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Oculocutaneous Albinism Type 2

[*OCA2. Includes: Brown OCA*]

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Summary

Disease 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 nerves at the chiasm associated with alternating strabismus, reduced stereoscopic vision, and an altered visual evoked potential (VEP). Individuals with OCA2 are usually recognized within the first year of life because of the ocular features of nystagmus and strabismus. Vision is stable after early childhood and no major change or further reduction in vision occurs related to the albinism. 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, but does not vary significantly from childhood 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 the clinical findings. The gene *OCA2* (previously called the *P* gene) is the only gene known to be associated with oculocutaneous albinism type 2. Testing for the 2.7-kb deletion found in individuals of African heritage is available on a clinical basis. Sequence analysis and mutation scanning of the *OCA2* gene are available clinically.

Management. Correction of refractive error with spectacles or contact lenses may improve visual acuity; strabismus surgery can be considered for cosmetic reasons. Hats with brims often reduce photophobia. Protection from sun exposure with body-covering clothing and sunscreens prevents burning, skin damage, and skin cancer; prolonged sun exposure should be avoided. Skin cancer is treated as for the general population.

Genetic counseling. OCA2 is inherited in an autosomal recessive manner. The parents of a proband are obligate heterozygotes and therefore carry one mutant 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. Prenatal testing is available on a limited basis.

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Diagnosis

Clinical Diagnosis

The diagnosis of oculocutaneous albinism type 2 (OCA2) [King, Hearing et al 2001] 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 routine ophthalmologic examination:
  - 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
- Misrouting of the optic nerves at the chiasm associated with alternating strabismus, reduced stereoscopic vision, and an altered visual evoked potential (VEP). A VEP is not necessary for the routine diagnosis of albinism, with misrouting implied by the finding of strabismus and reduced stereoscopic vision. In some individuals, particularly those who have moderate amounts of cutaneous and retinal pigment, or those who have foveal hypoplasia and no obvious nystagmus, a VEP may be necessary to demonstrate misrouting of the optic nerves. The VEP is performed with a technique specifically developed for demonstration of the misrouting and a regular VEP will not demonstrate this. Normal routing of the optic nerves, demonstrated with a VEP, excludes the diagnosis of albinism/OCA.

The clinical diagnosis of OCA is usually made in a child or an adult who has poor visual fixation early in life, nystagmus, and/or reduced visual acuity, associated with hypopigmentation of the skin and hair. The initial diagnosis is often suspected by the pediatrician at the four- or six-month well-baby checkup and the diagnosis is usually established after a complete eye examination by an ophthalmologist.

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.

Gene. *OCA2* (previously called the *P* gene) is the only gene known to be associated with oculocutaneous albinism type 2 [Gardner et al 1992, Rinchik et al 1993, Brilliant et al 1994, Kedda et al 1994, Lee et al 1995]. More than 50 *OCA2* mutations have been reported [Lee, Nicholls, Bundey, et al 1994; Lee, Nicholls, Schnur et al 1994; Spritz, Lee et al 1997; Oetting et al 1998; Oetting et al 1999; Passmore et al 1999; Kerr et al 2000; Kato et al 2003; King, Pietsch et al 2003; Suzuki, Miyamura, Tomita et al 2003; Suzuki, Miyamura, Matsunaga et al 2003; Yi et al 2003; Ito et al 2006; Hongyi et al 2007].

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing

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- Prenatal testing

Clinical testing

- **Targeted mutation analysis.** The majority of 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].

