Albinism

Albinism refers to a group of inherited abnormalities of melanin synthesis resulting in congenital hypopigmentation. It involves the skin, hair, and eyes (oculocutaneous albinism) or may be limited primarily to the eyes (ocular albinism). The estimated frequency of affected individuals in the USA is approximately 1/17,000.

GENETICS/BASIC DEFECTS

1. Classification of albinism (genetic heterogeneity)
   a. Oculocutaneous albinism (OCA): a common phenotype for a group of recessive genetic disorders of melanin synthesis. Mutations in at least 12 genes are responsible for this phenotype. Mutations in OCA-related genes result in reduction of melanin synthesis by the melanocytes
      i. Common types of OCA with cutaneous and ocular hypopigmentation without significant involvement of other tissue
         a) Oculocutaneous albinism 1 (OCA1): subdivided into OCA1A, OCA1B, OCA1ts
         b) Oculocutaneous albinism 2 (OCA2)
         c) Oculocutaneous albinism 3 (OCA3)
      ii. Less common types of OCA with more complex manifestations
         a) Hermansky-Pudlak syndromes
         b) Chediak-Higashi syndrome
   b. Ocular albinism
      i. Ocular albinism 1 (OA1): X-linked recessive
      ii. Autosomal recessive ocular albinism (AROA)
2. Molecular defects causing albinism
   a. OCA1 (tyrosinase related albinism)
      i. Caused by mutations of tyrosinase gene (*TYR*) located at 11q14-21
      ii. Several different types of mutations to the tyrosinase gene (missense, nonsense, and frameshift) are responsible for producing OCA1A and OCA1B
      iii. OCA1A (tyrosinase negative albinism with inactive enzyme) produced by null mutations of the *Tyr* gene
         a) 0% tyrosinase enzyme activity
         b) Over 100 mutations spanning all parts of the gene reported
         c) Compound heterozygotes with different maternal and paternal alleles in majority of patients
      iv. OCA1B (tyrosinase related albinism with partially active enzyme) produced by leaky mutations of the *Tyr* gene
         a) "Yellow" form of albinism with 5–10% activity of tyrosinase
         b) A base substitution within the gene may result in reduced rather than completely abolished enzyme activity
      v. OCA1ts (tyrosinase related albinism with thermolabile enzyme)
         a) A temperature sensitive tyrosinase is only partly functional
         b) The first reported cases had a missense substitution within the tyrosinase gene
   b. OCA2 (tyrosinase positive albinism)
      i. *OCA2* gene: the pink-eye dilution gene (*p*) located at 15q11-13
      ii. Caused by mutations of the *P* gene on the chromosome 15, homologous to the mouse pinked-eye dilution, or *P* gene
      iii. The mutated region is also deleted in Prader-Willi syndrome (PWS) and Angelman syndrome (AS), accounting for close linkage of OCA2 to PWS and AS
   c. OCA3 (Brown albinism)
      i. *OCA3* gene: tyrosinase-related protein-1 gene (*TRP1*) located at 9p23
      ii. The gene homologous to the mouse "brown" gene
      iii. Mutation of the gene possibly synergistic with a polymorphism or partially active mutation in OCA1 or OCA2
   d. OA1 (X-linked ocular albinism)
      i. *OA1* gene located at Xp22.3-22.2
      ii. Intragenic deletions, frameshift mutations, and point mutations identified
   e. OAR (autosomal recessive ocular albinism)
      i. Gene mapping: 6q13-q15
      ii. May not be a clinical entity
      iii. Tyrosinase in some cases
      iv. P protein in some cases
   f. Hermansky-Pudlak syndromes (HPS): a group of related disorders
      i. Hermansky-Pudlak syndrome 1 is caused by mutations of the *HPS1* gene which is localized to 10q23
      ii. HPS2 gene was localized to 5q13. Hermansky-Pudlak syndrome 2 is caused by mutation of the *APB1* gene, which is localized to 5q13, resulting in a defect in adapter complex 3 AP-3, β3A subunit
   g. Chediak-Higashi syndrome: defect in *CHS1* gene (lysosomal trafficking regular gene *LYST*) located at 1q42.1-q42.2
3. Pathophysiology
   a. Melanin in the skin
      i. Melanin, a photoprotective pigment in the skin, absorbs UV light from the sun, thus preventing skin damage
      ii. Normal skin tans upon sun exposure due to increased melanin pigment in the skin
      iii. Patient with albinism developing sunburn because of the lack of melanin

