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Oculocutaneous Albinism Type 4

[*OCA4*]

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Summary

Disease characteristics. Oculocutaneous albinism type 4 (OCA4) is characterized by hypopigmentation of the skin and hair plus the characteristic ocular changes found in all other 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 OCA4 are usually recognized within the first year of life because of hypopigmentation of the hair and skin and the ocular features of nystagmus and strabismus. Vision is likely to be stable after early childhood. 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.

Diagnosis/testing. Because OCA2 and OCA4 are phenotypically similar, it is not possible to accurately diagnose OCA4 based only on clinical findings. *MATP* (previously called *AIM1*) is the only gene known to be associated with OCA4. Molecular genetic testing of *MATP* is available clinically.

Management. Ophthalmologic care is most important for individuals with OCA4. Correction of refractive errors with spectacles or contact lenses improves visual acuity. Dark glasses may alleviate photophobia but dark lenses may reduce vision; a hat with a brim or visor best achieves reduction in photophobia. Strabismus surgery may be considered for cosmetic reasons. Excessive exposure to sun should be avoided; protective clothing and sunscreens prevent sunburn and secondary skin changes.

Genetic counseling. OCA4 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.

Diagnosis

Clinical Diagnosis

The diagnosis of oculocutaneous albinism type 4 (OCA4) is established by presence of the following features:

- **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)

  Note: (1) A VEP is not necessary for the routine diagnosis of albinism; misrouting is implied by the finding of strabismus and reduced stereoscopic vision. (2) 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. (3) The VEP is performed with a technique specifically developed for demonstration of the misrouting and a regular VEP will not demonstrate this. (4) Normal routing of the optic nerves, demonstrated with a VEP, indicates that the diagnosis is not albinism/OCA.

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. *MATP* (previously called *AIM1*) is the only gene known to be associated with oculocutaneous albinism type 4 (OCA4).

Clinical testing

- **Sequence analysis.** So far, 19 *MATP* mutations have been reported; the majority of mutations described are missense mutations, but deletions of one or a small number of bases and splice site mutations have been found [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005].

  A common missense mutation (D157N) accounts for 39% of mutant alleles in the Japanese population; individuals homozygous and compound heterozygous for this mutation have been identified [Inagaki et al 2004].

  Most individuals with OCA4 are compound heterozygotes. Approximately 27% of the individuals with OCA4 reported have only one mutation that can be detected by sequence analysis of the coding region and the intron-exon boundaries of *MATP* [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005]. It is probable 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 *MATP*.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Oculocutaneous Albinism Type 4

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*MATP* sequence variants	Unknown	Clinical Testing

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

OCA4 is the only phenotype associated with mutations in *MATP*.

Clinical Description

Natural History

The full range of phenotypes of OCA4 is not known, as only about 30 individuals have been described to date. The amount of cutaneous pigmentation in OCA4 is a continuum from minimal to near-normal [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005]. The amounts of iris and retinal pigments vary and visual acuity covers a wide range; however, no subtypes of OCA4 are recognized.

Individuals with albinism (including OCA4) 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.

Eye. Some children with albinism have nystagmus that is noticed by the parents and the examining physician in the delivery room. 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 three to four months, and the diagnosis is often considered at the four-to-six month well-baby checkup. The nystagmus can be 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 individuals are 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 individuals with the OCA1A subtype of oculocutaneous albinism type 1 (OCA1) is usually not observed in individuals with OCA4.

Visual acuity in individuals with OCA4 ranges from 20/30 to 20/400 and is usually in the range of 20/100 to 20/200 [Rundshagen et al 2004]. Vision is likely to be stable after early childhood and no major change or further reduction in vision should occur. The visual changes are likely not progressive, and loss of vision later in life should not be related to the albinism.

Skin/hair. The range of skin pigment in individuals with OCA4 is broad [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005]. Individuals with OCA4 are almost always born with some pigment in their hair that ranges in color from silvery white to light yellow. Scalp hair may be very light, but it is usually not completely white (not as white as a sheet of copy paper or fresh snow); some parents may refer to light yellow/blond hair color as "white" or "nearly white" if it is very lightly pigmented or is much lighter than the hair color of other family members at a similar age. Furthermore, the definition of "white" scalp hair is not easy in some young children because the hair may be sparse and short and because some shampoos discolor hair. It is helpful to hold a piece of white paper next to the hair to determine if it is truly white. Hair color may darken with time, but usually the hair color does not change dramatically between childhood and adulthood.

