduced or absent binocular functions, photoaversion, and strabismus are common. XLOA is a non-progressive disorder and the visual acuity remains stable throughout life, often slowly improving into the mid-teens.

Diagnosis/testing

A diagnosis of ocular albinism (OA) is probable in the presence of infantile nystagmus, iris translucency, substantial hypopigmentation of the ocular fundus periphery in males with mildly hypopigmented skin (most notably when compared to unaffected sibs), foveal hypoplasia, reduced visual acuity, and aberrant optic pathway projection as demonstrated by crossed asymmetry of the cortical responses on visual evoked potential testing. X-linked inheritance is documented by either a family history consistent with X-linked inheritance or the presence of typical carrier signs (irregular retinal pigmentation and mild iris transillumination) in an obligate carrier female. Molecular genetic testing of *GPR143* (previously *OA1*) detects pathogenic variants in more than 90% of affected males.

Management

Treatment of manifestations: Early detection and correction of refractive errors, use of sunglasses or special filter glasses for photoaversion, and prismatic spectacle correction for abnormal head posture. Strabismus surgery is

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often unnecessary but may be performed to improve peripheral visual fusion fields. The need for vision aids and special consideration in educational settings should be addressed.

Surveillance: For affected children younger than age 16 years: annual ophthalmologic examination (including assessment of refractive error and the need for filter glasses) and psychosocial and educational support. For adults: ophthalmologic examinations as needed.

Genetic counseling

XLOA is inherited in an X-linked manner. An affected male transmits the pathogenic variant to all of his daughters and none of his sons. The risk to the sibs of a male proband depends on the carrier status of the mother. If the mother is a carrier, the chance of transmitting the *GPR143* pathogenic variant in each pregnancy is 50%. Male sibs who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be carriers and will usually not be affected. Carrier testing of at-risk female relatives is most informative if the pathogenic variant has been identified in the proband. Prenatal testing is possible for a pregnancy at increased risk if the familial pathogenic variant is known.

Diagnosis

Suggestive Findings

Males

X-linked ocular albinism (XLOA) **should be suspected** in males with the following findings:

Ophthalmologic (common to all forms of albinism)

- **Infantile nystagmus.** Nystagmus usually develops during the first three months of life and may be preceded by a period of poor fixation and poor visual contact, giving rise to a suspicion of delayed visual maturation or cerebral visual impairment (CVI). The nystagmus is most frequently of the pendular or jerk type and is sometimes associated with head nodding (titubation). With age, the nystagmus tends to diminish, although it rarely disappears completely.

  Nystagmus amplitude and/or frequency often varies with horizontal gaze position. The gaze position in which the nystagmus is least severe is known as the null point. At the null point, the decrease in ocular oscillations reduces retinal image motion and thereby maximizes visual acuity. Therefore, affected individuals whose null point is eccentrically located will adopt a compensatory face turn. A similar dampening of nystagmus can be obtained with the convergence that occurs with focus at a close range; thus, visual acuity at close range tends to be better than visual acuity tested at distance.

- **Hypopigmentation of the iris.** Iris transillumination caused by hypopigmentation of the iris pigment epithelium (IPE), the posterior layer of the iris, is a frequent finding that is best visualized in a dark room by trans-scleral illumination with a light source placed directly on the bulbar conjunctiva or by slit lamp examination in which a strong beam is directed through an undilated pupil. Normally, incident light reflected from within the eye exits only through the pupil because it is blocked by the IPE. In albinism, reflected light can penetrate the iris. Since punctate iris transillumination defects can be seen in some individuals with light complexion, detection of these defects alone in this group is not a reliable indicator of albinism.

- **Hypopigmentation of the ocular fundus** resulting from decreased concentration of pigment in the retinal pigment epithelium (RPE), which allows visualization of the choroidal vessels. The hypopigmentation is generally more profound in the periphery of the ocular fundus.