Research testing

- **Sequence analysis/mutation scanning.** Most non-African individuals with OCA2 are compound heterozygotes. Approximately half of the reported non-African individuals have only one mutation 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 the *OCA2* gene [Oetting & King 1999; King, Hearing et al 2001; King, Oetting et al 2001]. It is hypothesized that additional pathologic mutations are located in the introns, where they produce alternative gene transcripts, or in regulatory regions of the gene. To date, techniques that would detect these types of mutations have not been applied to the *OCA2* gene. The majority of mutations in the non-African heritage population are missense mutations, but deletions of one or a small number of bases and base changes in introns are common.
  - The missense mutation A481T has been described in the Japanese population; normally pigmented individuals who are homozygous and individuals who are compound heterozygous for this mutation have been identified [Saitoh et al 2000; Suzuki, Miyamura, Tomita et al 2003; Ito et al 2006]. This mutation 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, Miyamura, Matsunaga et al 2003].
  - The V443I missense mutation is the most common mutation in the northern European populations.
  - A common 122.5-kb deletion mutation found in the Navajo population is associated with a high prevalence of OCA2 in this population [Yi et al 2003].

Note: The frequency of normal variants, the limited data of sequence analysis of affected and control groups, and difficulty with a functional assay for the gene product reduce the usefulness of sequence analysis for the diagnosis of OCA2. Most tested individuals will be found to have variants of the *OCA2* gene, and each newly identified variant must be tested in a large control sample of mixed ethnic background to determine if it represents a polymorphism or if it could be the pathologic mutation responsible for OCA2 in the family.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	2.7-kb deletion	Most individuals of sub-Saharan African heritage	Clinical Testing
Sequence analysis/mutation scanning	*OCA2* sequence variations other than 2.7-kb deletion	Unknown	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

Genetically Related (Allelic) Disorders

No other type of albinism or genetic forms of congenital hypopigmentation have been associated with mutations of the *OCA2* gene.

Prader-Willi syndrome and Angelman syndrome. The *OCA2* gene is located in the region of chromosome 15q involved in the development of Prader-Willi syndrome (PWS) and Angelman syndrome (AS). Individuals with PWS or AS are often hypopigmented, with lighter hair and skin pigment than that seen in unaffected family members, but the ocular features of albinism, including nystagmus and the lack of foveal development, are usually absent or not completely developed [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 presence of a deletion of 15q11.2-q12 [Nicholls et al 1996]. Individuals with PWS and AS with the ocular features of albinism have been reported; molecular studies indicate that the *OCA2* gene mutation is present on the non-deleted chromosome 15 in the reported individuals [Horsthemke et al 1997, Fridman et al 2003].

A paradox exists in the association of the *OCA2* gene 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 (the *OCA2* gene is not imprinted in this region). Individuals who are heterozygous for an *OCA2* gene mutation 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 mutation in the sub-Saharan African population.

Single-nucleotide polymorphisms of the *OCA2* gene 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, Umetsu, Harihara, Kido et al 2007; Yuasa, Umetsu, Harihara, Miyoshi et al 2007]. 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 the *OCA2* gene having the predominant effect [Frudakis et al 2003, Duffy et al 2004, Sturm & Frudakis 2004, Zhu et al 2004, Duffy et al 2007].

Clinical Description

Natural History

The amount of cutaneous pigmentation in OCA2 forms a continuum from minimal to near-normal [King, Hearing et al 2001; King, Oetting et al 2001]. No established categories or subtypes, as in oculocutaneous albinism type 1 (OCA1), exist in OCA2. The ocular features of all types of OCA2 are identical except for the amount 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 predictive clinical usefulness of this generalization is precluded by the existence of multiple exceptions.

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Individuals with OCA2 are usually recognized within the first year 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. An ophthalmologic examination showing foveal hypoplasia and reduced retinal pigment establishes the diagnosis.

Eye. Some children with albinism have nystagmus at birth that is noticed by the parents in the delivery room and by the examining physician. Many 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 by the age of 3-4 months, and the diagnosis is often raised at the 4-6 month well-baby checkup. The nystagmus can be very fast early in life and generally slows with time; 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.

Iris color ranges from blue to brown; the extreme iris transillumination associated with light blue 'pink' or 'ruby' eyes as seen with the OCA1A subtype of OCA1 is usually absent in OCA2.