   b. Consequence of the absence of melanin during the development of the eye
      i. Hypoplasia of fovea
      ii. Alteration of neural connections between the retina and the brain
   c. Melanin pathway
      i. Consisting of a series of reactions that converts tyrosine into 2 types of melanin, black-brown eumelanin and red-blond pheomelanin
      ii. Tyrosinase: a major enzyme in a series of conversions to melanin from tyrosine and it is also responsible for converting tyrosine to DOPA and then to dopaquinone, which subsequently converts to either eumelanin or pheomelanin
      iii. Two other enzymes involved in the formation of eumelanin: tyrosinase-related protein 1 (TRP1, DHICA oxidase) and tyrosinase-related protein 2 (TRP2, dopachrome tautomerase). Mutation of the TRP1 results in OCA3; mutation of the TRP2 does not cause albinism
      iv. P protein, a melanosomal membrane protein, believed to be involved in the transport of tyrosine prior to melanin synthesis. Mutation of this P gene causes OCA2
4. Pathogenesis of the ocular features
   a. Development of the optic system highly dependent on the presence of melanin
   b. Ocular features appear if melanin is reduced or absent
   c. Mechanisms
      i. Misrouting of the retinogeniculate projections resulting in abnormal decussation of optic nerve fibers
      ii. Sensation of photophobia and decreased visual acuity caused by light scattering within the eye
      iii. Light-induced retinal damage postulated as a contributing mechanism to decreased visual acuity
      iv. Foveal hypoplasia: the most significant factor causing decreased visual acuity

CLINICAL FEATURES

1. General clinical features of albinism
   a. Skin, hair, and eye discoloration caused by abnormalities of melanin metabolism (might not be obvious in ocular albinism)
   b. Reduced visual acuity due to foveal hypoplasia
   c. Translucent iris due to reduction in iris pigment
   d. Visible choroid vessels due to reduction in retinal pigment
   e. Photophobia due to iris pigmentary abnormalities
   f. Anomalous visual pathway projections due to misrouting of the optic nerves at the chiasm
   g. Nystagmus due to abnormal decussation of optic nerve fibers
   h. Alternating strabismus
   i. Hyperopia, myopia, and astigmatism
2. Oculocutaneous albinism 1 (OCA1)
   a. Incidence: approximately 1 in 40,000 individuals
   b. Oculocutaneous albinism 1A (OCA1A)
      i. Classic tyrosinase-negative OCA phenotype
      ii. Most severe form of OCA
      iii. White hair and white skin that does not tan
      iv. Blue and translucent irides that do not darken with age
      v. Foveal hypoplasia
      vi. No tanning potential
      vii. At risk for sun burning and skin cancer
      viii. Diminished visual acuity as low as 20/400
      ix. Photophobia and nystagmus worst in this subtype
   c. Oculocutaneous albinism 1B (OCA1B)
      i. Yellow mutant type OCA, referred to as Amish albinism, or xanthous albinism
      ii. Variable pigmentation ranging from very little cutaneous pigmentation to nearly normal skin pigmentation
      iii. Increased skin, hair, and eye pigment with age and tan with sun exposure
      iv. Yellow hair pigment develops in the first few years of life and continuously accumulates pigment, principally yellow-red pheomelanin, in the hair, eyes, and skin in the later life
      v. Decreased visual acuity improving with age
   d. Temperature-sensitive albinism (OVA1ts)
      i. A subtype of OCA1B
      ii. Mutation of the tyrosinase gene that produces a temperature-sensitive tyrosinase enzyme
      iii. The heat-sensitive tyrosinase enzyme activity is approximately 25% of the normal tyrosinase activity at 37°C. The activity improves at lower temperatures
      iv. Dark hair pigment in the arms and legs (cooler areas of the body) while axillary and scalp hair remains white
      v. Pigment is absent in the fetus because of high fetal temperature
3. Oculocutaneous albinism 2 (OCA2)
   a. Tyrosinase positive OCA
   b. Incidence: approximately 1 in 15,000 individuals
   c. Most prevalent type of albinism in all races and especially frequent among African-American population (1 in 10,000)
   d. Phenotypic variability
      i. Ranging from absence of pigmentation to almost normal pigmentation
      ii. Absence of black pigment (eumelanin) in the skin, hair, or eyes at birth
      iii. Gradual development of pigmentation with age
      iv. Increased pigmentation resulting in improved vision
4. Oculocutaneous albinism 3 (OCA3)
   a. Previously known as red/rufous OCA
   b. Incidence of the disease unknown
   c. Phenotype in African patients
      i. Light brown skin and hair
      ii. Blue-brown irides
      iii. Ocular features not fully consistent with diagnosis of OCA (no iris translucency, nystagmus, strabismus, or foveal hypoplasia)
   d. Phenotype in Caucasians and Asians: not known

