Genetic disorders of pigmentation

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Abstract

More than 127 loci are actually known to affect pigmentation in mouse when they are mutated. From embryogenesis to transfer of melanin to the keratinocytes or melanocytes survival, any defect is able to alter the pigmentation process. Many gene mutations are now described, but the function of their product protein and their implication in melanogenesis are only partially understood. Each genetic pigmentation disorder brings new clues in the understanding of the pigmentation process. According to the main genodermatoses known to induce hypo- or hyperpigmentation, we emphasize in this review the last advances in the understanding of the physiopathology of these diseases and try to connect, when possible, the mutation to the clinical phenotype.

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Introduction

The color of skin, hair, and eyes comes from the production, transport, and distribution of an essential pigment, the melanin. The melanin is synthesized by melanocytes that are specialized dendritic cells originating from the neural crest. The melanocytes are located in the epidermis and in the hair bulb, but also within some sensorial organs (choroids-iris stroma, inner ear) and central nervous system (leptomeninx). The melanin is produced within specialized organelles that shared characteristics with lysosomes, called melanosomes. The melanosomal enzyme tyrosinase has an essential role in melanogenesis. Its defect is involved in one of the first recognized genetic disease, the oculocutaneous albinism. Any defect occurring from the melanocyte development to the final transfer of the melanin to the keratinocytes, however, is able to induce pigmentary troubles.

Hypomelanosis

Genetic defects leading to hypomelanosis can be categorized in 6 groups: First, defects of embryological development of the melanocytes. Second, defects of melanogenesis. Third, defects of biogenesis of melanosomes. Fourth, defects of melanosome transport. Fifth, defects of survival of melanocytes. Sixth, other pigmentary troubles that genetic abnormalities are still not elucidated.

Hypomelanosis related to a defect of embryological development of melanocytes

Piebaldism

Piebaldism is a very rare autosomal dominant disorder with congenital hypomelanosis. Only melanocytes are involved in piebaldism. Pigmentary disorders are limited to hair and skin without neurological, ocular, or hearing...
defect. The topographical distribution of the lesions spreading to the anterior part of the trunk, abdomen, extremities, and the frontal part of the scalp is characteristic of the disease. The white forelock is the most frequent manifestation (80%-90% of cases). Hairs and subjacent skin are depigmented. Other pigmentary defects are hypo- and hyperpigmentations that give with the adjacent normal skin a “mosaic” pattern. The hypopigmented patches can be isolated (10%-20% of cases). Contrary to vitiligo, these patches are congenital, stable with time, and do not regim. Histopathological examination shows a total absence or almost absence of melanocytes within the bulb hair and epidermis.

Most patients have a loss-of-function and dominant negative mutations of the KIT gene, located on the chromosome 4 (4q12) (Table 1). This gene, human homologous for the murine locus white spotting, encodes for a tyrosine kinase receptor named c-kit. It is expressed on the surface of melanocytes, mast cells, germ cells, and hematopoietic stem cells. The c-kit ligand is the stem cell factor. Stem cell factor is involved in proliferation and survival of melanoblasts. Numerous mutations of the kit gene have been described. They are categorized in 4 phenotypic group of piebaldism with descending order of gravity.9 Interestingly, recent reports of pigmentation disorders occurring after treatment with new tyrosine kinase inhibitors (STI-571 and SU 11428) emphasized the importance of the c-kit/stem cell factor pathway in pigmentation.10-12

### Waardenburg syndrome

Waardenburg syndrome (WS) is a rare disorder associating congenital white patches with sensorineural deafness. According to the clinical manifestations and genetic abnormalities, 4 types are distinguished.

Waardenburg syndrome 1 is an autosomal dominant disorder. Transmission and clinical manifestations are highly variable within a same family. Hair and cutaneous presentation includes the white forelock, which is similar as the one observed in piebaldism and which is the most frequent manifestation (45% of cases). Alopecia and hypopigmented patches are other common manifestations (about one third of cases). Ocular manifestations are mainly represented by a heterochromia irides (about one third of cases) and dystopia canthorum (move of the internal canthus to external without any change of the external canthus), which is the only one constant clinical sign. Facial dysmorphia (mainly broad nasal root and synophrys) are observed in about two third of cases. Finally, deafness is noted in one third to one half of cases. This sensorineural deafness is more or less severe and can involve one or both sides. It is, however, usually stable with time.