Visual acuity in OCA2 is generally better than that in OCA1, but overlap is observed [Summers 1996; King, Hearing et al 2001; King, Oetting et al 2001]. Visual acuity for individuals with OCA2 ranges from 20/30 to 20/400 and is usually in the range of 20/100 to 20/200. Vision is stable after early childhood and there should be no major change or further reduction in vision. The visual changes are not progressive, and loss or change of vision later in life should not be related to the albinism.

Skin/hair. The range of skin pigment in OCA2 is broad [Okoro 1975; Lund et al 1997; King, Hearing et al 2001; King, Oetting et al 2001; Manga et al 2001]. Individuals with OCA2 are almost always born with pigmented hair; hair color at birth can range from light yellow to blond to brown. The scalp hair may be very light yellow, particularly in individuals with a northern European ethnic background. The scalp hair is usually not completely white (not as white as a sheet of copy paper or fresh snow); some parents may refer to the hair color as "white" or "nearly white" if it is very lightly pigmented. Hair color may darken with time, but there is often no dramatic change in hair color from childhood to adult.

Some Caucasians with OCA2 have red rather than blond hair and typical ophthalmologic findings [King, Willaert et al 2003].

It is now recognized that "brown OCA," initially characterized in the African and African-American population, is 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-nearly-normal cutaneous pigmentation and only appear hypopigmented when compared to other family members [Manga et al 2001, King et al 1985].

When hair color is blond or yellow, the skin usually has little or no 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 can still synthesize some melanin (as seen with the pigmented hair), but that the majority of the melanin is yellow pheomelanin rather than black-brown eumelanin. With the OCA2 brown phenotype, generalized skin pigmentation is present and may darken with sun exposure. Skin color is usually lighter than that of unaffected relatives.

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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 can develop. Melanoma is usually rare in individuals with OCA, 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, the social acceptability of wearing clothes that cover most of the exposed skin, and the fact that individuals with albinism often do not spend a great deal of time outside in the sun. Skin cancer in individuals with albinism is common in some 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 such as sunscreens [Okoro 1975].

Genotype-Phenotype Correlations

The lack of a functional assay for the activity of the protein product of the *OCA2* gene and the limited availability of data from molecular genetic testing of the *OCA2* gene in OCA2 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 mutations of this gene cannot be predicted with any degree of certainty at this time.

The 2.7-kb deletion

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

The V443I mutation is associated with residual function of the P protein 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 of the melanocortin-1 receptor *(MC1R*) gene [Sturm et al 2001; King, Willaert et al 2003].

Nomenclature

The ocular features of all types of oculocutaneous albinism (OCA) and X-linked ocular albinism (OA1) are similar and the terms "oculocutaneous albinism" and "albinism" can be used interchangeably when referring to these clinical features.

Individuals with OCA2 and moderate-to-nearly-normal cutaneous pigmentation were previously classified as having autosomal recessive or even X-linked recessive ocular albinism because of the presence of the cutaneous pigmentation. However, this description is confusing and no longer valid; it is now appropriate to classify oculocutaneous albinism according to the gene involved. Therefore, individuals with *OCA2*-related albinism, including those with minimal cutaneous hypopigmentation, are diagnosed with oculocutaneous albinism type 2 or OCA2, and those with *TYR*-related albinism are diagnosed with the OCA1B subtype of oculocutaneous albinism type 1 [King, Hearing et al 2001; King, Oetting et al 2001].

Brown OCA was initially described as a separate entity, and initial 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 Caucasian populations, brown OCA is actually part

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of the clinical spectrum of OCA2. Individuals with OCA2 may present with the classic OCA2 phenotype (yellow/blond hair, white 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

Prevalance of OCA2 is approximately 1/38,000-40,000 in most populations throughout the world except for the African population, in which the prevalence is 1/1,500-1/8,000, and the African-America 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, Hearing et al 2001; King, Oetting et al 2001]. OCA2 has been described in all major ethnic groups, including northern, central, eastern, and southern European, other Caucasian, African, African-American, and Asian populations. The increased prevalence in the sub-Saharan African and African-American populations is the result of the high heterozygote frequency. In Japan, 8% of albinism is caused by *OCA2* mutations [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 rate for OCA2 is approximately 1/100 in most populations, based on disease prevalence of 1/38,000-40,000. Based on the prevalence in the sub-Saharan African and African-American populations, the carrier rate is 1/22-1/32 in the sub-Sahara African population and 1/50 or less in the African-American population.

