GENEReviews

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Ocular Albinism, X-Linked

[*Nettleship-Falls Ocular Albinism, OA1, Ocular Albinism Type 1, XLOA*]

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Summary

Disease characteristics. X-linked ocular albinism (XLOA) is a disorder of melanosome biogenesis leading to congenital and persistent visual impairment in affected males. XLOA is characterized by congenital 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.

Diagnosis/testing. A diagnosis of ocular albinism (OA) is probable in the presence of congenital nystagmus, iris translucency, and significant hypopigmentation of the ocular fundus periphery in males with normal skin pigmentation and foveal hypoplasia, reduced visual acuity, and aberrant optic pathway projection, as demonstrated by crossed asymmetry of the cortical responses on visual evoked potential (VEP). 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 partial iris transillumination) in an obligate carrier female. Molecular genetic testing of the gene *GPR143(OA1*) detects mutations in more than 90% of affected males. Such testing is available on a clinical basis.

Management. Treatment for OA includes early correction of refractive errors, use of sunglasses or special filter glasses for photoaversion, and prismatic spectacle correction for abnormal head posture. Strabismus surgery is usually not required but may be performed for cosmetic purposes, particularly if the strabismus is marked or fixed. The need for vision aids and special training should be addressed. Surveillance for affected children younger than age 16 years includes annual ophthalmologic examination (including assessment of refractive error and the need for filter glasses) and psychosocial and educational support. In adults with OA, ophthalmologic examinations should be performed as needed.

Genetic counseling. XLOA is inherited in an X-linked manner. An affected male transmits the disease-causing mutation to all of his daughters and none of his sons. The risk to the sibs of a male proband depends upon the carrier status of the mother. If the mother is a carrier, the chance of transmitting the *GPR143* mutation in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will

usually not be affected. Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the proband. If the familial mutation is not known because an affected male is unavailable for testing, molecular genetic testing can be performed on at-risk female relatives, but with a lower degree of test sensitivity. Prenatal testing is clinically available for pregnancies of women who are carriers of a known *GPR143* mutation.

Diagnosis

Clinical Diagnosis

Affected males. All forms of albinism share the following ophthalmologic findings:

- **Congenital 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. With age, the nystagmus has a tendency to diminish; however, it rarely disappears completely.

  Nystagmus amplitude and/or frequency often vary 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 head turn. A similar dampening of nystagmus can be obtained with the convergence that occurs with focus at a close range.

- **Hypopigmentation of the iris.** Iris translucency 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 using 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 up to 15% of individuals with light complexion, detection of these defects in this group is not a reliable indicator of albinism. Viewed with the naked eye, decreased pigment in the melanocytes of the iris stroma could be interpreted to be decreased coloration of the iris.

- **Hypopigmentation of the ocular fundus** resulting from decreased 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. In some individuals, a more or less sharp demarcation is seen against a more pigmented RPE at the posterior pole within the vascular arcades.

- **Foveal hypoplasia** characterized by absence of the foveal pit and the annular reflex. The foveal area is inconspicuous and sometimes, retinal vessels extend through the normally avascular fovea. 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 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 a suitable 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 is a highly sensitive indicator of albinism [Sjostrom et al 2001].

None of the findings, however, is either specific or obligate for X-linked ocular albinism, and the diagnosis may be difficult in blond Caucasian males with only marginally subnormal vision.

The most consistent clinical diagnostic clue for XLOA is the presence of characteristic retinal pigment abnormalities in female relatives who are obligate carriers.

Carrier females. Depending on overall pigmentation, female carriers may show iris translucency and a more or less patchy hypopigmentation or a grayish 'mud-splattered' discoloration of the peripheral fundus.

Rarely, female carriers are affected, showing congenital nystagmus, foveal hypoplasia, low vision, and diffuse hypopigmentation of the ocular structures.

Testing

Skin biopsy. In spite of the absence of evident systemic manifestations in XLOA, light and electron microscopy may demonstrate characteristic aggregates of abnormal epidermal melanosome morphology (macromelanosomes) within keratinocytes and melanocytes in a majority of affected individuals and female carriers, making microscopy of skin biopsies an additional diagnostic test. However, with the availability of molecular genetic testing, skin biopsy is rarely indicated.

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.

