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Oculocutaneous Albinism Type 2 – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: OCA2

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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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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

Oculocutaneous albinism type 2 (OCA2) is characterized by hypopigmentation of the skin and hair and the characteristic ocular changes found in all types of albinism, including nystagmus; reduced iris pigment with iris translucency; reduced retinal pigment with visualization of the choroidal blood vessels on ophthalmoscopic examination; foveal hypoplasia associated with reduction in visual acuity; and misrouting of the optic nerve fiber radiations at the chiasm, associated with strabismus, reduced stereoscopic vision, and altered visual evoked potentials (VEP). Individuals with OCA2 are usually recognized within the first three to six months of life because of the ocular features of visual inattention, nystagmus, and strabismus. Vision is stable to slowly improving after early childhood until mid- to late teens, and no major change or loss of established visual acuity occurs related to the albinism. The amount of cutaneous pigmentation in OCA2 ranges from minimal to near-normal compared to others of the same ethnic and family backgrounds. Newborns with OCA2 almost always have lightly pigmented hair, brows, and lashes, with color ranging from light yellow to blond to brown. Hair color may darken with age but does not vary substantially from adolescence to adulthood. Brown OCA, initially identified in Africans and African Americans with light brown hair and skin, is part of the spectrum of OCA2.

Diagnosis/testing

The diagnosis of OCA2 is based on clinical findings. *OCA2* (previously called *P*) is the only gene in which pathogenic variants are known to cause oculocutaneous albinism type 2.

Management

Treatment of manifestations: Correction of refractive errors with spectacles or (when age-appropriate) contact lenses may improve visual acuity; strabismus surgery can be considered for either functional (improved

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peripheral fusion) or cosmetic reasons. Hats with brims and dark glasses or transition lenses often reduce discomfort in bright light (photodysphoria).

Protection from sun exposure with appropriate skin-covering clothing and sunscreens prevents burning, consequent skin damage, and the enhanced risk of skin cancer. Skin cancer, including a slightly enhanced risk for cutaneous melanoma, is treated as for the general population.

Surveillance: Annual ophthalmologic examination to reassess refractive errors, strabismus and/or face turn; annual to biennial skin examination for evidence of sun-related skin damage and/or precancerous or cancerous lesions.

Agents/circumstances to avoid: Prolonged sun exposure.

Genetic counseling

OCA2 is inherited in an autosomal recessive manner. The parents of a proband are obligate heterozygotes and therefore carry one mutated allele. Heterozygotes (carriers) are asymptomatic. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in an affected family member are known.

GeneReview Scope

Oculocutaneous Albinism Type 2: Included Disorders
• Brown OCA

For synonyms and outdated names see Nomenclature.

Diagnosis

Clinical Diagnosis

The diagnosis of oculocutaneous albinism type 2 (OCA2) [King et al 2001a] is established by presence of the following:

- Hypopigmentation of the skin and hair
- Characteristic ocular changes found in all types of albinism, including the following findings detected on complete ophthalmologic examination:
  - Infantile nystagmus (usually noticed between ages three and 12 weeks of life
  - Reduced iris pigment with iris transillumination
  - Reduced retinal pigment with visualization of the choroidal blood vessels on ophthalmoscopic examination
  - Foveal hypoplasia associated with reduction in visual acuity
- Misrouting of the optic nerve fiber projections at the chiasm associated with strabismus (that may not develop until later in infancy), reduced stereoscopic vision, and altered visual evoked potentials (VEP).

  Note: (1) The VEP is performed with a technique specifically designed to demonstrate the selective misrouting; a standard (conventional) simultaneous binocular VEP will not demonstrate this anomaly. (2) Normal routing of the optic nerves, demonstrated with a selective VEP, excludes the diagnosis of albinism/OCA. (3) A VEP is not necessary for the diagnosis of albinism because misrouting is implied by the finding of strabismus and reduced stereoscopic vision. In some individuals, particularly those who have

near normal amounts of cutaneous and retinal pigment, or those who have foveal hypoplasia and no obvious nystagmus, a VEP may be a useful adjunct to demonstrate misrouting of the retinal to occipital projections.