When hair color is blond or yellow, the skin is usually creamy white with little or no pigmentation. Skin color in individuals with OCA4 is not usually as white as that in individuals with the OCA1A subtype of oculocutaneous albinism type 1, reflecting the fact that skin melanocytes in individuals with OCA4 can still synthesize some melanin; however, the majority of the melanin is yellow pheomelanin rather than black-brown eumelanin.

Skin cancer risk. Over many years, exposure of lightly pigmented skin to the sun 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 OCA4 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 an individual with any type of OCA is very rare in northern areas of the US. 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 throughout 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 MATP protein and the limited data from *MATP* molecular genetic testing make genotype-phenotype correlations difficult [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005].

The amount of cutaneous pigmentation, ocular pigmentation, and visual development resulting from particular *MATP* mutations cannot be predicted at this time.

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.

Prevalence

Prevalence of OCA4 is thought to be on the order of 1/100,000 in most populations throughout the world. It is likely to be more common in Japan, where it accounts for 24% of individuals with OCA [Inagaki et al 2004, Inagaki et al 2005].

OCA4 has also been described in individuals of German and Turkish descent [Newton et al 2001, Rundshagen et al 2004, Ikinciogullari et al 2005].

Differential Diagnosis

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

Albinism. Most types of albinism are associated with the development of some cutaneous pigmentation. The differential diagnosis of albinism with pigmentation of the skin and hair includes the OCA1B subtype of oculocutaneous albinism type 1; oculocutaneous albinism type 2 (OCA2); oculocutaneous albinism type 3 (OCA3); Hermansky-Pudlak syndrome (HPS); and X-linked ocular albinism (OA1).

- **OCA1**. A detailed history of pigment development usually identifies individuals with OCA1. Visual acuity in individuals with OCA4 is likely to be better than that in individuals with OCA1, but may overlap [Summers 1996; King, Hearing et al 2001; King, Oetting et al 2001; Inagaki et al 2004; Rundshagen et al 2004].
- **OCA2**. Molecular genetic testing is necessary to distinguish OCA4 from OCA2.
- **OCA3.** Mutations of *TYRP1*, the gene encoding tyrosinase-related protein-1, are associated with rufous or red OCA3 [Boissy et al 1996, Manga et al 1997]; this phenotype has only been described in the African population.
- **Hermansky-Pudlak syndrome (HPS).** A medical history of bleeding or bruising and an analysis of platelet dense bodies are necessary to establish the diagnosis of HPS.
- **OA1**. Males with X-linked ocular albinism have normal skin and hair pigment, which is obvious in families with darker constitutional pigmentation. In families with light constitutional pigmentation, a young boy with OA1 may have light hair (even be "tow-headed") and appear to have oculocutaneous albinism rather than ocular albinism. The correct diagnosis may be established by family history; it usually becomes clear with time. Molecular genetic testing of the *OA1* gene provides an objective and non-invasive means of diagnosis.

Other. Although individuals with red skin and light hair have been described in Papua, New Guinea, the association of this phenotype with OCA3 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 this phenotype are not available.

The existence of another autosomal gene associated with either ocular albinism or oculocutaneous albinism has not been substantiated, although families with OCA that do not map to the loci for the genes *TYR* (OCA1), *P* (OCA2), *TYRP1* (OCA3), or *MATP* (OCA4) have been reported.