Molecular Genetic Testing—Gene. *GPR143(OA1*) is the only gene known to be associated with X-linked ocular albinism.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier diagnosis
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

Sequencing and multiplex PCR analyses of the *GPR143* gene coding region are clinically available

- Such testing is expected to detect more than 90% of hemizygous mutations in affected males [Schnur et al 1998, Hegde et al 2002, Faugere et al 2003]. About 48% of reported mutations are intragenic deletions and about 43% are point mutations [Hegde et al 2002].
- If the *GPR143* mutation has previously been identified in an affected male, molecular genetic testing can be performed for at-risk female relatives.
- If the familial mutation is not known because an affected male is not available for testing, molecular genetic testing for unknown heterozygous mutations can be performed on females but with a lower degree of test sensitivity.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Methods	Mutations Detected	Mutation Detection Rate in Affected Males	Test Availability
Sequence analysis	*GPR143* sequence variants	>90%	Clinical Testing
Multiplex PCR	*GPR143* intragenic deletions		

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

Testing Strategy for a Proband

- To establish the diagnosis of **albinism**, the presence of nystagmus, reduced iris and retinal pigment, foveal hypoplasia, and reduced visual acuity are sufficient.
- If any of the above signs is absent, a VEP or other techniques to demonstrate aberrant optical pathways are required.
- ERG is very rarely required.
- To establish the diagnosis of XLOA in a male who represents a simplex case (i.e., no other known affected males in the family) or who has equivocal findings:
  - Examine the iris and fundus of the mother (or any daughter) for carrier changes;
  - If the mother does not show carrier signs, perform molecular genetic testing of *GPR143*;
  - If no *GPR143* mutation is identified, perform a skin biopsy to look for characteristic macromelanosomes.

Genetically Related (Allelic) Disorders

With the exception of contiguous gene syndromes, no other phenotypes are associated with mutations 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], or late-onset sensorineural deafness [Bassi et al 1999].

Clinical Description

Natural History

XLOA is a disorder of melanosome biogenesis leading to congenital and persistent visual impairment in affected males.

Affected males. All types of albinism share a similar ophthalmologic phenotype, which in typical cases includes congenital 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.

Pathologic hypersensitivity to light, called "photoaversion," "photophobia," or "photodysphoria," is present in most affected individuals but varies in intensity and significance from one individual to another. In some affected individuals, photophobia is the most incapacitating symptom.

Significant refractive errors are common, most often as hypermetropia with oblique astigmatism. High myopia is also found in some affected individuals.

Most affected individuals have reduced or absent binocular functions as a consequence of misrouted optic pathway projections, and squinting (strabismus) is common. A positive angle kappa 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 affected males [Charles et al 1993].

The optic nerve head in OA is often small with blurred margins and is slightly dysplastic, with an irregular entrance of the retinal vessels.

XLOA is characterized by absence of clinically apparent systemic involvement (*albinismus solum bulbi*), and the universal defect in melanosome biogenesis does not seem to lead to hair and skin hypopigmentation. Nevertheless, in families with dark complexion, affected males tend to be more lightly pigmented than their unaffected sibs. In some affected males, irregular depigmented spots are present on the arms and legs.

Carrier females may be considered to be mosaic with respect to the *GPR143* mutation because of random X-chromosome inactivation that leads to variable degrees of ocular hypopigmentation.

- Most carrier females demonstrate iris translucency, which is most prominent in the periphery of the iris. In addition, the ocular fundus shows an easily recognizable pattern of irregular coarse depigmentation and grayish splotches and streaks. Carrier signs are present in 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* mutation, or partial monosomy of the X chromosome.

Genotype-Phenotype Correlations

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

Nomenclature

Ocular albinism, Forsius-Eriksson type (OMIM 300600) (also designated Åland island eye disease [AIED]), a rare X-linked cone-rod dysfunction, is allelic or identical with incomplete congenital stationary night blindness [personal communication]. Several affected males in the family originally described from Åland in the Baltic Sea had hypopigmented fundi, erroneously classified as ocular albinism, Forsius-Eriksson type [McKusick 1968].

Autosomal recessive ocular albinism (AROA) (OMIM 203310) [O'Donnell et al 1978] is now believed to be part of the spectrum of OCA1 and OCA2 [King, Hearing et al 2001; King, Oetting et al 2001]. At this time, there is no evidence for a distinct AROA and this term should not be used.

Prevalence

A minimum birth prevalence of one male in 60,000 liveborn children has been reported [Rosenberg & Schwartz 1998].

Differential Diagnosis

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

Congenital nystagmus is usually the initial clinical sign leading to suspicion of an underlying visual sensory disorder and to an ophthalmological examination. Congenital nystagmus is not specific to XLOA, as it can appear as an isolated finding (so-called primary motor nystagmus) or as part of a hereditary retinal disorder, some of which are X-linked. Although congenital nystagmus is often a secondary manifestation of bilateral congenital eye disorders associated with vision loss (such as 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 congenital 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 congenital nystagmus.