The clinical diagnosis of OCA is usually made in an individual who has poor visual fixation and/or reduced visual acuity early in life, and nystagmus, associated with hypopigmentation of the skin, hair, and eye. The diagnosis is often suspected by the pediatrician at the two- or four-month well-baby check-up, and the diagnosis is usually established after a thorough medical eye examination by an ophthalmologist.

Molecular Genetic Testing

Gene. *OCA2* (previously called *P*) is the only gene in which pathogenic variants are known to cause oculocutaneous albinism type 2 [Gardner et al 1992, Rinchik et al 1993, Brilliant et al 1994, Kedda et al 1994, Lee et al 1995].

Clinical testing

- **Targeted analysis for pathogenic variants**
- **Sequence analysis.** Most non-Africans with OCA2 are compound heterozygotes. Approximately one third of the reported non-African individuals have only one pathogenic variant detectable by sequence analysis of the coding region, the intron-exon boundaries, and several hundred bases of the 5' promoter region and 3' untranslated region of *OCA2* [Oetting & King 1999, King et al 2001a, King et al 2001b, Gargiulo et al 2011]. To date, no pathogenic variant has been reported beyond 20 bp into the intron region of an exon/intron boundary. Approximately 20% of all individuals who have complete sequencing of the entire coding sequences and the flanking intron sequences have shown only one pathogenic variant. Cryptic splice sites or variants in regulatory regions could affect transcriptional regulation [King et al 2001a].

Table 1. Molecular Genetic Testing Used in Oculocutaneous Albinism Type 2

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Method [3]
OCA2	Targeted analysis for pathogenic variants	2.7-kb deletion	Most individuals of sub-Saharan African heritage; less common in other populations [4]
	Sequence analysis [5]	*OCA2* sequence variations other than 2.7-kb and other large deletions [6]	Unknown
	Deletion/duplication analysis [7]	2.7-kb deletion and other exon or whole-gene deletions [8]	Unknown

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Most individuals of sub-Saharan African heritage with OCA2 are homozygous for a common 2.7-kb deletion. The 2.7-kb deletion is less common in the US African American population and has been found in the Puerto Rican population [Kedda et al 1994, Spritz et al 1995, Stevens et al 1995, Durham-Pierre et al 1996, Puri et al 1997, Stevens et al 1997, Kerr et al 2000, Santiago Borrero et al 2006].
5. 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.
6. The majority of pathogenic variants in the non-African heritage population are missense variants, but deletions of one or a small number of bases and base changes in introns are common. The missense variant p.Ala481Thr has been described in the Japanese population; normally pigmented individuals who are homozygous and individuals who are compound heterozygous for this pathogenic variant have been identified [Saitoh et al 2000, Suzuki et al 2003b, Ito et al 2006]. This pathogenic variant was associated with substantial residual function of the P protein (hypomorphic mutation) and may not in itself be sufficient to cause OCA2 [Sviderskaya et al 1997, Suzuki et al 2003a]. The p.Val443Ile missense variant is the most common pathogenic variant in the northern European populations. A common 122.5-kb deletion found in the Navajo population is associated with a high prevalence of OCA2 in this population [Yi et al 2003].
7. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
8. See Table A, LSDB and HGMD

Testing Strategy

To confirm/establish the diagnosis in a proband. To confirm a firm clinical diagnosis (with concordance between the dermatologic and ophthalmologic features), perform complete sequence analysis of *OCA2*.

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

Note: (1) Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder. (2) Although some adult carriers may manifest clinically insignificant punctate iris transillumination defects at diligent biomicroscopic examination, a fraction of the normal population also does (depending on ethnic or national origin), thus making this observation useless for clinical counseling.

Prenatal testing and preimplantation genetic testing for at-risk pregnancies require prior identification of both pathogenic variants in an affected member of the family.

