**Chapter 16  Disorders of Skin Color**

Human skin color is mainly determined by melanin pigments, carotene, and hemoglobin. Of these, melanins contribute the most. Racial differences in skin color result from differences in the kinds and amounts of melanin. Most diseases of abnormal pigmentation are caused by elevated or reduced melanin content; the disorders involving skin color tend to be congenital or to be caused by autoimmune reaction or sun exposure.

When carotene, a precursor of vitamin A, is taken into the body, it accumulates in the horny cell layer and subcutaneous fat layer, resulting in yellowish skin color (carotinoid pigmentation). This chapter also discusses dermal deposition of extrinsic substances caused by tattooing or injury. Although abnormalities of the blood vessels and hemoglobin may also cause changes in skin color, they are not included here.

### A. Diseases of depigmentation

#### 1. Oculocutaneous albinism (OCA)

**Synonym:** Congenital albinism

**Outline**

- There is congenital abnormality in melanin synthesis (**Fig. 1.18**). Pigment in skin, hair, and eyes is reduced or absent from birth.
- All types are autosomal recessive.
- Patients tend to be prone to skin cancer, from high photosensitivity to sunlight.
- Sunscreen is essential.

**Classification**

Oculocutaneous albinism (OCA) is classified by the causative genes into OCA1, OCA2, OCA3 and OCA4 (**Table 16.1**). It is also seen as a symptom of hereditary diseases including Hermansky-Pudlak syndrome and Chédiak-Higashi syndrome.

**Pathology**

Melanocytes are normal in number and size; however, immature melanosomes (stage I, II and III) are observed by electron microscopy (**Fig. 16.1**). In Chédiak-Higashi syndrome, giant lysosomes are detected in the skin, leukocytes, and other organs.

**Diagnosis, Examinations**

The maturity of melanosomes in melanocytes should be observed by electron microscopy. In the severest OCA1 cases, there are only immature melanosomes that lack melanin deposition (stage I or II). In OCA in which some pigment production remains, stage III melanosomes are seen and there may also be a few stage IV melanosomes. Prenatal diagnosis may be conducted.

<table>
<thead>
<tr>
<th>Table 16.1 Major types of oculocutaneous albinism (OCA).</th>
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<tbody>
<tr>
<td>OCA type 1 Tyrosine-related</td>
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<tr>
<td>1A Complete lack of synthesis of tyrosinase (formerly tyrosinase-negative type)</td>
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<tr>
<td>1B Dysfunction of tyrosinase synthesis (formerly yellow mutant type)</td>
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<tr>
<td>1mp Minimal-pigment albinism</td>
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<tr>
<td>1ts Temperature-sensitive</td>
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<tr>
<td>OCA type 2 P protein-related type (formerly tyrosinase-positive type)</td>
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<td>OCA type 3 TRP-1 related</td>
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<td>OCA type 4 MATP-gene type</td>
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<tr>
<td>HPS type Hermansky-Pudlak syndrome</td>
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<tr>
<td>CHS type Chédiak-Higashi syndrome</td>
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</table>
Disorders of Skin Color

Use of sunscreen is essential from birth, in order to protect the skin from UV-related cancer and skin aging. The eyes are protected by tinted contact lenses or sunglasses.

Types of oculocutaneous albinism (OCA)

1) OCA1

This is caused by tyrosinase gene mutation. OCA1 is classified into subtypes including OCA1A, in which tyrosinase activity is completely lost from such mutation (this type used to be classified as tyrosinase negative OCA), and OCA1B, in which some tyrosinase activity remains. All OCA1 subtypes are autosomal recessively inherited.

When melanin is not synthesized, as is the case in OCA1A, the skin appears white to pink, and the hair is white from birth. The skin is easily sunburned, and sun-exposed areas of the body are prone to malignant tumor (e.g., basal cell carcinoma, squamous cell carcinoma, malignant melanoma). The iris and choroid membrane are blue, and the ocular fundus is pink; the eyes appear blue when lit edge-on, and pink when lit head-on (pink-eye). Patients have a characteristic facial expression of squinting and looking out of the corner of the eyes, from photophobia and impaired eyesight that cannot be corrected. Horizontal nystagmus may be present. When melanin is scant but present, pigment may gradually appear in hair and skin as the patient grows, although it is impossible to distinguish these cases from OCA1A at birth.

2) OCA2

OCA2 is caused by mutation in the P protein gene on chromosome 15. It is autosomal recessive. In mice, the P protein works to convey tyrosine to melanosomes; however, the functions of human P protein have not been clarified.

Pigment may be largely or completely absent at birth; it is impossible to distinguish OCA2 from OCA1 only by the clinical symptoms. In OCA2 the eye color is bluish gray and the hair is pale yellow to blonde; both come to contain more pigment as the patient ages.

3) OCA3

OCA3 is caused by genetic mutation in TRP-1 (tyrosinase-related protein 1), which controls melanin synthesis. It tends to occur in patients of African descent. The skin color is reddish brown, and the hair is light reddish brown to red. Eye symptoms do not usually occur.
4) OCA4

OCA4 is caused by abnormality in the membrane-associated transporter protein (MATP). OCA4 is mainly seen in patients of African or Japanese ancestry. In Japan, it occurs with the second-most frequency, after OCA1. Pigment is present in the skin in small amounts. The hair is light yellow in many cases; however, there are some cases in which the hair is brown (Fig. 16.3). The eyes are blue, gray or reddish brown. Nystagmus is found in about half of all cases.

5) Hermansky-Pudlak syndrome (HPS)

Some causative genes that are thought to be associated with intracellular protein transport have been identified in Hermansky-Pudlak syndrome (HPS). HPS is classified by the causative genes into four subtypes: HPS1, HPS2, HPS3 and HPS4. It is autosomal recessive. Pigment appears in the skin and hair to some extent (Fig. 16.4). Pulmonary fibrosis or granulomatous colitis may occur as a complication by deposition of ceroid-lipofuscin. There is a hemorrhagic tendency in HPS, which manifests as susceptibility to bruising and nasal or gingival hemorrhaging.

6) Chédiak-Higashi syndrome (CHS)

Abnormality of the LYST gene on chromosome 1 (1q42) disturbs the normal function of microtubules. It is autosomal recessive. The main symptoms are partial albinism from melanocyte trafficking failure and photosensitive disorder. The hair is red and the skin color is cream, although sun-exposed areas such as the face sunburn to a dark red. Neutrophilic immune compromise often leads to bacterial infection. Histopathologically, giant lysosome granules (peroxidase-positive) are found in the peripheral leukocytes. During exacerbation, lymphatic and histiocytic infiltrate is found in the systemic organs, and acute symptoms of pancytopenia occur. Symptomatic therapies are performed for infection. Bone marrow transplantation may also be conducted. The prognosis is poor; most patients with CHS die young in the so-called “accelerated phase,” which is a lymphoproliferation into various organs resulting in hemophagocytosis, infection and bleeding.

2. Vitiligo vulgaris

Outline

- Because melanocytes are reduced or lost, hypopigmented patches (leukoderma) occur.
- Autoimmunity against melanocytes or melanin is thought to cause vitiligo vulgaris; however, the pathogenesis is unknown.