- **Foveal hypoplasia,** characterized by diminution or absence of the foveal pit (umbo) and the annular foveal reflex. The foveal area is inconspicuous and sometimes retinal vessels extend through the normally avascular fovea. Optical coherence tomography (OCT) can document the retinal thinning. Some affected males in pedigrees with congenital X-linked nystagmus and molecular confirmation of XLOA have foveal hypoplasia as an isolated finding [Preising et al 2001].
- **Reduced visual acuity.** In most individuals with albinism, the best corrected visual acuity is between 20/40 (6/12) and 20/200 (6/60). XLOA is a non-progressive disorder and the visual acuity typically slowly improves until mid-to-late teens and then remains stable throughout life.
- **Aberrant optic pathway projections** consisting of an excessive crossing of the retino-striate fibers in the optic chiasm; i.e., the visual input from the right eye is almost exclusively directed towards the left hemisphere and vice-versa [Schmitz et al 2003, Lauronen et al 2005]. This "misrouting" can be demonstrated in specialized laboratories by selective VEP technique adapted for use in clinical practice [Soong et al 2000, Hoffmann et al 2005]. Lateral placement of recording electrodes over the occipital area allows for the detection of interhemispheric asymmetries in amplitude following monocular stimulation with a pattern-onset grating. Rather than the typical near-equal response from each hemisphere, the response amplitude is disproportionately larger in the hemisphere contralateral to the stimulated eye. Some authors contend that this VEP technique, albeit cumbersome, is a highly sensitive indicator of albinism [Sjöström et al 2001]. In several forms of albinism, MR imaging found variations in the size and configuration of the optic chiasm compared to normal controls. However, this feature is neither distinctive nor unique and, thus, is not helpful in clinical diagnosis [Schmitz et al 2003].

Dermatologic

- **Hypopigmentation** of hair and skin compared to others of the same racial or ethnic backgrounds, especially when compared to unaffected male sibs. Of course, the cutaneous color spectrum is broad and overlaps the entire spectrum of other forms of albinism.

Note: None of the above findings is either specific or obligate for X-linked ocular albinism, and the diagnosis may be difficult in blond northern European males with only minimally reduced central visual acuity.

Family history

- Maternal male relatives with ocular albinism
- The most consistent clinical diagnostic clue for XLOA: presence of characteristic retinal pigment abnormalities in female relatives who are obligate carriers

Heterozygous Females

Depending on overall ethnic and racial skin and adnexal pigmentation, heterozygous females may show iris transillumination and a coarse pattern of blotchy hypo-and hyperpigmentation of the retinal pigment epithelium that becomes more dramatic outside the vascular arcades. Some carriers have isolated patches of hypopigmented skin that does not tan to the same degree as uninvolved skin.

Rarely, heterozygous females are affected, showing infantile nystagmus, foveal hypoplasia, reduced visual acuity, and diffuse hypopigmentation of the ocular structures.

Establishing the Diagnosis

The diagnosis of XLOA **is established** in a proband with identification of a pathogenic variant in *GPR143* (see Table 1). If molecular testing is not available, the finding of macromelanosomes on skin biopsy would also establish the diagnosis.

Molecular testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *GPR143* is performed first followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *GPR143* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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.

Table 1. Molecular Genetic Testing Used in X-Linked Ocular Albinism

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GPR143	Sequence analysis [3, 4]	43% [5] (~90% [6])
	Gene-targeted deletion/duplication analysis [7]	48% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by deletion/duplication analysis.
5. Schnur et al [1998], Hegde et al [2002], Faugère et al [2003]
6. Due to the high prevalence of deletions in this X-linked gene, attempts at sequence analysis may detect amplification failure resulting in an apparent detection rate of ~90% in affected males [Personal communications, Baylor Miraca Genetics Laboratory, Houston, TX]. Standard clinical laboratory practice does not consider assay failure to be diagnostic; therefore, deletion/duplication analysis would be necessary to confirm a diagnosis.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

X-linked ocular albinism (XLOA) is a disorder of melanosome biogenesis leading to congenital and persistent visual impairment and mild to moderate skin changes in affected males.

Affected Males

Ophthalmologic phenotype is shared by all types of albinism, which in typical cases includes infantile nystagmus, reduced visual acuity, hypopigmentation of the iris pigment epithelium and the retinal pigment epithelium, foveal hypoplasia, and abnormal optic pathway projections. None of these findings is, however, either specific or obligate.

