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

- 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.
Topical steroids and PUVA are useful treatments.

**Classification**

Vitiligo vulgaris is classified into focal, segmental, generalized and universal types. Vitiligo vulgaris in which leukoderma distribution is not associated with cutaneous innervation is called generalized vitiligo vulgaris. When unilateral leukoderma runs parallel to cutaneous nerves, it is called segmental vitiligo vulgaris.

**Clinical features, Epidemiology**

Vitiligo vulgaris often occurs in men and women about age 20. The incidence has been calculated as between 1% and 2% of the population. Familial cases account for 1% to 2% of all cases. Sharply circumscribed complete leukoderma occurs. There is a slight increase in pigmentation at the periphery of the eruptions. The lesions are irregular in shape and size, and they often coalesce (Figs 16.5-1 and 16.5-2). Gray hair is seen around the leukoderma. It is asymptomatic.

Generalized vitiligo vulgaris occurs most frequently on areas prone to mechanical stimulation, such as the seborrheic areas and the extremities, lumbar region, abdomen, intertriginous areas, face and neck.

Segmental vitiligo vulgaris occurs unilaterally on certain innervated areas. Young people are most commonly affected. Pernicious anemia, hyperthyroidism, and autoimmune diseases such as Addison’s disease may develop as complications.

**Pathogenesis**

The cause has not been identified. Autoimmunity against melanocytes and melanins and abnormal peripheral nerve function are thought to be involved.

**Pathology**

In the early stages, there is melanocyte degeneration with reduced or lost dopa response and lymphocytic and histiocytic infiltration into in the dermal upper layer. In the final stages, melanocytes are lost and melanin granules are absent in the basal layer.

**Differential diagnosis**

The disease should be differentiated from piebaldism, nevus depigmentosus, senile leukoderma, Vogt-Koyanagi-Harada disease, melanoleukoderma, pityriasis versicolor and Hansen’s disease.

**Treatment**

Topical and oral PUVA therapies and topical steroids are the first-line treatments. Leukoderma on the face and fingers can be concealed by special cosmetics to alleviate psychological distress. Steroids and sedatives are given in small doses, and
surgical intervention (Fig. 16.6) and narrowband UVB exposure are also conducted.

3. Piebaldism

**Synonym:** Partial albinism

**Definition**

Piebaldism is characterized by localized leukoderma with leukotrichia on the forehead and frontal region of the head. Few melanocytes are found around the areas of leukoderma and white hair; albinism develops locally. A congenital, autosomal dominant disease, it occurs with a frequency of 1 in 200,000.

**Clinical features**

Triangular or diamond-shaped leukotrichia and leukoderma are seen on the forehead and frontal region of the head (white forelock) at the time of birth. These do not enlarge or shrink with age. Contralateral geographic vitiligo occurs on the extremities and trunk. Small pigmented patches often occur within the leukoderma.

**Pathogenesis, Pathology**

Piebaldism is caused by abnormality in the c-kit gene. In fetal development, melanoblasts migrate from the neural crest to the epidermis to anchor and differentiate into melanocytes. The c-kit gene on chromosome 4 (4q12) encodes a receptor that is associated with the migration and anchoring of melanoblasts. Because piebaldism is autosomal dominant, abnormality occurs in half of each receptor, leaving an area on which melanoblasts do not anchor, and resulting in leukoderma. Histopathologically, melanocytes are lacking at the sites with leukotrichia and leukoderma.

**Diagnosis, Treatment**

Diagnosis is made by history-taking of autosomal dominant expression, and white forelock and small pigmented patches on leukoderma. Waardenburg-Klein syndrome, whose symptoms are similar to those of piebaldism, is accompanied by facial displasia and deaf-mutism. Skin graft and cultured pigmented cell transplantation have been reported to be effective.
Disorders of Skin Color

4. Sutton nevus

**Synonym:** Halo nevus

**Definition, Pathogenesis, Clinical features**

Sutton nevus has nevocellular nevus (lentigo) in the center, surrounded by oval leukoderma (Fig. 16.7). It tends to occur in children and young men and women, on the trunk, face and neck. Autoimmunization occurs against melanin at the center of the lentigo, and immunoreaction occurs against melanin at the periphery of the lentigo; this is thought to be the mechanism of Sutton nevus. Leukoderma may also be produced at the periphery of a malignant melanoma, angioma, blue nevus, soft fibroma, and seborrheic keratosis; it is called Sutton’s phenomenon.

**Pathology**

Degenerated or destroyed nevus cells and melanocytes, with dense lymphocytic and macrophagic infiltration, are found at the periphery.

**Treatment**

The treatments for vitiligo vulgaris are applied. The central nevus may be removed. It may heal spontaneously.

**Prognosis**

Leukoderma enlarges centrifugally. At the same time, the central nevus discolors, flattens and eventually disappears. As the nevus disappears, the leukoderma heals spontaneously. Excision of the central nevus induces spontaneous healing and prevents vitiligo vulgaris, a complication.