X-linked congenital nystagmus (OMIM 310700) is a diagnosis of exclusion, characterized by normal electroretinogram (ERG) and normal optical pathways. In the absence of any demonstrable sensory defect, the involuntary eye movements are denoted 'motor nystagmus.' Over 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. Two X-chromosomal loci, Xp11.4-p11.3 and Xq27, have been identified.

Ocular albinism with sensorineural deafness (OMIM 103470). In addition to ocular albinism, indistinguishable from XLOA including the presence of macromelanosomes in the skin, this syndrome consists of 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 mutation in the tyrosinase gene, *TYR* [Morell et al 1997].

Ocular albinism with late-onset sensorineural deafness (OMIM 300650). This X-linked condition with a disease locus at Xp22.3 was reported in a large Afrikaner kindred. The disorder is possibly an allelic *GPR143* variant or a contiguous gene defect [Winship et al 1993].

Oculocutaneous albinism, inherited in an autosomal recessive manner, includes types with moderate pigmentation of skin and hair that may be misinterpreted as ocular albinism.

- Oculocutaneous albinism type 1 (OCA1) is caused by mutations in the gene *TYR* that encodes the protein tyrosinase. Individuals with OCA1A have white hair, white skin that does not tan, and fully translucent irides that do not darken with age. At birth, individuals with OCA1B 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. Molecular genetic testing of the tyrosinase gene, TYR, is clinically available.
- Oculocutaneous albinism type 2 (OCA2) is caused by mutations in the *OCA2* gene (previously called the *P* gene). 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 4 (OCA4) is caused by mutations in the *MATP* gene (previously called *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. This X-linked condition 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 has 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 caused by a mutation in the *NYX* (nyctalopin) gene, which is 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 (OMIM 300071). This X-linked condition 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.) Female carriers are asymptomatic. The condition is caused by mutations in the *CACNA1F* gene [Bech-Hansen et al 1998].

Blue cone monochromacy (OMIM 303700) (sometimes referred to as X-linked incomplete achromatopsia). Blue cone monochromacy 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 C203R substitution that encodes for a non-functional 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]. (See the *GeneReview*Red-Green Color Vision Defects for more information about the red pigment and green pigment genes.)

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

***PAX6* mutations** can result in congenital nystagmus and foveal hypoplasia in individuals with only mild iris hypoplasia (see Aniridia). Note: Such individuals virtually never have iris transillumination.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Medical history and physical examination, including a careful evaluation of pigmentation status at birth and later to help distinguish between oculocutaneous and ocular albinism
- A complete ophthalmologic evaluation

Treatment of Manifestations

- Refractive errors should be treated with full spectacle correction as early as possible.
- Photoaversion can be relieved by sunglasses or special filter glasses, although many prefer not to wear them because of the reduction in vision from the dark lenses.
- Abnormal head posture with dampening of the nystagmus in a null point may be corrected with prismatic spectacle correction
- Strabismus surgery is usually not required but may be performed for cosmetic purposes, particularly if the strabismus is marked or fixed. The need for vision aids and special training should be addressed.

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 only be undertaken when needed.

Therapies Under Investigation

An animal model, the Oa1 knock-out mouse has been constructed displaying the essential characteristics of XLOA [Surace et al 2005]. Decreased a- and b-wave ERG amplitudes in the Oa1 (-/-) model, however, are not present in humans with XLOA. Adeno-associated viral vector-mediated Oa1 gene transfer to the retina of the Oa1(-/-) mouse model results in significant rescues of both functional and morphologic abnormalities. These experiments open potential therapeutic perspectives.

Tissue-specific control of Oa1 transcription is regulated by the microphthalmia transcription factor Mitf [Vetrini et al 2004]. Subretinal injections of an adeno-associated virus-mediated construct consisting of a small fragment of the Oa1 promotor cloned in front of a reporter gene was expressed specifically in the retinal pigment epithelium. These results point to a possibility for future therapeutic measures to influence melanosome biogenesis [Vetrini et al 2004].

No trials for X-linked ocular albinism have been initiated so far (April 2006).

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetic counseling should be offered routinely to parents of newly diagnosed children and to young adults.

Nystagmus dampening has been achieved by bilateral horizontal rectus recession surgery in some centers, but this is not a generally accepted treatment.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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

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 or be a carrier of the disease-causing mutation.

- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, it is appropriate to examine the retina of the mother to look for evidence of the carrier status. Alternatively, if the mutation in the proband is known, the mother should be tested for that mutation. Possible genetic explanations for a single occurrence of an affected male in the family:
  - The proband has a *de novo* mutation. In this instance, the proband's mother does not have the mutation. The only other family members at risk are the offspring of the proband.
  - The proband's mother has a *de novo* gene mutation and may or may not have retinal changes of the carrier state. One of two types of *de novo* gene mutations may be present in the mother:
    - **a** A germline mutation 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 mutation 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, each offspring of the proband's mother has a risk of inheriting the mutation; none of the sibs of the proband's mother, however, is at risk of inheriting the mutation.