Clinical Characteristics

Clinical Description

The amount of cutaneous (including hair, lash, brow, and iris) pigmentation in OCA2 forms a continuum from minimal to near normal [King et al 2001a, King et al 2001b]. No established categories or subtypes, as in

oculocutaneous albinism type 1 (OCA1), exist for OCA2. Newborns nearly always have some yellow or tan color in the hair, eyebrows, and lashes. The ocular features of all types of OCA2 are identical except for the density of iris and retinal pigment present. The phenotypic range of pigmentation is also dependent on the ethnic background of the family, and individuals with OCA2 from families with darker constitutional pigmentation generally tend to be more pigmented than those from families with lighter constitutional pigmentation; however, the spectrum of the variations precludes the predictive clinical utility of this generalization.

Individuals with OCA2 are usually recognized within the first few months of life because of the ocular features of nystagmus and strabismus. In many families, particularly in those with darker constitutional pigmentation, the cutaneous hypopigmentation is also obvious at birth and suggests the diagnosis.

Eye. A few children with albinism have nystagmus at birth that is noticed by the parents and by the examining physician in the delivery room. However, most children with albinism do not have nystagmus at birth and the parents note slow wandering eye movements and a lack of visual attention. The parents may become concerned because the child does not seem to focus well, but the lack of nystagmus may delay the diagnosis.

Most children with albinism develop nystagmus before age three to four months, and the diagnosis is often raised at the two- to four-month well-baby checkup. The nystagmus, which can be rapid early in life, generally slows during the first decade; however, nearly all individuals with albinism have nystagmus throughout their lives. Nystagmus is more noticeable when the individual is tired, angry, or anxious, and less marked when they are well rested and feeling well.

For some, the nystagmus has a "null point" or direction of gaze in which the movement is minimized, leading to a compensatory face-turn that may be socially disconcerting and may lead to eye-muscle surgical intervention as the child matures.

The strabismus found in most individuals with albinism is usually not associated with the development of amblyopia unless the often substantial refractive errors are ignored in infancy and childhood.

Iris color ranges from blue to brown; the extreme iris transillumination associated with diaphanous light "grey-blue," "pink," or "ruby" eyes seen with the OCA1A subtype of OCA1 is typically not present in OCA2. However, transillumination of the globe and/or the iris in a darkened room will be seen by the careful and skilled observer.

Visual acuity in OCA2 is generally better than that in OCA1 (and always better than in OCA1A), but overlap is observed [Summers 1996, King et al 2001a, King et al 2001b]. Final (adult) visual acuity for individuals with OCA2 ranges from 20/25 to 20/200 and is usually in the range of 20/60 to 20/100. Best corrected visual acuity is stable after early childhood and never deteriorates (although refractive errors may change). Any loss of vision later in life should be explainable by changes in refraction, development of cataract, or causes unrelated to albinism.

Skin/hair. The range of skin pigment in OCA2 is broad [Okoro 1975, Lund et al 1997, King et al 2001a, King et al 2001b, Manga et al 2001]. Individuals with OCA2 are almost always born with lightly pigmented hair; hair color at birth or the first few months of life can range from light yellow to blond to brown. The scalp hair may be light yellow, particularly in individuals of northern European ancestry. The scalp hair is never completely white; some parents may refer to the hair color as "white" or "nearly white" if it is very lightly pigmented. Scalp, brow, lash, and pubic hair color will usually darken with time but often with no substantive change in color after adolescence.

Some individuals of northern European ancestry who have OCA2 have red rather than blond hair and typical ophthalmologic findings [King et al 2003b].

"Brown OCA," initially characterized in the African (of Nigerian and Ghanan ancestry) and African American population, is now recognized as part of the spectrum of OCA2; individuals with the "brown" phenotype in these

populations are born with light brown hair and skin, but individuals from other populations (northern European, Asian) with the ocular features of albinism can have moderate to near-normal cutaneous pigmentation and only appear hypopigmented when compared to sibs and other family members [Manga et al 2001, King et al 1985].