5. Ocular albinism 1 (OA1)
   a. X-linked recessive OA (XLOA)
   b. Incidence of the disease approximately 1 in 50,000 individuals
   c. Extreme variability in clinical expression
   d. Involving eyes only
      i. Decreased visual acuity
      ii. Refractive errors: typical findings
         a) Hypermetropia
         b) Astigmatism
      iii. Hypopigmentation of the fundus and the iris
      iv. Absent foveal reflex (foveal hypoplasia)
      v. Congenital nystagmus
      vi. Photophobia
      vii. Strabismus
      viii. Iris translucency
      ix. Posterior embryotoxon
      x. Loss of stereoscopic vision due to misrouting of the optic tracts
   e. Normal skin
   f. Male manifesting complete phenotype
   g. Carrier females
      i. Normal vision
      ii. Hypopigmented streaks (characteristic patchy hypopigmentation as a result of mosaic inactivation of the affected X chromosomes) in the periphery
      iii. Marked iris translucency
   h. Severity depending on ethnic background: less severe in races exhibiting very dark constitutive skin pigmentation than those more lightly pigmented
6. Autosomal recessive ocular albinism (OAR)
   a. Children with ocular features of albinism and normal cutaneous pigmentation born to normally pigmented parents
   b. Classified as autosomal recessive because both males and females are affected
   c. Not considered a clinical entity
7. Hermansky-Pudlak syndrome
   a. A group of related disorders
      i. Common oculocutaneous albinism
      ii. A platelet storage disorder
      iii. Ceroid-lipofuscin lysosomal storage disease
   b. An autosomal recessive disorder with very variable expression
   c. Incidence of the disease rare, except in Puerto Rico where its frequency is 1 in 1800 individuals
   d. Bleeding diathesis resulting from a platelet storage pool deficiency
   e. Ceroid storage disease
      i. Accumulation of a Ceroid-lipofuscin material in various organ systems
      ii. Pulmonary fibrosis
      iii. Granulomatous colitis and gingivitis
      iv. Kidney failure
      v. Cardiomyopathy
8. Chediak-Higashi syndrome
   a. An autosomal recessive disorder with variable expression
   b. Consisting of a very rare group of conditions
   c. Severe immune disorder
      i. Abnormal intracellular granules in most cells, especially white cells
      ii. Susceptible to bacterial infections
      iii. Defective neutrophils function
      iv. Episodes of macrophage activation known as accelerated phases:
         a) Fever
         b) Anemia
         c) Neutropenia
         d) Occasionally thrombocytopenia
         e) Hepatosplenomegaly
         f) Lymphadenopathy
         g) Jaundice
   d. Hypopigmentation of skin, hair, irides, and ocular fundi
   e. Bleeding diathesis
      i. Easy bruising
      ii. Mucosal bleeding
      iii. Epistaxis
      iv. Petechiae
   f. Eye symptoms
      i. Photophobia
      ii. Nystagmus
      iii. Reduced stereoacuity
      iv. Strabismus
   g. Often succumb during childhood to severe viral and bacterial infections, bleeding or development of the accelerated phase
   h. May develop a peripheral and cranial neuropathy in survivors
      i. Autonomic dysfunction
      ii. Weakness and sensory deficits
      iii. Loss of deep tendon reflexes
      iv. Clumsiness with a wide-based gait
      v. Seizures
      vi. Abnormal EEG
      vii. Abnormal EMG with decreased motor nerve conduction velocities