- Hypersensitivity to light, often called "photoaversion," "photophobia," or more appropriately "photodysphoria," is present in most affected individuals but varies in intensity and significance from one individual to another. In some affected individuals, photodysphoria is the most incapacitating symptom.
- Substantial refractive errors are common, most often as hypermetropia with oblique astigmatism. High myopia or compound myopic astigmatism may occur in some affected individuals.
- Most affected individuals have reduced or absent binocular functions as a consequence of misrouted optic pathway projections, and ocular misalignment (strabismus). A positive angle lambda is often found in individuals with albinism [Brodsky & Fray 2004].
- Posterior embryotoxon, a developmental anomaly of the anterior chamber angle, has been reported in 30% of a small series of affected males [Charles et al 1993].

Dermatologic phenotype. XLOA is characterized by mild cutaneous and adnexal involvement (*albinismus solum bulbi*), and the universal defect in melanosome biogenesis that may escape clinical notice, if not compared to unaffected sibs. Nevertheless, in families with dark complexion, affected males tend to be more lightly pigmented than their unaffected sibs. In some affected males, irregular hypopigmented spots are present on the arms and legs.

Prognosis. Persons with XLOA have normal life span, development, intelligence, and fertility.

Heterozygous Females

Heterozygous females may be considered mosaic with respect to the *GPR143* pathogenic variant because random X-chromosome inactivation leads to variable degrees of ocular and cutaneous hypopigmentation.

- Most heterozygous females demonstrate iris transillumination, which is most prominent in the periphery of the iris. In addition, the ocular fundus shows an easily recognizable pattern of irregular coarse hypopigmentation of the retinal pigment epithelium in splotches and streaks, more dramatic in the peripheral retina. Carrier signs are present in at least 80% to 90% of heterozygotes. Therefore, absence of carrier signs does not exclude a diagnosis of XLOA.
- On occasion, carrier females are affected as severely as males as a result of either skewed X-chromosome inactivation, homozygosity for a *GPR143* pathogenic variant, or partial or total monosomy of the X chromosome.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified [Schiaffino et al 1999].

Even in the same family, the cutaneous and adnexal coloration and the visual acuities may vary widely [Preising et al 2011, Trebušak Podkrajšek et al 2012].

Prevalence

A minimum birth prevalence of one male in 60,000 live born children has been reported in a Danish cohort [Rosenberg & Schwartz 1998] and of approximately one in 50,000 in a US cohort [King et al 1995].

Genetically Related (Allelic) Disorders

With the exception of contiguous gene syndromes, no phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *GPR143*.

Contiguous gene syndromes. In interstitial deletions of the X chromosome involving genes around Xp23, contiguous gene syndromes may arise. In such cases, XLOA may be associated with X-linked ichthyosis [Schnur

et al 1989], Kallmann syndrome [Zhang et al 1993], sensorineural deafness [Bassi et al 1999], and congenital nasal pyriform aperture stenosis [Somsen et al 2014].

Differential Diagnosis

"Congenital" nystagmus is usually the initial clinical sign leading to suspicion of an underlying visual sensory or central nervous system disorder and to an ophthalmologic examination. Congenital or infantile nystagmus (which typically begins two to eight weeks after birth) is not specific or unique to XLOA, as it can appear as an isolated finding (so-called primary motor nystagmus) or as part of a hereditary ocular disorder, some of which are X-linked. Although infantile nystagmus is often a secondary manifestation of bilateral congenital eye disorders associated with vision loss (e.g., corneal opacities, aniridia, cataracts, retinopathy of prematurity, and optic nerve hypoplasia), the differential diagnosis in males with XLOA is usually limited to visual disorders in which infantile nystagmus is the predominant finding and the eye is anatomically normal.

A family history of X-linked inheritance for similarly affected individuals along with typical clinical findings supports the diagnosis of XLOA and further testing may not be indicated. However, when the family history is negative, XLOA must be distinguished from other forms of albinism and from X-linked disorders associated with infantile nystagmus.