When hair color is "blond" or yellow, the skin usually has little generalized pigmentation and the skin color is creamy white. It should be noted that skin color in OCA2 is not as "white" as that found in the OCA1A subtype of oculocutaneous albinism type 1, reflecting the fact that the melanocytes in the skin of individuals with OCA2 still can synthesize some melanin (as seen with the pigmented hairs), but that most melanin is yellow pheomelanin rather than black-brown eumelanin. With the OCA2 brown phenotype, generalized skin pigmentation is present and may darken over time and with sun exposure. Skin color is usually lighter than that of sibs and unaffected relatives.

Skin cancer risk. Long-term (i.e., over many years) exposure to the sun of lightly pigmented skin can result in coarse, rough, thickened skin (pachydermia), solar keratoses (premalignant lesions), and skin cancer. Both basal cell carcinoma and squamous cell carcinoma may occur. Melanoma is rare in individuals with OCA2, even though skin melanocytes are present.

Skin cancer is unusual in individuals with all forms of OCA in the US because of the availability of sunscreens and the social acceptability of wearing clothes that cover the exposed skin, and because individuals with albinism often avoid prolonged time outside in the sun. In contrast, skin cancers in individuals with albinism are common in parts of the world such as sub-Saharan Africa because of the increased amount of sun exposure through the year, the cultural differences in protective dress, and the lack of skin-protective agents [Okoro 1975].

Genotype-Phenotype Correlations

The lack of a functional assay for the activity of the protein product of *OCA2* and the limited availability of data from *OCA2* molecular genetic testing make genotype-phenotype correlations difficult [Sviderskaya et al 1997].

Genotype-phenotype correlations are not useful clinically and the amount of cutaneous pigmentation, ocular pigmentation, and visual development resulting from particular pathogenic variants in this gene cannot be predicted with any certainty.

The 2.7-kb deletion

- Homozygosity for the 2.7-kb deletion in the African and African American populations is associated with yellow/blond hair, creamy tan skin, and blue-to-tan irides, but this phenotype varies even in those who are homozygous for this pathogenic variant.
- African individuals with the "brown" phenotype are usually compound heterozygotes for this deletion; the pathogenic variant on the homologous *OCA2* allele has not been identified. In contrast, African American individuals with the "brown" phenotype can be compound heterozygous for two *OCA2* pathogenic missense variants.

The p.Val443Ile variant is associated with residual function of the P protein (encoded by *OCA2*) and progressive development of cutaneous pigment with time in the affected individual [Saitoh et al 2000].

Individuals with OCA2 and red hair have common variants in *MC1R*, the gene encoding melanocortin-1 receptor [Sturm et al 2001, King et al 2003b].

Nomenclature

Individuals with OCA2 and moderate to near-normal cutaneous pigmentation were previously classified as having autosomal recessive or even X-linked ocular albinism because of the presence of the cutaneous

pigmentation. However, this description is both confusing and no longer valid; it is now appropriate to classify oculocutaneous albinism according to the gene involved.

- Individuals with *OCA2*-related albinism, including those with minimal cutaneous hypopigmentation, are diagnosed with oculocutaneous albinism type 2 or OCA2;
- Individuals with *TYR*-related albinism are diagnosed with the OCA1B subtype of oculocutaneous albinism type 1 [King et al 2001a, King et al 2001b].

Brown OCA was described initially in Nigeria and Ghana as a separate entity, and early family studies suggested that it was distinct from the classic OCA2 phenotype in Africa. Molecular studies now show that in the African, African American, and white populations, brown OCA is actually part of the clinical spectrum of OCA2. Individuals with OCA2 may present with the classic OCA2 phenotype (yellow/blond hair, creamy-tan skin, and blue/hazel irides), a more pigmented phenotype like brown OCA, or an intermediate phenotype between the classic and the brown phenotype [King et al 1985, King & Rich 1986, Manga et al 2001].