DIAGNOSTIC INVESTIGATIONS

1. Ophthalmologic examination for detection of reduced retinal pigment with visualization of the choroidal blood vessels (OCA1) and foveal hypoplasia
2. Visual acuity reduction
3. Hair bulb incubation assay for tyrosinase activity
   a. OCA1A: no tyrosinase activity
   b. OCA1B: greatly reduced activity of tyrosinase but still present
4. Visual-evoked potential (VEP): an accurate diagnostic test for albinism by demonstrating an asymmetry of VEP between the two eyes secondary to misrouting of optic pathways
5. Electron microscopy of skin and hair bulb: not routinely performed but probably the best diagnostic method for albinism
6. Ultrastructural examination of skin: The presence of macromelanosomes in the skin is considered specific for OA1
7. Molecular genetic analysis

a. Genetic sequence analysis of the tyrosinase (*TYR*) gene to differentiate between various forms of albinism
   i. Rarely used for confirmatory diagnostic testing
   ii. Most commonly used for carrier detection
   iii. Prenatal diagnosis
b. Molecular genetic testing is available clinically by sequencing of the entire coding region of mutation scanning of *OCA1* gene
c. Testing for the 2.7-kb deletion found in individuals of African heritage: available clinically. Sequence analysis of the *OCA2* gene is available on a research basis
d. Molecular genetic testing of the gene *OA1* is available clinically and detects mutations in >90% of affected males

8. Hermansky-Pudlak syndrome
   a. Simple blood clotting tests
   b. Electron microscopic examination of platelets for identification of the absence of dense bodies (delta granules)
9. Chediak-Higashi syndrome
   a. Blood smear: identification of neutrophils containing giant cytoplasmic granules
   b. Defective neutrophils chemotaxis or killing
   c. Prolonged bleeding time caused by impaired platelet function

GENETIC COUNSELING

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive oculocutaneous albinism: 25% recurrence risk of being affected
      ii. X-linked recessive ocular albinism:
         a) If the mother is a carrier: 50% of brothers affected and 50% of sisters carriers
         b) If the mother is not a carrier: The recurrence risk is low but still exists since the risk of germline mosaicism in mothers is not known but is likely rare
   b. Patient's offspring
      i. Autosomal recessive oculocutaneous albinism: recurrence risk not increased unless the spouse is also a carrier in which case, there is a 50% recurrence risk (as in the pseudodominance)
      ii. X-linked recessive ocular albinism: none of the sons will be affected; all daughters will be carriers
2. Prenatal diagnosis
   a. Genetic sequence diagnosis possible on fetal DNA obtained from amniocentesis or CVS for pregnancies at 25% risk when the disease-causing mutations of the *TYR* gene in an affected family member is known
      i. OCA1: available clinically in families with an identified *OCA1* mutation
      ii. OCA2: possible in families with an identified *OCA2* mutation
      iii. XLOA: available clinically in families with an identified *OA1* mutation
   b. Fetoscopy (a high risk procedure) to obtain fetal skin biopsy to demonstrate the lack of melanin in skin melanocytes: an invasive procedure not recommended clinically
3. Management
   a. Albinism
      i. Skin care: avoid prolonged sun exposure to protect skin from ultraviolet radiation and minimize the risk of malignancy
         a) Protective clothing
         b) Sun screens
      ii. Ophthalmologic care
         a) Use of sunglasses for photophobia
         b) Correction of refractory errors secondary to hyperopia, myopia, or astigmatism to improve visual acuity
         c) Considering strabismus surgery for better ocular alignment
      iii. Ensure full benefits of a good education
         a) Provide large print textbooks
         b) Seating at the front of classroom
   b. Hermansky-Pudlak syndrome
      i. Treat extreme bleeding diathesis with platelet and blood transfusions
      ii. High dose of steroids for Granulomatous colitis or pulmonary fibrosis
   c. Chediak-Higashi syndrome
      i. Treat infections
      ii. Bone marrow transplantation: improves immunological status but no effect on ocular and cutaneous albinism