Histopathological studies have shown the absence of melanocytes in the inner ear. This absence of melanocytes in the vascular stria of cochlea could explain the deafness. In hypopigmented patches, melanocytes are also absent, whereas in normal pigmented skin, melanocytes are normal or presented short dendrites with abnormal melanosomes.

Waardenburg syndrome 3 is a very rare disorder with autosomal dominant or recessive transmission. Waardenburg’s syndrome 3 presents the same clinical manifestations as WS1, but patients had more severe hypopigmentations and present axial and limb musculoskeletal anomalies.

Waardenburg syndrome 1 and 3 result from loss-of-function mutations of PAX3 gene, located in chromosome 2 (2q35-q37.3). In the mouse, PAX3 mutations result in the splotch phenotype. PAX3 encodes for a transcription factor with 4 functional domains. In patients presenting WS1 and WS3 syndrome, mutations have been described in each of these 4 domains. PAX3 is expressed in the primitive streak and in 2 bands of cells at the lateral extremity of the neural plate. The clinical manifestations observed in WS1 and WS3 can be explained by a deregulation of the genes regulated by PAX3, occurring early in the embryogenesis in the cells originating from the neural crest. It is now demonstrated that PAX3 regulates microphthalmia-associated transcription factor (MITF). Microphthalmia-associated transcription factor activates transcription of melanocyte proteins including tyrosinase and tyrosinase-related protein 1, and thus takes a central role in melanogenesis. Moreover, it has been recently demonstrated that MITF mediates survival of melanocytes via regulation of Bcl2. Defects in regulation of MITF could

### Table 1 Hypomelanosis related to a defect of embryological development of melanocytes

<table>
<thead>
<tr>
<th>Disorder type</th>
<th>Inheritance</th>
<th>Mouse phenotype</th>
<th>Gene (function[s])</th>
<th>Mapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piebaldism</td>
<td>AD</td>
<td>White spotting</td>
<td>KIT (proliferation and survival of melanoblasts)</td>
<td>4q12</td>
</tr>
<tr>
<td>WS1</td>
<td>AD</td>
<td>Sploch</td>
<td>PAX3 (regulates MITF)</td>
<td>2q35-q37.3</td>
</tr>
<tr>
<td>WS2</td>
<td>AD</td>
<td>Microphthalmia</td>
<td>MITF (activates transcription of tyrosinase, mediates survival of melanocytes via regulation of Bcl2)</td>
<td>3p14.1-p12.3</td>
</tr>
<tr>
<td>WS3</td>
<td>AD or AR</td>
<td>Splotch</td>
<td>PAX3 (regulates MITF)</td>
<td>2q35-q37.3</td>
</tr>
<tr>
<td>WS4</td>
<td>AR</td>
<td>Piebald-lethal</td>
<td>EDNRB (embryological development of neurons of ganglions of the gastrointestinal tract and melanocytes)</td>
<td>13q22</td>
</tr>
<tr>
<td>WS3</td>
<td></td>
<td>Lethal spotting</td>
<td>EDN3 (embryological development of neurons of ganglions of the gastrointestinal tract and melanocytes)</td>
<td>20q13.2-q13.3</td>
</tr>
<tr>
<td>WS3</td>
<td></td>
<td>Dom</td>
<td>SOX10 (regulates transcription of MITF and plays a role in the survival of neural crest cells)</td>
<td>22q13</td>
</tr>
</tbody>
</table>

AD indicates autosomal dominant; AR, autosomal recessive.
explain the pigmentary and hearing symptoms observed in WS1 and WS3.

The inheritance of WS2 can be autosomal dominant or less frequently recessive. The clinical manifestations of WS2 are similar to those observed in WS1, except for dystopia canthorum and facial abnormalities that are lacking. Hair and cutaneous pigmentation troubles are less frequent whereas deafness and heterochromia irides are more frequent. All the manifestations observed in patients with WS2 can be explained by a defect of the melanocyte lineage. Thus, the biologic abnormalities responsible for WS2 phenotype should occur after the melanoblasts have been differentiated from the others cells originating from the neural crest.

Waardenburg syndrome 2 is genetically a heterogenic group. Mutations responsible for the WS2 phenotype are numerous and are far to be all characterized. The most frequent mutations affect the MITF gene that is located in chromosome 3 (3p14.1-p12.3). In the mouse, MITF mutations result in the microphthalmia phenotype. Microphthalmia-associated transcription factor encodes for a transcription factor that is essential for melanogenesis and melanocyte survival (see previous sections). Recently, another gene involved in WS2 with autosomal recessive transmission has been discovered. The gene SLUG (8q11) encodes a zinc-finger transcription factor expressed in migratory neural crest cells including melanoblasts.