Prevalence

Prevalence of OCA2 is approximately 1:38,000-1:40,000 in most populations throughout the world except the African population, in which the prevalence is estimated at 1:1,500-1:3,900, and the African-American population, in which the prevalence is estimated to be as high as 1:10,000 [Spritz et al 1995, Stevens et al 1995, Lund et al 1997, Stevens et al 1997, King et al 2001a, King et al 2001b].

OCA2 has been described in all major ethnic groups, including northern, central, eastern, and southern European, other white, African, African-American, and Asian populations. In Japan, 8% of albinism is caused by *OCA2* pathogenic variants [Inagaki et al 2004, Hong et al 2006].

The proportion of individuals with OCA2 with moderate-to-near-normal cutaneous pigmentation is unknown in most populations. The prevalence of "brown" OCA in African populations is less than that of classic OCA2, but exact figures are not available.

The carrier frequency for OCA2 is:

- Approximately 1:100 in most populations, based on disorder prevalence of 1:38,000-1:40,000
- 1:22-1:32 in the sub-Sahara African population, based on disorder prevalence of 1:1,500-1:3,900
- 1:50 or less in the African American population, based on disorder prevalence of 1:10,000

Genetically Related (Allelic) Disorders

No other type of albinism or genetic form of congenital hypopigmentation has been associated with pathogenic variants in *OCA2*.

Prader-Willi syndrome (PWS) and **Angelman syndrome (AS).** *OCA2* is located in the region of chromosome 15q involved in causation of Prader-Willi syndrome (PWS) and Angelman syndrome (AS). Individuals with PWS or AS are often hypopigmented, with lighter hair and skin pigmentation than that of unaffected family members, but the ocular features of albinism, including nystagmus and the lack of foveal development, are usually absent or not completely manifest [Wiesner et al 1987, King et al 1993, Smith et al 1996, Thompson et al 1999, Mah et al 2000, Saitoh et al 2000]. The hypopigmentation correlates with the occurrence of a deletion of 15q11.2-q12 (on one allele) that includes the *OCA2* locus [Nicholls et al 1996]. Individuals with PWS and AS with the ocular features of albinism have been reported; molecular studies indicate that an independent *OCA2* pathogenic variant is present on the non-deleted chromosome 15 in the reported individuals [Horsthemke et al 1997, Fridman et al 2003], thus resulting in manifestation of the more complete phenotype.

A paradox exists in the association of *OCA2* and pigmentation, with no explanation at present: individuals with PWS or AS with a deletion are hypopigmented, suggesting that haploinsufficiency of the P protein may be involved (*OCA2* is not imprinted in this region). Individuals who are heterozygous for an *OCA2* pathogenic variant in a typical family with OCA2 have haploinsufficiency for functional P protein; however, they are normally pigmented, including those who are heterozygous for the 2.7-kb deletion in the sub-Saharan African population.

Single-nucleotide polymorphisms of *OCA2* are also associated with normal variation in eye and skin color [Rebbeck et al 2002, Frudakis et al 2003, Duffy et al 2004, Sturm & Frudakis 2004, Zhu et al 2004, Duffy et al 2007, Lao et al 2007, Norton et al 2007, Yuasa et al 2007a, Yuasa et al 2007b]. Skin and eye color appear to be under multigenic control [Barsh 2003, Frudakis et al 2003, Shriver et al 2003, Sturm & Frudakis 2004, Duffy et al 2007], with variation in *OCA2* having the predominant effect both evolutionarily and physically [Frudakis et al 2003, Duffy et al 2004, Sturm & Frudakis 2004, Zhu et al 2004, Duffy et al 2007].

Differential Diagnosis

Albinism. OCA can also be caused by mutation of *TYR* (OCA1), *TYRP1* (OCA3), *MATP* (OCA4), at least seven genes associated with Hermansky-Pudlak syndrome (HPS 1-7), *LYST* (Chediak-Higashi syndrome), *MYO5A* (Griscelli syndrome type 1), and *RAB27A* (Griscelli syndrome type 2).