5. Vogt-Koyanagi-Harada disease

**Outline**

- Vogt-Koyanagi-Harada disease is caused by autoimmunization against melanocytes.
- Uveitis, leukoderma, leukotrichia and alopecia occur.
- The treatments for the skin lesions are oral and local steroids and PUVA therapies.

**Clinical features**

Vogt-Koyanagi-Harada disease progresses rapidly, and the main symptom is eye lesion. Cutaneous lesions appear during recovery after remission of inflammation (about 2 months after onset) (Fig. 16.8). Melanocytes are destroyed, leading to irregular-shaped diffuse cutaneous leukoderma, symmetrically around the eyes in particular. The eyebrows, eyelashes and hair become white from pigment loss. Alopecia may be present.

There are three stages: prodromal, eye disease and recovery. In the prodromal stage, there are persistent headaches, slight fever,
dizziness, and pain in the eyes for 5 to 7 days. In the eye disease stage, acute bilateral uveitis develops. Sensorineural deafness and disequilibrium frequently occur. These symptoms persist for 1 to 2 months and then gradually subside. The main symptoms of the recovery stage are those of the prodrome stage and eye disease stage. Loss of uveal melanocytes results in light red color of the entire fundus oculi.

**Pathogenesis**

Vogt-Koyanagi-Harada disease is thought to be caused by allergy or viral infection. It should be grouped with autoimmune diseases because of the autoimmune reaction against melanocytes. HLA-DR4 is highly associated with the occurrence of Vogt-Koyanagi-Harada disease.

**Diagnosis, Differential diagnosis**

Diagnosis is made by the characteristic clinical features.

**Treatment**

The main treatment is systemic steroids. Steroid pulse therapies (1,000 mg methylprednisolone administered intravenously for 3 consecutive days) and immunosuppressants (e.g., cyclosporine) are also used for eye involvement. Steroids and PUVA therapies are applied to the cutaneous lesions.

### 6. Senile leukoderma

Sharply circumscribed, round or irregular-shaped leukoderma of 4 mm to 10 mm in diameter appear diffusely on the trunk and extremities of men and women in their 30s, increasing in number with age. Senile leukoderma is essentially identified with idiopathic guttate hypomelanosis. Pathological findings show a reduction in the number of activated melanocytes and melanosomes and dysfunction in melanocytes and melanosomes from melanocytic senescence.

### 7. Nevus depigmentosus

Nevus depigmentosus is a common nevoid abnormality present in about 1 in 125 neonates. Because of the congenital melanocytic dysfunction in skin, incomplete hypopigmented patches are seen at birth or shortly thereafter (Fig. 16.9). The patches vary in shape and distribution from solitary and irregular to multiple and band-like. Size, distribution and number of nevus depigmentosus patches remain the same over the course of a lifetime.

### 8. Leukoderma pseudosyphiliticum

Leukoderma pseudosyphiliticum most commonly occurs on the lumbar regions and buttocks of men in their 20s and 30s.
whose skin is naturally dark, in Asians in particular. Multiple, sharply circumscribed, incomplete hypopigmented patches of 1 cm to 2 cm in diameter occur, often coalescing to become reticu-
lar. It is asymptomatic. The reticular leukoderma resembles syphilitic leukoderma; nevertheless, the two can be differentiat-
ed: Syphilitic leukoderma tends to occur on exposed sites, and the standard serologic test for syphilis is positive.

B. Disorders of hyperpigmentation

1. Ephelides

**Clinical features**

Multiple round smooth-surfaced brown patches about 3 mm in diameter occur on the sun-exposed areas of the face, neck and forearms (Fig. 16.10). Ephelides darkens with sun exposure (especially exposure to UVR) in summer and tends to fade in winter. It worsens with age and is most remarkable at puberty; it lightens thereafter.

**Pathogenesis, Pathology**

Ephelides tends to run in families; it is thought to be autosomal dominant. However, it can be autosomal recessive in severe cases. Melanocytes are activated by hereditary factors, and melanosomes markedly increase in the basal keratinocytes. Melanocytes in patients with ephelides have well-developed dendritic spines and enhanced functions; however, the number of melanocytes does not change.

**Diagnosis, Treatment**

Differentiation from lentigo, Peutz-Jeghers syndrome, xeroderma pigmentosum, and progeria is necessary. Sunscreen is useful for blocking UVR.

2. Melasma

**Synonym:** Chloasma

**Clinical features**

Melasma tends to occur in women in their 30s or older. It is rare in men. Sharply demarcated light brown patches occur on the face (forehead, cheeks, and around the mouth, in particular), usually symmetrically. Melasma patches are irregular in size and shape. The disorder is aggravated by UVR in summer, and it subsides in winter (Fig. 16.11). Pregnancy may trigger the onset (chloasma gravidarum).