Waardenburg syndrome 4 is an autosomal recessive disorder presenting with white forelock, isochromia irides, and additional feature of Hirschsprung’s disease (neonatal intestinal obstruction, megacolon). Patients with WS4 usually do not, however, present dystopia canthorum, broad nasal root, white skin patches, or neonatal deafness. This phenotype results from mutations in several different genes. The endothelin-B receptor (EDNRB) gene (mapping in 13q22), the gene for its ligand, the endothelin-3 (EDN3) (mapping in 20q13.2 q13.3), and the SOX10 gene (mapping in 22q13) have been identified. Heterozygous mutations in the EDNRB gene or the EDN3 gene result in Hirschsprung’s disease alone, whereas homozygous mutations result in WS4. Interaction between EDNRB and its ligand EDN3 is essential for the embryological development of neurons of ganglia of the gastrointestinal tract and melanocytes. Because Hirschsprung’s disease is characterized by a congenital absence of intrinsic ganglion cells of the myenteric and submucosal plexi of the gastrointestinal tract, the cutaneous and gastrointestinal clinical manifestations induced by these mutations are explained. Heterozygote mutations of the transcription factor gene SOX10 also lead to WS4. Some patients with SOX10 mutations also exhibit signs of myelination deficiency in the central and peripheral nervous systems. SOX10 encodes a transcription factor that, along with PAX3, regulates transcription of MITF and plays a role in the survival of neural crest cells. This can explain the clinical manifestations similar to other WS syndromes. On the other hand, the Ret protein is expressed during embryogenesis throughout the peripheral nervous system including the enteric nervous system, and the lack of normal SOX10-mediated activation of RET transcription may lead to intestinal aganglionosis (Hirschsprung’s disease clinical symptoms). Moreover, overexpression of genes coding for structural myelin proteins such as P0 due to mutant SOX10 may explain the dysmyelination phenotype observed in the patients with an additional neurological disorder.

**Hypomelanosis related to a defect of melanogenesis**

These disorders involve only the pigmentedary cells (melanocytes and cells of the pigmentary retinal epithelium). Oculocutaneous albinism (OCA) types 1 to 4 and ocular albinism (OA) 1 are concerned (Table 2).

**Oculocutaneous albinism**

Oculocutaneous albinism type 1 is one of the 2 most common OCA. The transmission is autosomal recessive. Oculocutaneous albinism type 1 is characterized by absence of pigment in hair, skin, and eyes. Ocular manifestations (severe nystagmus, photophobia, reduced visual acuity) are often in forefront.

Oculocutaneous albinism type 1 is divided into 2 types: type 1-A, with complete lack of tyrosinase activity because of production of an inactive enzyme, and type 1-B, with reduced activity of tyrosinase. In OCA1-A, there is no activity of tyrosinase. Melanosomes are normally present within melanocytes and well-transferred to the keratinocytes. Only melanosomes in early stages (I or II) are, however, found, without any mature melanosomes (stage III or IV). In OCA1-B, a little level of tyrosinase activity persists. It results a progressive and subtle pigmentation of

### Table 2 Hypomelanosis related to a defect of melanogenesis

<table>
<thead>
<tr>
<th>Disorder type</th>
<th>Inheritance</th>
<th>Mouse phenotype</th>
<th>Gene (function[s])</th>
<th>Mapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCA1</td>
<td>AR</td>
<td>Albino</td>
<td>TYR (encodes tyrosinase)</td>
<td>11q14-q21</td>
</tr>
<tr>
<td>OCA2</td>
<td>AR</td>
<td>Pink-eye dilution</td>
<td>P (modulating the intracellular transport of tyrosinase)</td>
<td>15q11.2-q12</td>
</tr>
<tr>
<td>OCA3</td>
<td>AR</td>
<td>Brown</td>
<td>TYRP1 (encodes a melanogenic enzyme, the DHICA)</td>
<td>9q23</td>
</tr>
<tr>
<td>OCA4</td>
<td>AR</td>
<td>Underwhite</td>
<td>MATP (likely a transporters)</td>
<td>5p</td>
</tr>
<tr>
<td>OA1</td>
<td>XR</td>
<td></td>
<td>OA1 (encodes a melanosomal protein of unknown function)</td>
<td>Xp22.3</td>
</tr>
</tbody>
</table>

DHICA indicates dihydroxyindol carboxylic acid; XR, X-linked recessive.
hair, skin, and nevi. Suntanning remains impossible. Ocular manifestations are present but less severe. The tyrosinase activity is about 5% to 10%. Melanosomes of type 3 are present.