Clinically, albinism is associated with the development of some cutaneous pigmentation (except in OCA1A), and the differential diagnosis for individuals with albinism who have pigment in their skin and hair includes the OCA1B subtype of oculocutaneous albinism type 1, OCA2, OCA3, OCA4, Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome, Griscelli syndrome, and X-linked ocular albinism (OA1).

The diagnosis of albinism is made with an ophthalmologic examination. Different types can be distinguished in the following manner:

- A careful history of pigment development usually identifies individuals with OCA1.
- Molecular studies can distinguish OCA2 and OCA4
- A detailed medical history focused on bleeding or bruising and an analysis of platelet dense bodies are necessary to establish the diagnosis of HPS.
- A detailed medical history of recurrent infections and an examination of peripheral leukocytes may reveal findings that suggest the diagnosis of Chediak-Higashi syndrome.
- The presence of pancytopenia, immunodeficiency, hemophagocytic syndrome, and/or demyelination of the white matter of the brain suggest the diagnosis of Griscelli syndrome.

Many of the ocular features of oculocutaneous albinism (OCA) and X-linked ocular albinism (OA1) (also known as Nettleship-Falls ocular albinism) are similar; however, the two conditions are separable molecularly, if not clinically. Males with X-linked ocular albinism (OA1) typically have less pigment in their skin, scalp, brow, and lash hair than their unaffected sibs and immediate relatives. However, this may be a difficult clinical judgment in some families: the distinction is obvious in families with darker constitutional pigmentation, but in families with light constitutional pigmentation, a young boy may have light hair (even be "tow-headed") and appear to have oculocutaneous albinism rather than ocular albinism. The correct diagnosis becomes clear when the ophthalmologist dilates the pupils of the eyes of the mother of a male child and finds the classic mosaic retinal pigmentation of the X-linked carrier state. A skin biopsy to demonstrate giant melanosomes by electron microscopy (EM) in the skin was used in the past to make the diagnosis of OA1 in this situation; *OA1* molecular genetic testing is now possible, offering a more objective (and less invasive) diagnosis.

The existence of another autosomal gene that is related to ocular or oculocutaneous albinism has not been substantiated, although families with OCA that do not map to the loci for *TYR* (OCA1), *OCA2* (OCA2), or *MATP* (OCA4) have been reported in several studies. Pathogenic variants in *TYRP1,* the gene encoding

tyrosinase-related protein-1, are associated with rufous or red OCA3 [Durham-Pierre et al 1994]; this phenotype has been described only in the African population. Although individuals with red skin and light hair have been described in Papua, New Guinea, the association of this phenotype with red/rufous OCA found in Africa is unknown. Affected individuals in Papua, New Guinea have nystagmus and reduced visual acuity, but the retina is normally pigmented and foveal hypoplasia is not present [Hornabrook et al 1980]. Molecular studies of individuals with this phenotype are not available.

Naturally blond hair is rare in humans and found almost exclusively in Europe and Oceania. Recently an arginine-to-cysteine change at a highly conserved residue in tyrosinase-related protein 1 (TYRP1) was found as a major determinant of blond hair in Solomon Islanders. This pathogenic missense variant is predicted to affect catalytic activity of TYRP1 and causes blond hair through a recessive mode of inheritance. The pathogenic variant, occurring at a frequency of 26% in the Solomon Islands, is absent outside of Oceania [Kenny et al 2012].

Congenital motor nystagmus presents as infantile nystagmus associated with reduced visual acuity *FRMD*-related infantile nystagmus. Some individuals with congenital motor nystagmus have been reported to have retinal hypopigmentation and foveal abnormalities; however, the studies were done before the molecular analysis of the different types of OCA was available, suggesting that they may have included individuals with OCA who were diagnosed incorrectly with congenital nystagmus. The visual evoked potential analysis to evaluate misrouting of the optic nerves is normal in congenital motor nystagmus. A single X-linked gene, *FRMD7*, for "congenital infantile nystagmus" has been reported [Tarpey et al 2006, Self et al 2007].

