

Albinism and the C-Series of Alleles.

In many series of multiple alleles, there is a dominance hierarchy. For example, in vertebrates, the **C gene** codes for the presence of the enzyme tyrosinase. **Tyrosinase** is the enzyme which synthesizes the pigment **melanin**. Depending upon the further action of other genes, the melanin may be some shade of black, grey, brown, red, orange, yellow, etc. In the domestic cat, the C genes occur as several different alleles:

Key:

C - full expression of melanin, full color.

$c^B$  - Burmese color, dark sepia (blackish brown) colored fur.

$c^S$  - Siamese color, dark color points on extremities (nose, ears, paws, tail) and white to light brown on the rest of the body; blue eyes; somewhat cross-eyed due to abnormal optic nerve pathways in the optic chiasma. (It is more correctly called  $c^h$  from the standpoint of comparative mammalian genetics, but the use of  $c^S$  is entrenched in the cat literature.)

$c^a$  - blue-eyed albino, white fur, blue eyes, very rare, cross-eyed

c - pink-eyed albino, white fur, pink eyes, very rare, cross-eyed

$c^B$  and  $c^S$  are incompletely dominant, and the heterozygote is called Tonkinese, which has dark color points on a lighter brown body. Otherwise, the dominance hierarchy is:

$$C > c^B \text{ or } c^S > c^a > c$$

Heterozygotes for an albino allele also have abnormal optical nerve pathways.

The Siamese allele is particularly interesting because it codes for a temperature-sensitive form of the enzyme. The Siamese allele of the cat is homologous to the Himalayan allele of the rabbit. If you shave the white fur off of the back of a Himalayan rabbit, and keep ice-packs applied to the bare spot while the fur grows back, the new fur will be black instead of white. The enzyme is able to function under the slightly lower temperature present on the extremities, but not at the higher temperatures found on the main part of the body.

The white tigers are reported to also be the result of a C series mutation, and are cross-eyed.

Ocularcutaneous Albinism In Humans

There are several different genes which cause ocularcutaneous albinism in humans. The terminology has been revised several times, and I am following that of McKusick's Mendelian Inheritance in Man on line (as of August 1998). One is tyrosinase-negative albinism (type IA OCA), "cc" which is homologous to the pink eyed albino of cats, mice, rats, etc.. These albinos have white skin, white hair, and pale grey to blue eyes. There is a pronounced red reflectance of the eye which is due to the reflection of light from the cutaneous blood vessels. Severe nystagmus (crossed eyes), photophobia, and reduced visual acuity are common features.

A second is tyrosinase-positive albinism (type II OCA) "pp" and appears to encode an integral membrane transporter protein. Tyrosinase-positive albinos have

white skin like tyrosinase–negative albinos. The hair of tyrosinase–positive albinos is white in very young children, but becomes darker with age (pale blond to light brown in adults who would have had dark skin otherwise, such as “Negroes”). In the case of tyrosinase–positive albinism, tyrosinase is present in the tissues. "Clinically, it is difficult to distinguish tyrosinase-positive from tyrosinase-negative albinism especially in Caucasoids. Pigmented nevi in tyr-positive cases may be the only clue. In blacks with this form of albinism, the hair is yellow and many pigmented spots develop in the skin." There appears to be a block in the formation of eumelanin with a continuing formation of pheomelanin. Tyrosinase-positive oculocutaneous albinism (OCA, type II) is the most prevalent type of albinism throughout the world. Lee et al. (1994) gave the overall frequency of OCA2 in the United States as approximately 1 per 36,000; however, the incidence is about 1 per 10,000 among African-Americans and is said to have a prevalence of 1/1,100 in the Ibo of Nigeria (Okoro, 1975) and a rate of about 1/3,900 in Negroids of South Africa (Kromberg and Jenkins, 1982, 1984) where it is the most common recessive genetic disorder of this group. Throughout sub-Saharan Africa, it is responsible for many deaths, with skin cancer and gross visual impairment being important sequelae. Whereas OCA2 is much less frequent among Caucasians, OCA1 is uncommon in African-Americans and Africans. In OCA2 in both Africans and Caucasians, some pigment is present at birth and lost later. On the contrary, most persons with OCA1 albinism show completely white hair at birth, even though with some alleles of tyrosinase deficiency a certain amount of pigment may develop later (King, 1992).

In New York City rather numerous cases of a tyrosinase-positive OCA are seen in Puerto Rican families from the Aguadilla-Arecibo area of northwestern Puerto Rico. "Albinism in dark-skinned persons such as Puerto Ricans is not always obvious because freckled skin and reddish hair may be present. Red reflex on transillumination of the iris (*in tyrosinase-negative albinism*) and nystagmus are important clues to the diagnosis." This may be due to an allele of type II OCA. [There are also at least two alleles of type I OCA frequently found in P.R. as well.]

There is a second type of tyrosinase negative oculocutaneous albinism (type IB OCA) in which the hair is white at birth and becomes yellow in color. This is due to an allele of the original (type IA). There are several reports of "c" gene mutations in which tyrosinase activity was reduced but not completely absent. The phenotypes of these mutations resemble type II OCA, and further confuse the situation.

There is also a temperature-sensitive c allele (OCA1) in humans, which is said to be equivalent to the Siamese allele of cats. "King et al. (1989, 1991) described a temperature-sensitive abnormality of tyrosinase resulting in oculocutaneous albinism. At age 29 years, the proband showed white axillary hair, scalp hair that was white with a yellow tint, pubic hair that was dark yellow to light brown, hair on the arm that was reddish blonde, and hair on the leg that was dark brown. No ocular pigment was present. Analysis of the pedigree suggested that the index case and her similarly affected brother were genetic compounds. This is the human equivalent of the temperature-related forms of albinism seen in the Siamese cat and the Himalayan mouse. Giebel et al. (1991) reported the Himalayan phenomenon in humans, i.e., peripheral pigmentation in oculocutaneous albinism associated with temperature-sensitive tyrosinase. In a patient with type I OCA in which hypopigmentation was related to local body temperature, Giebel et al. (1991) found that CGG (arg) at codon 422 in tyrosinase was converted to CAG (gln). The proband and her 2 affected

brothers completely lacked melanin pigment at birth but after puberty developed slight pigmentation of facial and pubic hair and extensive pigmentation in relatively cool parts such as the hair of the arms and legs. Kwon et al. (1989) showed that the temperature-sensitive tyrosinase in the Himalayan mouse is due to a his420-to-arg mutation, only 2 amino acids away from the human codon 422 substitution described by Giebel et al. (1991). By in vitro mutagenesis and introduction of the codon 422 mutation into HeLa (an "immortal" human cancer cell line) cells, Giebel et al. (1991) demonstrated that the codon 422 substitution resulted in thermosensitivity of tyrosinase; tyrosinase activity was 28% of normal in cells cultured at 31 degrees C and only 1.4% of normal in cells cultured at 37 degrees C."

In a North Carolina case, the mother had light golden brown hair, cream-colored skin, light blue irises of the eyes, and there was no red reflectance of the eyes. She was CC pp. The father had white skin, white hair, grey irises of the eyes, and a pronounced red reflectance of the eyes. He was cc PP. Their children were all Cc Pp, and had normal pigment. [Infant type II albinos do show red reflectance of the eyes, but it disappears in children and adults.]

If two (Cc Pp) double heterozygotes marry, what are the expected genotypic and phenotypic ratios in the children?