X-linked congenital nystagmus (OMIM 310700) is a diagnosis of exclusion, characterized by normal electroretinogram (ERG) and normal optic pathways. In the absence of any demonstrable sensory defect, the involuntary eye movements are denoted "motor nystagmus." More than 50% of carrier females manifest congenital nystagmus, simulating autosomal dominant inheritance [Kerrison et al 1999]. Families with X-linked congenital nystagmus have absence of male-to-male transmission. Three X-chromosome loci, Xp11.4, Xp22.2 (*GPR143*), and Xq26.2 (*FRMD7*), have been identified. *FRMD7* may manifest slightly different clinical and oculomotor characteristics than XLOA [Kumar et al 2011]. See also *FRMD7*-Related Infantile Nystagmus.

The **oculocutaneous albinisms,** inherited in an autosomal recessive manner, include types with moderate pigmentation of skin and hair that may be occasionally misinterpreted as "ocular albinism."

- Oculocutaneous albinism type 1 (OCA1) is caused by pathogenic variants in *TYR* that encodes the protein tyrosinase. Individuals with OCA1A (OMIM 203100) have white hair, white skin that does not tan, and fully translucent irides that do not darken with age. At birth, individuals with OCA1B (OMIM 606952) have white or very light yellow hair that darkens with age, white skin that over time develops some generalized pigment and may tan with sun exposure, and blue irides that change to green/hazel or brown/tan with age. Ocular findings are very similar to those of XLOA. The diagnosis of OCA1 is established by clinical findings of hypopigmentation of the skin and hair and characteristic eye findings.
- Oculocutaneous albinism type 2 (OCA2) (OMIM 203200) is caused by pathogenic variants in *OCA2* (previously called *P*). The amount of cutaneous pigmentation in OCA2 ranges from minimal to near normal. Newborns with OCA2 almost always have pigmented hair, with color ranging from light yellow to blond to brown. Hair color may darken with time. Brown OCA, initially identified in Africans and African Americans with light brown hair and skin, is part of the spectrum of OCA2.
- Oculocutaneous albinism type 3 (OCA3) (OMIM 203290) is caused by pathogenic variants in *TYRP1* (encoding tyrosinase-related protein 1, also called glycoprotein 75 or GP 75). Originally described in southern African blacks, the disorder is characterized by bright copper-red hair, lighter tan skin, and diluted pigment in the iris and fundus. This has been called "rufous oculocutaneous albinism."
- Oculocutaneous albinism type 4 (OCA4) is caused by pathogenic variants in *SLC45A2* (previously called *MATP* or *AIM1*). The amount of cutaneous pigmentation in OCA4 ranges from minimal to near normal. Newborns with OCA4 usually have some pigment in their hair, with color ranging from silvery white to light yellow. Hair color may darken with time, but does not vary significantly from childhood to adulthood. This form of albinism is rarer than OCA2, except in the Japanese population.

Complete congenital stationary night blindness is characterized by night blindness (nyctalopia), moderate to severe myopia, normal fundi, complete lack of dark adaptation, and characteristic ERG. A subset of affected individuals have congenital nystagmus and mildly reduced visual acuity. The rod (dark-adapted) ERG shows a normal a-wave, indicating normal photoreceptor function, but an undetectable b-wave, indicating post-receptor dysfunction. This response pattern is often referred to as a "negative ERG" because the negative potential of the initial a-wave is not followed by the positive potential of the b-wave. The cone (light-adapted) ERG is mildly reduced and can show a squared-off b-wave caused by loss of the ON-response. The condition is inherited in an X-linked manner and caused by pathogenic variants in *NYX* (nyctalopin), a member of the leucine-rich proteoglycan family involved in cell adhesion and axon guidance. The protein product is found in ON-bipolar cells connected to both rods and cones.