Additional confusion may occur in infants with blue cone monochromacy (males) (red-green color vision defects) or rod monochromacy (achromatopsia) (both genders), in which nystagmus begins early in life, the foveas are underdeveloped, and myopia is common, leading to an exaggerated impression of underpigmentation of the retina. The severe loss of color perception clinically and the electroretinographic responses of abnormal cone and rod signals should separate these two entities from the albinisms.

See Oculocutaneous Albinism: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluation Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with oculocutaneous albinism (OCA), the following evaluations are recommended:

- Evaluation of the pigmentation status of the skin and adnexa (eyebrows, eyelashes, and where appropriate, pubic hair)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Correction of refractive errors with spectacles or (when age-appropriate) contact lenses of the refractive errors of either hyperopia or myopia and astigmatism found in most individuals with albinism can optimize visual acuity. Of note, visual acuity is never correctable to normal.

Strabismus surgery is usually not mandatory (because the strabismus in most individuals with albinism is not associated with the development of amblyopia); however, if the strabismus is marked or fixed, surgery can be considered to improve peripheral binocular fusion or appearance. When an anomalous null point creates a substantial face turn, strabismus surgery may reposition the null point into a more central, straight-ahead location to allow more socially acceptable head position.

Photodysphoria (discomfort in bright light; as distinct from photophobia, painful aversion of light associated with intraocular inflammation) is common among individuals with OCA; however, the severity of discomfort varies and is not completely concordant with the amount of pigment present in the iris or the skin.

- Dark glasses or transition lenses may be helpful, but many individuals with albinism prefer to go without the tint because of the reduction in vision from the dark lenses. Note: Going without dark glasses does not harm vision.
- Darkly tinted contact lenses do not improve visual function because the reduction of transmission of the thin contact lens is no match for the density of a tinted spectacle lens.

A hat with a brim (such as a baseball hat with a visor) is helpful to reduce overhead glare and to reduce some photodysphoria and to provide some sun protection to the face.

Skin care in OCA2 is determined by the amount of pigment in the skin and the cutaneous response to sunlight. Individuals with white skin that does not tan need to be protected from any prolonged sun exposure for prevention of burning, skin damage, and skin cancer. This can be for exposures as short as five to ten minutes in highly sensitive individuals and 30 minutes or more in less sensitive individuals. Prolonged periods in the sun require skin protection with clothing (hats with brims, and long sleeves, pants, and socks) and appropriate sunscreens after the guidance and education from a dermatologist.

Even early in life, a (pediatric) dermatologic consultation is warranted to teach parents about the use of sun-protective clothing and interpretation of the often confusing numerical values and contents of sun-protective lotions and formulas.

Skin cancer is treated as for the general population.

Prevention of Primary Manifestations

No dietary or ophthalmologic procedures or exercises will prevent or alter the clinical features of albinism.

Surveillance

The following are appropriate:

- Annual ophthalmologic examination and reassessment and accurate correction of refractive errors, and related strabismus or face turn
- Annual to biennial search for evidence of sun-related skin damage and pre-cancerous or cancerous lesions, especially in areas of high intensity or prolonged sunlight exposure

Agents/Circumstances to Avoid

Prolonged unprotected sun exposure should be avoided.

Evaluation of Relatives at Risk

Relatives at risk for OCA2 can be identified by clinical findings (hypopigmentation and eye features); additional testing is not indicated.

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

Pregnancy Management

No form of classic OCA impairs fertility or compromises pregnancy or gestation.

An obligate carrier (heterozygous) fetus of a mother with OCA2 faces no additional risks over an unaffected fetus of an unaffected mother.

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.

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

OCA2 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 mutated allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each full 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

- All unaffected offspring of an individual with OCA2 are obligate heterozygotes (carriers) for one pathogenic variant in *OCA2*.
- Most families have no history of OCA2, but families with two-generation pseudodominance have been reported. Two-generation pseudodominance results from an affected individual having children with an individual who is a heterozygote.
- Because of the high carrier rate for *OCA2* mutated alleles in African populations, a family history for OCA2 and affected individuals from multiple generations are often found in African families.
- A few reports document two parents with OCA having unaffected children. In these reports, one parent had OCA1 and the other parent had OCA2; the offspring were double heterozygotes, but they had normal pigmentation and normal ocular and visual function.