Oculocutaneous albinism type 1 are caused by loss-of-function mutations in the TYR gene (11q14-q21). In mouse, TYR mutations result in the albino phenotype. TYR encodes tyrosinase, an essential enzyme in melanogenesis. Mutations in OCA1-A can occur in all the 4 functional domains of tyrosinase. In OCA1-B, most mutations occur in the third one (involved in bond with the substrate). Contrary to OCA1-A, this kind of mutations induces a major decrease of tyrosine affinity for tyrosinase, but the remaining affinity explains the weak enzymatic activity.

Oculocutaneous albinism type 2 is the most common form of OCA. Transmission is autosomal recessive. During childhood, phenotype is similar to OCA1; however, progressively little amount of pigment is accumulated into skin and eyes (cf Fig. 1). This pigmentation is higher in black people compared with white people. With time, lentigos, pigmented nevi, and freckles can be seen in photo-exposed areas but suntanning is impossible. Ocular manifestations are also less severe, and nystagmus and visual acuity tend to get better with time. No pigment can be observed in hair bulps; however, pigmentation is available after incubation with tyrosine. In melanocytes, melanosomes stage I and II are seen as well as some partially pigmented stage III melanosomes. Melanosomes in stage IV are sometimes observed but remain very rare. The disorder results from a loss-of-function mutation of the P gene (15q11.2-q12). In mouse, P mutations result in pink-eye dilution phenotype. The P gene encodes a melanosomal membrane that may play a major role in modulating the intracellular transport of tyrosinase and a minor role for Tyrp1.

Oculocutaneous albinism type 3 is an autosomal recessive disorder most common seen in African origin people. At birth, skin and hairs are light brown and iris is gray or light brown. With time, hairs and iris can become darker whereas there are few skin color changes. People affected can tan a little. Ocular manifestations are present but are usually less severe. Nystagmus is constant. Tyrosinase measurement is normal. Ultrastructural analysis of melanocytes shows eumelanosomes and pheomelanosomes in all stages. In people of black skin, pheomelanin is, however, normally absent, which explains their dark color of hair and skin. Oculocutaneous albinism type 3 results from loss-of-function mutations of the tyrosinase-related protein 1 (TYRP1) gene (9q23). In mouse, mutation of the TYRP1 gene results in the brown phenotype. TYRP1 encodes a melanogenic enzyme, the dihydroxyindol carboxylic acid oxidase. This enzyme is downstream of tyrosinase in melanogenesis. It is necessary for eumelanin synthesis but not for pheomelanin synthesis. This explains the decrease of eumelanin in patients with OCA3 associated with the abnormal presence of pheomelanin in black subjects.

Oculocutaneous albinism type 4 is a rare and recently described autosomal recessive form of OCA. Phenotype is similar to OCA2. Oculocutaneous albinism type 4 results from mutations in membrane-associated transporter protein (MATP) gene (5p). MATP gene is the human ortholog of underwhite gene in mouse. The encoded protein is predicted to span the membrane of melanosome 12 times and likely functions as a transporter. This similarity with tyrosinase-related protein 1 function probably explains the similar phenotype between these 2 OCA.

Ocular albinism

Ocular albinism 1 is an X-linked recessive disorder and is the most frequent OA. Ocular albinism is a rare form of albinism usually limited to the eyes. In fact, hypopigmentation in the skin is light but real and most easily seen in black people. On the other hand, ocular abnormalities of albinism are present (including photophobia and nystagmus). Ultrastructural analysis shows within normal melanocytes giant melanosomes called “macromelanosomes.” These macromelanosomes are present in skin, iris, and retina. Ultrastructural analysis of the retinal pigment epithelium cells suggested that the giant melanosomes may form by abnormal growth of single melanosomes rather than by the fusion of several organelles. OA1 results from loss-of-function mutations in the OA1 gene (Xp22.3) that encodes a
Hypomelanosis related to a defect of biogenesis of melanosomes

The third group concerns disorders due to a defect in melanosome biogenesis. Phenotypically, extrapigmentary abnormalities are associated with OCA. This can be explained by the involvement of melanosomes but also of the other lysosome-related organelles. Hermansky-Pudlak syndrome types 1 to 7 (HPS1-7) and Chediak-Higashi syndrome (CHS) are part of this group (Table 3).