REFERENCES

Abadi R, Pascal E: The recognition and management of albinism. Ophthalmic Physiol Opt 9:3–15, 1989.

Biswas S, Lloyd IC: Oculocutaneous albinism. Arch Dis Child 80:565–569, 1999.

Boissy RE, Nordlund JJ: Albinism. Emedicine, 2001. http://www.emedicine.com

Carden SM, Boissy RE, Schoettker PJ, et al.: Albinism: modern molecular diagnosis. Br J Ophthalmol 82:189–195, 1998.

Creel DJ, Summers CG, King RA: Visual anomalies associated with albinism. Ophthalmic Paediatr Genet 11:193–200, 1990.

Hasanee K, Ahmed IIK: Albinism. Emedicine, 2001. http://www.emedicine.com

Hsieh YY, Wu JY, Chang CC, et al.: Prenatal diagnosis of oculocutaneous albinism two mutations located at the same allele. Prenat Diagn 21:200–201, 2001.

King RA: Oculocutaneous albinism type 1. Gene Reviews, 2002. http://www.genetests.org

King RA: Oculocutaneous albinism type 2. Gene Reviews, 2003. http://www.genetests.org

King RA, Summers GC, Haefemeyer JW, et al.: Facts about albinism. Available at: www.cbc.umn.edu/iac/facts.htm

King RA, Summers CG: Albinism. Dermatol Clin 6:217–228, 1988.

King RA, Hearing VJ, Creed DJ, et al.: Albinism. In Scriver CR, Beaudet al., Sly WS, Valle D (eds): The Metabolic & Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill, 2001, Chapter 220, pp 5587–5627.

King RA, Pietsch J, Fryer JP, et al.: Tyrosinase gene mutations in oculocutaneous albinism 1 (OCA1): definition of the phenotype. Hum Genet 113:502–513, 2003.

Lang GE, Rott HD, Pfeiffer RA: X-linked ocular albinism. Characteristic pattern of affection in female carriers. Ophthalmic Paediatr Genet 11:265–271, 1990.

Nagle DL, Karim MA, Woolf EA, et al.: Identification and mutation analysis of the complete gene for Chediak-Higashi syndrome. Nat Genet 14:307–311, 1996.

Oetting WS: Albinism. Curr Opin Pediatr 11:565–571, 1999.

Oetting WS: New insights into ocular albinism type 1 (OA1): Mutations and polymorphisms of the OA1 gene. Hum Mutat 19:85–92, 2002.

Oetting WS, King RA: Molecular basis of albinism: mutations and polymorphisms of pigmentation genes associated with albinism. Hum Mutat 13:99–115, 1999.

Oetting WS, Brilliant MH, King RA: The clinical spectrum of albinism in humans. Mol Med Today 2:330–335, 1996.

Oetting WS, Gardner JM, Fryer JP, et al.: Mutations of the human P gene associated with Type II oculocutaneous albinism (OCA2). Hum Mutat 12:434, 1998.

Oetting WS, Fryer JP, Shriram S, et al.: Oculocutaneous albinism type 1: the last 100 years. Pigment Cell Res 16:307–311, 2003.

Okulicz JF, Shah RS, Schwartz RA, et al.: Oculocutaneous albinism. J Eur Acad Dermatol Venereol 17:251–256, 2003.