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 at-risk family members is possible if the pathogenic variants in the family have been identified.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for OCA2 are possible [Hongyi et al 2007].

Fetal skin biopsy. A fetal skin biopsy will not provide an accurate diagnosis and is not appropriate for prenatal diagnosis of OCA2.

Requests for prenatal testing for conditions which (like OCA2) do not affect intellect or life span are not common. 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.

- **National Organization of Albinism and Hypopigmentation (NOAH)**
  PO Box 959
  East Hampstead NH 03826-0959
  Phone: 800-473-2310 (toll-free); 603-887-2310
  Fax: 800-648-2310 (toll-free)
  Email: info@albinism.org
  www.albinism.org
- **National Library of Medicine Genetics Home Reference**
  Oculocutaneous albinism
- **eyeGENE - National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  www.nei.nih.gov/eyegene

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. Oculocutaneous Albinism Type 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
OCA2	15q12-q13	P protein	Retina International Mutation Database Mutations of the P-Gene Albinism Database Mutations of the P gene	OCA2	OCA2

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 Oculocutaneous Albinism Type 2 (View All in OMIM)

203200	ALBINISM, OCULOCUTANEOUS, TYPE II; OCA2
611409	OCA2 MELANOSOMAL TRANSMEMBRANE PROTEIN; OCA2

Gene structure. *OCA2* reference sequence NM_000275.2 has 24 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Variants are listed in the Albinism database. More than 42 benign variants have been described in many exons and introns throughout the gene.

Pathogenic variants. See Albinism database and HGMD and other LSDB (Table A). More than 147 *OCA2* pathogenic variants have been reported [Lee et al 1994a, Lee et al 1994b, Spritz et al 1997, Oetting et al 1998, Oetting & King 1999, Passmore et al 1999, Kerr et al 2000, Kato et al 2003, King et al 2003a, Suzuki et al 2003a, Suzuki et al 2003b; Yi et al 2003, Ito et al 2006, Hongyi et al 2007, HGMD (www.hgmd.cf.ac.uk, accessed 15 June 2012]. Most are missense variants, but deletions of one or a small number of bases and base changes in introns are common. The most common *OCA2* pathogenic variant is the 2.7-kb deletion in the African and African American populations. The p.Val443Ile amino acid substitution is the most common in the northern European populations. Most individuals with OCA2 are compound heterozygotes for *OCA2* pathogenic variants, with different maternal and paternal variants, and approximately half of the non-African reported individuals have only one identifiable pathogenic variant; the second variant was not detected by the methods used. (For more information, see Table A.)

Normal gene product. The protein product of *OCA2*, known as the P protein, is a transmembrane protein found in the melanosomal membrane [Brilliant et al 1994, Rosemblat et al 1994, Lee et al 1995]. The precise function of the P protein is unknown. Studies supporting a role in maintenance of proper intramelanosomal pH or in the melanosomal structural matrix have been reported [Brilliant 2001]. The P protein (NP_000266.2) has 838 amino acid residues.

Abnormal gene product. Few studies are available on mutated P protein. The full-length normal human *OCA2* cDNA or *OCA2* cDNA-containing pathogenic variants associated with OCA2 (p.Ala481Thr, p.Val443Ile) have been expressed in mouse melanocytes derived from an animal with a pathogenic variant in the murine homologue (*pink-eyed dilution* or *p*) of *OCA2* [Sviderskaya et al 1997]. The murine cells with the normal cDNA synthesized significantly more melanin than did those with the p.Ala481Thr variant construct, and those with the p.Val443Ile construct synthesized a minimal amount of melanin. The mechanisms by which the mutated protein alters the ability of the cell to synthesize melanin are unknown.

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Chapter Notes

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Revision History

- 7 January 2021 (ma) Chapter retired: outdated
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