Differential Diagnosis

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

Albinism. OCA can also be caused by mutations of the tyrosinase gene (OCA1), the *TYRP1* gene (OCA3), the *MATP* gene (OCA4), and at least seven genes responsible for Hermansky-Pudlak syndrome (HPS 1-7).

Most types of albinism are associated with the development of some cutaneous pigmentation, 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), and X-linked recessive ocular albinism (OA1). The diagnosis of albinism is made with an ophthalmologic examination, and a careful history of pigment development usually identifies individuals with OCA1. Molecular studies are necessary to distinguish OCA2 and OCA4, and a careful medical history of bleeding or bruising and an analysis of platelet dense bodies are necessary to establish the diagnosis of HPS.

Males with X-linked ocular albinism (OA1) have normal skin and hair pigment, and this is obvious in families with darker constitutional pigmentation. 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 usually becomes clear with time. Although a skin biopsy to demonstrate by electron microscopy (EM) the giant melanosomes in the skin was used in the past to make the diagnosis of OA1 in this situation, molecular genetic testing of the *OA1* gene is now clinically available, offering a more objective and less invasive means of 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 the

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genes *TYR* (OCA1), *OCA2* (OCA2), or *MATP* (OCA4) have been reported in several studies. Mutations of the gene for tyrosinase-related protein-1 *(TYRP1)* are associated with rufous or red OCA3 [Durham-Pierre et al 1994]; this phenotype has only been described in the African population. Individuals with red skin and light hair have been described in Papua, New Guinea, but the association of this phenotype with red/rufous OCA found in Africa is unknown. The 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.

Congenital motor nystagmus presents with nystagmus associated with reduced visual acuity. 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 incorrectly diagnosed with congenital nystagmus. The visual evoked potential analysis to evaluate misrouting of the optic nerves is normal in congenital motor nystagmus.

Management

Evaluation Following Initial Diagnosis

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

- Evaluation of the pigmentation status of the skin
- Complete ophthalmologic evaluation, including a search for the presence of nystagmus, reduced iris and retinal pigment, foveal hypoplasia and reduced visual acuity, and strabismus

Treatment of Manifestations

- Correction with spectacles or contact lenses of the refractive errors hyperopia or myopia and astigmatism found in the majority of individuals with albinism can improve visual acuity. Except in rare circumstances, visual acuity cannot be restored to normal because of the foveal hypoplasia, but visual acuity can be improved with correction of refractive errors.
- The alternating strabismus found in most individuals with albinism is generally not associated with the development of amblyopia. Strabismus surgery is usually not required, but can be considered for cosmetic reasons if the strabismus is marked or fixed.
- Photophobia is commonly present in individuals with OCA, but the degree of discomfort varies and is not totally dependent on the amount of melanin pigment present in the iris or skin. Dark glasses may be helpful for individuals with albinism, but many prefer to go without dark glasses because of the reduction in vision from the dark lenses. Going without dark glasses is not harmful to vision. In general, opaque contact lenses or darkly tinted lenses do not improve visual function.
- A hat with a brim (such as a baseball hat with a visor) is often the best way to achieve reduction in photophobia and sun protection.
- Skin cancer is treated as for the general population.

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Prevention of Primary Manifestations

No dietary or ophthalmologic procedures or exercises can prevent the development of the clinical features of albinism.