Incomplete congenital stationary night blindness is characterized by congenital nystagmus, reduced visual acuity, and moderate night-blindness. Iris translucency is not part of the disorder and ERG shows characteristic negative ERG and severely reduced double-peaked cone amplitudes. (The designation "negative ERG" describes an ERG with an a:b wave ratio above unity.) The condition is inherited in an X-linked manner and caused by pathogenic variants in *CACNA1F* [Bech-Hansen et al 1998]. Female carriers are asymptomatic.

Blue cone monochromacy (OMIM 303700), sometimes referred to as X-linked incomplete achromatopsia, is a rare disorder (<1 in 100,000) characterized by X-linked inheritance, photophobia, congenital nystagmus, reduced visual acuity (20/60-20/200), impaired red-green color perception, and characteristic ERG. Fundi are usually normal, but atrophic macular changes have been reported. Formal color vision testing reveals absent or severely reduced responses to red-green stimuli and normal responses to blue stimuli. Standard ERG testing shows absent cone responses with normal rod responses. The S-(blue) cone response is normally undetectable by ERG because S-(blue) cones constitute about 5% of the total cone population. By special techniques, the blue cone response can be amplified and measured in a clinical setting.

Two common molecular defects are associated with this phenotype [Nathans et al 1989]. One is a deletion of a regulatory sequence (locus control region) upstream of the visual pigment genes, which consists of one red pigment (opsin) gene and one or more green (opsin) genes. The second defect involves unequal homologous recombination between red and green opsin genes (coding to a single mutated red opsin) or a 5' red-green hybrid gene having a p.Cys203Arg (c.607T>C, NM_000513.2) substitution that encodes for a nonfunctional protein. A rare third molecular defect found in a single family involved a deletion of exon 4 in an isolated red gene [Ladekjaer-Mikkelsen et al 1996].

Other disorders with sensory retinal early-onset nystagmus include autosomal dominant motor nystagmus, complete and incomplete achromatopsia, blue cone monochromacy, and other autosomal recessive stationary cone dysfunctions including enhanced S-cone syndrome, cone dystrophy with supernormal rod response, and Leber congenital amaurosis. In most of these diagnostic groups, the ERG is essential to establish the diagnosis.

***PAX6* pathogenic variants** can result in infantile nystagmus and foveal hypoplasia in individuals with only mild iris hypoplasia (see Aniridia). Such individuals do not have iris transillumination.

Failure to detect a pathogenic variant in *GPR143* should lead the clinician to re-assess the patient for other non-ocular and constitutional features that will be useful for additional molecular diagnostic studies.

Ocular albinism with sensorineural deafness (OMIM 103470) is characterized by ocular albinism indistinguishable from XLOA (including the presence of macromelanosomes in the skin); additional findings are congenital deafness and vestibular dysfunction. In some affected individuals, heterochromia iridis and a prominent white forelock are present. Inheritance is autosomal dominant. A relation between this disorder and Waardenburg syndrome type 2 has been suggested and may result from digenic interaction between a transcription factor, *MITF*, and a missense pathogenic variant in *TYR* (encoding tyrosinase) [Morell et al 1997].

Ocular albinism with late-onset sensorineural deafness (OMIM 300650), an X-linked condition with a disease locus at Xp22.3, was reported in a large Afrikaner kindred. The disorder is possibly caused by an allelic *GPR143* variant or a contiguous gene defect [Bassi et al 1999].

Hermansky-Pudlak Syndrome (HPS) is a multisystem disorder characterized by: tyrosinase-positive oculocutaneous albinism; a bleeding diathesis resulting from a platelet storage pool deficiency; and, in some cases, pulmonary fibrosis, granulomatous colitis, or immunodeficiency. The albinism is characterized by: hypopigmentation of the skin and hair; and ocular findings of reduced iris pigment with iris transillumination, reduced retinal pigment, foveal hypoplasia with significant reduction in visual acuity (usually in the range of 20/50 to 20/400), nystagmus, and increased crossing of the optic nerve fibers. Hair color ranges from white to brown; skin color ranges from white to olive and is usually a shade lighter than that of other family members. Because of the wide phenotypic variability in the colors of skin and hair in HPS, an observer might initially consider ocular albinism in the differential diagnosis, especially in a person of the less common ethnogeographic backgrounds; however, the clinician should always query the manifestations of the common bleeding diathesis in HPS. HPS is inherited in an autosomal recessive manner and is caused by pathogenic variants in *HPS1*, *AP3B1* (*HPS2*), *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1* (*HPS7*), *BLOC1S3* (*HPS8*), and *BLOC1S6* (*PLDN*).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked ocular albinism (XLOA), the following evaluations are recommended:

- Medical history and physical examination, including a careful evaluation of pigmentation status at birth and later to distinguish between oculocutaneous and ocular albinism
- A complete ophthalmologic evaluation
- Dilated retinal examination of any at-risk possible carrier (mother, daughter) for the classic retinal carrier state
- Dermatologic consultation for sun-protective lotion and sun-protective clothing and avoidance of associated cumulative solar damage
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Refractive errors should be treated with appropriate spectacle correction as early as possible.

Photodysphoria can be relieved by sunglasses, transition lenses, or special filter glasses, although many prefer not to wear them because of the reduction in vision from the dark lenses when indoors.

Abnormal head posture with dampening of the nystagmus in a null point may be modified with prismatic spectacle correction.

Strabismus surgery is usually not required but may be performed for cosmetic purposes, particularly if the strabismus or the face turn is marked or fixed. The need for vision aids and the educational needs of the visually impaired should be addressed.

Dermatologic counseling for age-appropriate sun-protective lotions and clothing should be sought.

Prevention of Secondary Complications

Appropriate education for sun-protective lotions and clothing (preferably by an informed dermatologic consultant) is indicated to moderate the cumulative lifelong effects of solar radiation.

Surveillance

Children younger than age 16 years with ocular albinism should have an annual ophthalmologic examination (including assessment of refractive error and the need for filter glasses) and psychosocial and educational support.

In adults, ophthalmologic examinations should be undertaken when needed, typically every two to three years.

Agents/Circumstances to Avoid

Although no formal trials exist, standard care avoids use or application of sun-sensitizing drugs or agents.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Nystagmus dampening has been achieved by bilateral horizontal rectus recession surgery in some centers, but this is not a generally accepted treatment nor is there evidence from a comparative clinical trial that such intervention improves the final visual outcome.

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

X-linked ocular albinism is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have ocular albinism nor will he be hemizygous for the *GPR143* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child with the same pathogenic variant and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If pedigree analysis reveals that the proband is the only affected family member, it is appropriate to examine the retina of the mother for evidence of classic mosaic pigmentation of the retinal pigment

epithelium. Alternatively, if the *GPR143* pathogenic variant in the proband is known, the mother should be tested for that pathogenic variant. Possible genetic explanations for a single occurrence of an affected male in the family:

- The proband has a *de novo* pathogenic variant. In this instance, the proband's mother does not have the pathogenic variant. The only other family members at risk are the offspring of the proband.
- The proband's mother has a *de novo* pathogenic variant and may or may not have retinal changes. One of two types of *de novo* pathogenic variants may be present in the mother:

  a. A germline pathogenic variant that was present at the time of her conception, is present in every cell of her body, and can be detected in DNA extracted from her leukocytes; or

  b. A pathogenic variant that is present only in her ovaries (termed "germline mosaicism") and cannot be detected in DNA extracted from leukocytes. Germline mosaicism has not been reported in XLOA, but it has been observed in many X-linked disorders and should be considered in the genetic counseling of at-risk family members.

  Note: In both a and b above, all offspring of the proband's mother are at risk of inheriting the pathogenic variant, whereas the sibs of the proband's mother are not.

Sibs of a proband

- The risk to sibs depends on the genetic status of the mother.
- If the *GPR143* pathogenic variant has been detected in the mother's leukocyte DNA, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and the *GPR143* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism. Germline mosaicism in mothers is not reported in XLOA but has been documented in other X-linked disorders and is likely rare.
- If the pathogenic variant is not known but the mother of a single affected male has normal fundus pigmentation, the risk to the sibs of a proband appears to be low but is likely to be greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. An affected male will transmit the *GPR143* pathogenic variant to:

- All his daughters, who will be heterozygotes and will usually not be affected (see Clinical Description, Heterozygous Females);
- None of his sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

Heterozygote (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *GPR143* pathogenic variant has been identified in an affected male.