Peracha MO, Eliott D, Garcia-Valenzuela E: Ocular manifestations of albinism. eMedicine J, 2001. Emedicine, 2001. http://www.emedicine.com

Rosenberg T, Schwartz M: Ocular albinism, X-linked. Gene Reviews, 2004. http://genetests.org

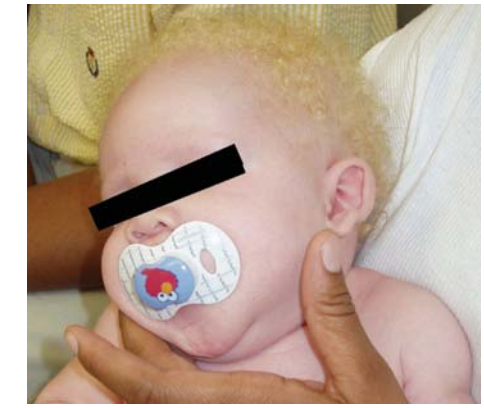
Rosenberg T, Schwartz M: X-linked ocular albinism: prevalence and mutations-a national study. Eur J Hum Genet 6:570–577, 1998.

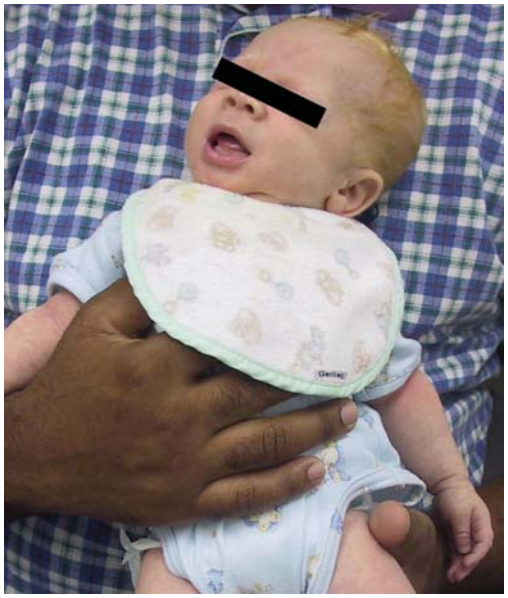
Russell-Eggitt I: Albinism. Ophthalmol Clin North Am 14:533–546, 2001.

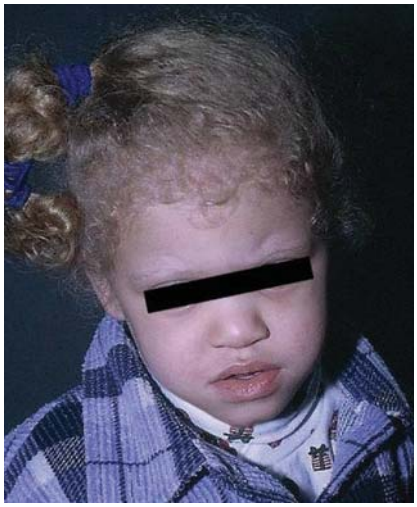
Sarangarajan R, Boissy RE: Tyrp1 and oculocutaneous albinism type 3. Pigment Cell Res 14:437–444, 2001.

Shen B, Samaraweera P, Rosenberg B, et al.: Ocular albinism type 1: more than meets the eye. Pigment Cell Res 14:243–248, 2001.

Spritz RA: Molecular genetics of oculocutaneous albinism. Semin Dermatol 12:167–172, 1993.







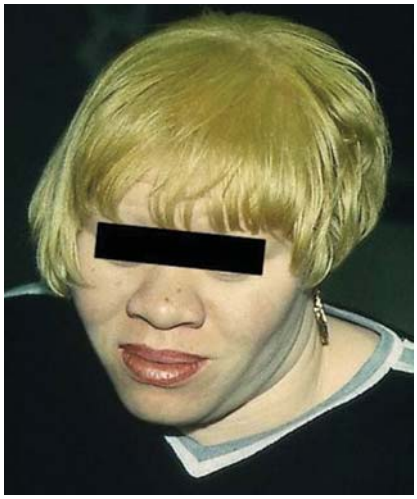


Fig. 1. Oculocutaneous albinism in different age groups including one set of identical twins.