Learning Objectives

- Describe the genetics and biochemistry of OCA1
- Describe the typical clinical presentation of OCA1
- Review the screening and diagnostic options for OCA1 in the prenatal setting
- Create a plan for genetic counseling of family members for patients with OCA1
- Understand the importance of thorough ophthalmic management of patients with OCA1 and the negative outcomes associated with a lack of appropriate medical management in this patient population.

Pretest Questions

1. What is the genetic defect that leads to the development of type 1 Oculocutaneous Albinism (OCA1) and absence of melanin pigment?
   a. Mutation in tyrosinase related protein gene
   b. Mutation in the tyrosinase gene and loss of enzymatic activity
   c. Mutation in the membrane associated transporter gene
   d. **Mutation in phenylalanine hydroxylase**
   e. **Mutation in dopamine decarboxylase**

2. Which of the following clinical features is always present in OCA1 and are they present at birth?
   a. Coloboma and glaucoma, present at birth
   b. Cataract and glaucoma, present at birth
   c. Cataract and glaucoma, develops during adolescence
   d. Iris transillumination and nystagmus, present at birth
   e. Iris transillumination and nystagmus, develops after 1 year
   f. Glaucoma, develops at around age 10

3. What is the mode of inheritance of OCA1?
   a. Autosomal dominant
   b. Autosomal recessive
   c. X-linked recessive
   d. Mitochondrial
4. What characteristic finding is found upon fundoscopic examination of the retina?

   a. Loss of foveal reflex as result of foveal hypoplasia
   b. Retinal detachment due to instability of the retinal pigment epithelium
   c. Macular hole with vitreomacular traction
   d. Central serous chorioretinopathy
   e. Epiretinal membrane and macular pseudohole

Answers: 1) b, 2) d, 3) b, 4) a

Case Study (The following case study was adapted from a case report published by Akeo et al., Archives of Ophthalmology, 1996, REF#8).

A couple recently sought genetic counseling after the birth in 1998 of a male infant with tyrosinase-negative OCA. The absence of tyrosinase activity in the epidermal melanocytes was confirmed by the electron microscopic DOPA reaction test performed on their male child. A DNA analysis revealed the presence of one of the two known mutations in the father, but no maternal gene mutation could be identified.

Molecular genetic testing for OCA1 by specialized laboratories involves sequencing of the 5 coding exons of the TYR gene and adjacent intronic sequences. Currently, this type of testing detects 70-80% of mutations causing the OCA1 phenotype. Over 90 different tyrosinase gene mutations have been reported worldwide in cases of tyrosinase-negative OCA, many in recent years.

When this woman became pregnant a second time in 2004, skin from the upper trunk of the fetus was obtained by ultrasound-guided biopsy at the 20th week of gestation. The electron microscopic DOPA reaction test was performed on the fetal skin specimen, which demonstrated melanocytes containing stage I and II, but not stage III or IV, melanosomes. Only stage I and II melanosomes were observed even after incubation with L-DOPA, indicating the lack of tyrosinase activity. Accordingly, a diagnosis of tyrosinase-negative OCA was made. The parents requested that the pregnancy be terminated.

Genetics and Biochemistry of OCA

Albinism is a genetic disease that results in reduced or absent production of melanin pigment with associated clinical characteristics of hypopigmentation of the skin, hair, and eyes. There are four main types of OCA. Type 1 OCA (OCA1, OMIM 203100) is the most severe form of albinism and is caused by mutations in the tyrosinase gene. OCA1 is further subdivided into two types. Type 1A that is characterized a complete lack of tyrosinase enzymatic activity whereas type 1B exhibits reduced tyrosinase activity (1). OCA2, or tyrosinase positive OCA, is caused by mutation in the P protein gene. OCA3 is associated with mutation in the tyrosinase related protein gene. OCA4 is associated with mutations in the membrane associated transporter gene.
OCA1 is an autosomal recessive disorder caused by mutations in the TYR gene on chromosome 11q with a prevalence of approximately 1 in 40,000 (1), but the actual incidence of disease can vary depending on the population being studied. Most cases of OCA1 are inherited in an autosomal recessive or compound heterozygous mode of inheritance. OCA1 is not a disease of a single gene mutation, but in fact can result from a variety of different types of mutations including missense, nonsense, and frameshift mutations (2). Human tyrosinase is an integral membrane copper binding glycoprotein that contains 529 amino acids. This enzyme catalyzes the oxidation of tyrosine via incorporation of molecular oxygen to form dopa and subsequently catalyzes the oxidation of dopa to dopaquinone (3), reactions required for the ultimate production of melanin pigment. The oxidation of tyrosine depends upon the enzyme’s interaction with copper and thus mutations altering enzyme secondary structure affecting the interaction between copper and molecular oxygen abolishes enzymatic activity. Consequently there is a lack of melanin pigment production. In animals, the expression of tyrosinase occurs in specialized organelles known as melanosomes, which are present in melanin-producing melanocytes. These specialized cell types are present in skin, iris and retinal pigment epithelium of the eyes, and hair (3).

**Typical Clinical Presentation and Management of OCA1**

- White skin
- White eyelashes
- Iris transillumination
- Nystagmus
- Absence of pigment in the retinal pigment epithelium and choroidal vessel prominence
- Highly astigmatic refractive errors
- Foveal Hypoplasia (no foveal reflex)
- Reduced Visual Acuity
- Photophobia
- Abnormal optic chiasm decussation of temporal optic nerve fibers is present in most

**Diagnosis and Management of OCA**

**Prenatal Diagnosis:**

*Option #1:* Acquisition of fetal cells using amniocentesis, followed by genetic analysis of fetal genomic tyrosinase by allele-specific hybridization and polymerase chain reaction amplification of the mutated gene (5).

*Option #2:* At 20 weeks gestation, an electron microscopic examination of a fetal skin biopsy can reveal the presence or absence of melanin in epidermis and hair-bulb melanocytes (6, 7).

**Postnatal Diagnosis:**

Postnatal diagnosis is based largely on clinical and ocular examination. Postnatal diagnosis was previously supported by determining hair bulb tyrosinase activity. Recent progress in linear PCR
and automated DNA sequencing techniques allows rapid determination of specific tyrosinase mutations (6, 7).

**Management:**

The management of OCA involves protecting the skin and maximizing vision. Skin protection with UV barriers and clothing is particularly important due to the substantially increased risk of skin cancers. As children, albinos should be carefully and fully refracted in order to prevent anisometropic amblyopia. If strabismus develops, it is correctly surgically. Special education and low vision aids may be necessary, but most albino children attend regular school (4).

**References**