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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *GPR143* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for X-linked ocular albinism 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.

- **Genetic and Rare Diseases Information Center (GARD)**
  Ocular albinism type 1
- **National Library of Medicine Genetics Home Reference**
  Ocular albinism
- **National Organization of Albinism and Hypopigmentation (NOAH)**
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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. Ocular Albinism, X-Linked: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GPR143	Xp22.2	G-protein coupled receptor 143	Albinism Database Mutations of the Ocular Albinism-1 gene	GPR143	GPR143

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 Ocular Albinism, X-Linked (View All in OMIM)

300500	ALBINISM, OCULAR, TYPE I; OA1
300808	G PROTEIN-COUPLED RECEPTOR 143; GPR143

Gene structure. *GPR143* contains nine exons (NM_000273.2) spanning 40 kb of genomic DNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Normal variants have been reported, including a highly polymorphic dinucleotide repeat (OA1-CA) with more than five different alleles at intron 1 [Schiaffino et al 1995, Oetting 2002].

Pathogenic variants. More than 115 different pathogenic variants have been reported; most appear to be private. They include missense and splice site variants, small deletions and insertions, and large deletions covering multiple exons of *GPR143*. Studies suggest that the spectrum of pathogenic variants (e.g., prevalence of deletions) may vary between the European and North American populations [Bassi et al 1995, Rosenberg & Schwartz 1998, Schnur et al 1998, Bassi et al 2001, Oetting 2002, Camand et al 2003, Faugère et al 2003]. (See Table A, HGMD and Albinism databases.)

Normal gene product. *GPR143* encodes a protein of 404-424 (NP_000264.2) amino acids that is expressed exclusively in the retinal pigment epithelium and the iris pigment epithelium of the eye and in the melanocytes of the skin. The mature *GPR143* product is a 60-kd pigment cell-specific integral membrane glycoprotein, which represents a novel member of the G-protein coupled receptor (GPCR) superfamily (GPCR-143) [Schiaffino et al 1996]. In contrast to other GPCRs that localize to the plasma membrane, the protein encoded by *GPR143* is targeted to intracellular organelles and may regulate melanosome biogenesis through signal transduction from the organelle lumen to the cytosol [Schiaffino & Tacchetti 2005].

When expressed in COS7 cells that lack melanosomes, GPCR-143 displays a considerable and spontaneous capacity to activate heterotrimeric G proteins and the associated signaling cascade. These findings indicate that heterologously expressed GPCR-143 exhibits two fundamental properties of GPCRs: being capable of activating heterotrimeric G proteins and providing proof that GPCR-143 can actually function as a canonic GPCR in mammalian cells [Innamorati et al 2006].

Abnormal gene product. Most individuals with XLOA have a small intragenic *GPR143* pathogenic variant which results in a phenotype similar to that observed in those exhibiting a complete deletion of *GPR143*, suggesting that most *GPR143* alleles are null. Deletions and splice pathogenic variants are expected to produce either no product or rapidly degraded truncated proteins. By expressing mutant proteins in COS cells, pathogenic missense variants could be divided into three groups (I, II, and III) based on the ability to exit the endoplasmic reticulum (ER) and traffic to the lysosomal compartment. Class I pathogenic variants result in a

gene product that is unable to exit the ER, presumably because of misfolding. The pathogenesis of these variants is therefore similar to that of the larger deletions/splice pathogenic variants. Class II pathogenic variants exit the ER with low efficiency. Class III pathogenic variants are able to exit the ER and traffic to the lysosomal compartment, and loss of function rather than incorrect trafficking is responsible for the disease in individuals expressing these abnormal alleles [d'Addio et al 2000, Shen et al 2001].

Chapter Notes

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- 5 April 2011 (me) Comprehensive update posted live
- 22 May 2006 (me) Comprehensive update posted live
- 12 March 2004 (me) Review posted live
- 30 September 2003 (tr) Original submission

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