Sibs of a proband

- The risk to the sibs of a male proband depends upon the carrier status of the mother.
- If the mother has the gene mutation, the chance of transmitting the *GPR143* mutation in each pregnancy is 50%. Male sibs who inherit the gene mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
- If the mother is not a carrier, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism. The risk for germline mosaicism in mothers is not known but is likely rare.
- The risk to the sibs of a proband appear to be low when:
  - The mother of a male who is the only affected family member does not have the *GPR143*

    gene mutation present in her son

    OR
  - The mutation is not known but the mother of a single affected male has normal fundus pigmentation.

Offspring of a proband. Affected males transmit the disease-causing mutation to all of their daughters and none of their sons.

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

Carrier Detection

- Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the proband.
- If the familial mutation is not known because an affected male is unavailable for testing, molecular genetic testing can be performed on at-risk female relatives but with a lower degree of test sensitivity.

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 testing 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 the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing is possible for pregnancies of women who are carriers of a known *GPR143* mutation. The usual procedure is to perform chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation for sex determination. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has 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 Ocular Albinism, X-Linked

Gene Symbol	Chromosomal Locus	Protein Name
GPR143	Xp22.3	G-protein coupled receptor 143

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 Ocular Albinism, X-Linked

300500	ALBINISM, OCULAR, TYPE I; OA1

Table C. Genomic Databases for Ocular Albinism, X-Linked

Gene Symbol	Locus Specific	Entrez Gene	HGMD
GPR143	GPR143	4935 (MIM No. 300500)	GPR143

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

Normal allelic variants: The *GPR143* gene contains nine exons spanning 40 kb of genomic DNA. Benign variants have been reported, including single nucleotide polymorphisms and a highly polymorphic dinucleotide repeat (OA1-CA) with more than five different alleles at intron 1 [Schiaffino et al 1995, Oetting 2002].

Pathologic allelic variants: More than 60 different mutations have been reported; most seem to be private mutations. They include missense mutations, splice mutations, small deletions and insertions, and large deletions covering multiple exons of the *GPR143* gene. Studies suggest that the mutation profile (e.g., prevalence of deletion mutations) 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, Faugere et al 2003]. (See HGMD and Albinism databases.)

Normal gene product: The *GPR143* gene encodes a protein of 404 amino acids that is exclusively expressed in the retinal pigment epithelium and the iris pigment epithelium of the eye and in the melanocytes of the skin. The mature *GPR143* gene product is a 60-kd pigment cell-specific integral membrane glycoprotein, which represents a novel member of the G protein-coupled receptor (GPCR) superfamily (G-protein coupled receptor 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, G-protein coupled receptor 143 displays a considerable and spontaneous capacity to activate heterotrimeric G proteins and the associated signaling cascade. These findings indicate that heterologously expressed G-protein coupled receptor 143 exhibits two fundamental properties of GPCRs: being capable of activating heterotrimeric G proteins and providing proof that G-protein coupled receptor 143 can actually function as a canonical GPCR in mammalian cells [Innamorati et al 2006].

Abnormal gene product: Most individuals with XLOA bear mutations in the *GPR143* gene that produce a phenotype similar to that observed in those exhibiting a complete deletion of *GPR143* gene, suggesting that most *GPR143* alleles are null. Deletions and splice mutations are expected to produce either no product or rapidly degraded truncated proteins. By expressing mutant proteins in COS cells, missense mutations could be divided into three groups (I, II, and III) based on the ability to exit the ER and traffic to the lysosomal compartment. Class I mutations result in a gene product that is unable to exit the ER, presumably because of misfolding. The pathogenesis of these mutations is therefore similar to the larger deletions / splice mutations. Class II mutants exit the ER with low efficiency. Class III mutants 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 mutant alleles [d'Addio et al 2000, Shen 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 National Organization of Albinism and Hypopigmentation (NOAH)
PO Box 959
East Hampstead NH 03826-0959
Phone: 800-473-2310; 603-887-2310
Email: noah@albinism.org
www.albinism.org

PanAmerican Society for Pigment Cell Research
www.paspcr.org

The Vision of Children Foundation
12671 High Bluff Drive Suite 300
San Diego CA 92130
Phone: 858-799-0810
Fax: 858-794-2348
www.visionofchildren.org

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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Chapter Notes

Revision History

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