Prevention of Secondary Complications

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 very sensitive individuals and 30 minutes or more in less sensitive individuals. Prolonged periods in the sun require skin protection with clothing (hats with brims, long sleeves and pants, socks) and sunscreens with a high SPF number (total blocks with SPF 45-50+). Sunscreens with lower SPF values (for example, SPF-15, or 30) can be used if the individual does not burn routinely with sun exposure.

Surveillance

- Annual ophthalmologic examination and reassessment for accurate correction of refractive error
- Annual search for evidence of sun-related skin damage and cancerous or pre-cancerous lesions when living in a location with high sun exposure

Agents/Circumstances to Avoid

Prolonged sun exposure should be avoided.

Testing of Relatives at Risk

Relatives with OCA2 are clinically apparent because of the hypopigmentation and eye changes, and additional testing is not indicated.

Therapies Under Investigation

Search ClinicalTrials.gov 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

Genetics clinics, staffed by genetics professionals, provide 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 may include disease-specific and/or umbrella support organizations.

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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

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 mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The unaffected offspring of an individual with OCA2 are obligate heterozygotes (carriers) for a disease-causing mutation in the *OCA2* gene.
- Most families have no history of OCA2, but families with two-generation pseudodominance have been identified. 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* mutant alleles in African populations, a family history for OCA2 and affected individuals from multiple generations are often found in African families.

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 is available on a clinical basis for at-risk relatives on a clinical basis once the mutations have been identified in the proband.

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 test 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

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed [Hongyi et al 2007].

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

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 such as OCA2 that do not affect intellect or lifespan are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. 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 Oculocutaneous Albinism Type 2

Gene Symbol	Chromosomal Locus	Protein Name
OCA2	15q11.2-q12	P protein

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 Oculocutaneous Albinism Type 2

203200	OCULOCUTANEOUS ALBINISM, TYPE II; OCA2

Table C. Genomic Databases for Oculocutaneous Albinism Type 2

Gene Symbol	Locus Specific	Entrez Gene	HGMD
OCA2	OCA2	4948 (MIM No. 203200)	OCA2

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

Normal allelic variants: Mutations and variants are listed in the Albinism database. *OCA2* has 24 exons. More than 42 polymorphisms have been described in many exons and adjacent introns throughout the gene.

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Pathologic allelic variants: See Albinism database. More than 50 mutations of *OCA2* have been reported. Most are missense mutations, but deletions of one or a small number of bases and base changes in introns are common. The most common *OCA2* mutation is the 2.7-kb deletion mutation in the African and African-American populations. The V443I missense mutation is the most common in the northern European populations. Most individuals with OCA2 are compound heterozygotes for *OCA2* mutations, with different maternal and paternal mutations, and approximately half of the non-African reported individuals have only one identifiable mutation; the second mutation was not detected by the methods used. (For more information, see Genomic Databases table above.)

Normal gene product: The protein product of the *OCA2* gene, 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].

Abnormal gene product: Few studies are available on mutant P protein. The full-length normal human *OCA2* cDNA or *OCA2* cDNA-containing mutations associated with OCA2 (A481T, V443I) have been expressed in mouse melanocytes derived from an animal with a mutation in the murine homologue (*pink-eyed dilution* or *p*) of the *OCA2* gene [Sviderskaya et al 1997]. The murine cells with the normal cDNA synthesized significantly more melanin than did those with the A481T mutation construct, and those with the V481T construct synthesized a minimal amount of melanin. The mechanisms by which the mutant protein alters the ability of the cell to synthesize melanin are unknown.

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

The Albinism Database (HUGO)
www.albinismdb.med.umn.edu/

National Library of Medicine Genetics Home Reference
Oculocutaneous albinism

PanAmerican Society for Pigment Cell Research
www.paspcr.org

References

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

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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

- 20 June 2007 (cd) Revision: mutation scanning and sequence analysis available clinically
- 20 December 2005 (me) Comprehensive update posted to live Web site
- 17 July 2003 (me) Review posted to live Web site
- 25 April 2003 (rk) Original submission