Congenital motor nystagmus. 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, these studies were done before the molecular basis of OCA was understood, suggesting that individuals with OCA might have been included incorrectly. The visual evoked potential analysis to evaluate misrouting of the optic nerves is normal in congenital motor nystagmus.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with oculocutaneous albinism type 4 (OCA4):

- Complete ophthalmologic evaluation including measurement of visual acuity and refractive error and assessment for strabismus

Treatment of Manifestations

- Ophthalmologic care is the most important part of the ongoing care for most individuals with OCA4.
- The majority of individuals with albinism have significant hyperopia or myopia and astigmatism. Correction of these refractive errors with spectacles or contact lenses can improve visual acuity. Except in the very unusual individual, correction of refractive errors cannot restore visual acuity to normal because of the foveal hypoplasia.
- Photophobia is common 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. In general, opaque contact lenses or darkly tinted lenses do not improve visual function. 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. 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.
- 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.

Prevention of Secondary Complications

- The skin care necessary for individuals with OCA4 to prevent sunburn and secondary skin changes 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. 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 sun screen with a high SPF number (total blocks with SPF 45-50+). The amount of skin pigmentation varies, and protection of the skin with sunscreen correlates with skin pigmentation and the ability to tan. Sunscreens with lower SPF values (for example, SPF 8, 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

Agents/Circumstances to Avoid

- Excessive exposure of the skin to the sun

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

OCA4 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, but may be lighter in pigmentation for their ethnic group.

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 OCA4 are obligate heterozygotes (carriers) for a disease-causing mutation in *MATP*.
- Most families have no history of OCA4, but families with two-generation pseudodominance may occur. These result from an affected individual having children with a reproductive partner who is heterozygous (i.e., a carrier).

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 available on a clinical basis once the mutations have been identified in the family.

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. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

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 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 ten to 12 weeks' gestation. Both disease-causing alleles must be identified before prenatal testing can be performed.

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

A fetal skin biopsy will not provide an accurate diagnosis and is not appropriate for prenatal diagnosis of OCA4.

Requests for prenatal testing for conditions such as OCA4 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 4

Gene Symbol	Chromosomal Locus	Protein Name
SLC45A2	5p13.3	Membrane-associated transporter 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 4

606202	SOLUTE CARRIER FAMILY 45, MEMBER 2; SLC45A2
606574	OCULOCUTANEOUS ALBINISM, TYPE IV; OCA4

Table C. Genomic Databases for Oculocutaneous Albinism Type 4

Gene Symbol	Locus Specific	Entrez Gene	HGMD	GeneCards	GenAtlas
SLC45A2	SLC45A2	51151 (MIM No. 606202)	SLC45A2	*SLC45A2*	MATP

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

Molecular Genetic Pathogenesis

Although not yet observed in humans, the phenotype resulting from heterozygosity of a single *Matp* mutation in mice results in hypopigmentation that may be analogous to some of the so-called autosomal dominant forms of albinism reported in humans.

Normal allelic variants: *MATP* has seven exons, and sequence polymorphisms are found in many exons and adjacent introns throughout the gene. Eight polymorphisms have been described.

Pathologic allelic variants: See International Albinism homepage. Nineteen mutations of *MATP* have been reported. Most are missense mutations, but deletions of one or a small number of bases and base changes have been detected. The most common *MATP* mutation in Japanese individuals is the D157N missense mutation [Inagaki et al 2004]. Most individuals with OCA4 are compound heterozygotes for *MATP* mutations, with different maternal and paternal mutations. Approximately 17% of reported Japanese individuals have only one identifiable mutation; the second mutation cannot be detected with the methods used [Inagaki et al 2004]. (For more information, see Genomic Databases table above.)

Normal gene product: The MATP protein is a transmembrane protein [Newton et al 2001]. The precise function of the MATP protein is unknown, although it shares high homology with known sucrose proton symporters.

Abnormal gene product: The mechanisms by which the mutant protein alters the ability of the cell to synthesize melanin are unknown. However, tyrosinase, the rate-limiting enzyme in the biosynthesis of melanin that is associated with OCA1, appears to be mis-localized in mouse melanocytes that are homozygous for mutant *MATP* alleles [Costin et al 2003]. This phenotype is shared with melanocytes that are mutant for the *P* gene, associated with OCA2 [Toyofuku et al 2002].

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

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

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

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

- 14 June 2007 (cd) Revision: sequence analysis and prenatal diagnosis available clinically
- 17 November 2005 (me) Review posted to live Web site
- 21 April 2005 (mb) Original submission