Hermansky-Pudlak syndrome

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder. Bleeding and lysosomal ceroid storage are associated to partial OCA. The degree of pigmentation depends on people and their ethnic origin, but usually increases with time. Suntanning, however, remains very difficult. Ocular manifestations of albinism, such as nystagmus and reduced visual acuity, are present. Bleeding manifestations (epistaxis, gingival bleeding, bloody diarrhea, petechial purpura, and genital bleeding) are usually not very severe. Visceral involvements are represented by interstitial pulmonary fibrosis, restrictive lung disease, and granulomatous colitis. Renal failure and cardiomyopathy have been also reported.

Hair bulb tyrosinase is present. Ultrastructural studies show macromelanosomes within melanocytes and adjacent keratinocytes. Melanosomes with stages I to III are frequent, but stage IV are rare. Prolonged bleeding time with a normal platelet count is also noted. Electronic microscopy shows the absence of dense bodies in platelets. Lysosomal ceroid storage is observed in visceral involvement. Ceroid substance comes from the degradation of lipids and glycoproteins within lysosomes. The ceroid storage in HPS suggests a defect in mechanisms of elimination of lysosomes.

Hermansky-Pudlak syndrome type 1 is the most common HPS and results from mutations in HPS1 gene (10q23.1). In mouse, HPS1 mutations result in the pale-ear phenotype. Hermansky-Pudlak syndrome types 1 and 4 encode cytosolic proteins that form a lysosomal complex called biogenesis of lysosome-related organelles complex-3 (BLOC3). This complex is involved in the biogenesis of lysosomal-related organelles by a mechanism distinct from that operated by AP3 complex.

Hermansky-Pudlak syndrome type 2 differs from the other forms of HPS in that it includes immunodeficiency in its phenotype. Hermansky-Pudlak syndrome type 2 results from mutations in AP3B1 gene (5q14.1). In mouse, AP3B1 mutations result in the pearl phenotype. AP3B1 encodes the beta-3A subunit of the AP3 complex. AP3 is involved in protein sorting to lysosomes. Moreover, CD1B binds the AP3 adaptor protein complex. The defects in CD1B antigen presentation may account for the recurrent bacterial infections observed in patients with HPS2.

Hermansky-Pudlak syndrome type 3 results from mutations in HPS3 gene (3q24). This type of mutation is more frequent in Puerto Rico. In mouse, HPS3 mutations result in the cocoa phenotype. Hermansky-Pudlak syndrome type 3 encodes a cytoplastic protein of unknown function but which could be involved in early stages of melanosome biogenesis and maturation.

Hermansky-Pudlak syndrome type 4 results from mutations in HPS4 gene (22q11.2-q12.2). In mouse, HPS4 mutations result in the light-ear phenotype. Hermansky-Pudlak syndrome type 4 is involved in the formation of BLOC3 (see HPS1).

Hermansky-Pudlak syndrome type 5 results from mutations in HPS5 gene (11p15-p13) and HPS6 from mutations in HPS6 gene (10q24.32). In mouse, HPS5 mutations result in the ruby eye 2 (ru2) phenotype, whereas HPS6 mutations result in the ruby eye (ru) phenotype. Ru and ru2 proteins are cytosolic proteins that form a lysosomal complex called BLOC2. As for BLOC3, this complex is involved in the biogenesis of lysosomal-related organelles by a mechanism distinct from that operated by AP3 complex (adaptor protein complex 3).

Hermansky-Pudlak syndrome type 7 is caused by mutation in the DTNBP1 gene (6p22.3). In mouse, DTNBP1 mutations result in the sandy phenotype. DTNBP1 encodes dysbindin, a protein that binds to ε- and β-dystrobrevins, components of the dystrophin-associated protein complex in muscle and nonmuscle cells. But
dysbindin is also a component of the BLOC1. This explains why dysbindin is important for normal platelet-dense granule and melanosomes biogenesis and how its mutations lead to the HPS phenotype.53

Chediak-Higashi syndrome

Chediak-Higashi syndrome (CHS) is a very rare autosomal recessive syndrome that associates a partial OCA and an immunodeficiency syndrome. Cutaneous pigmentation is usually not very decreased and hairs are blond or light brown with steel metal highlights. Iris is pigmented and the visual acuity remains normal. Photophobia and nystagmus could be seen. Manifestations of immunodeficiency occur from the first months of life. Recurrent cutaneous and systemic pyogenic infections and severe hemophagocytic lymphoproliferative syndrome caused by uncontrolled T-cell and monocyte migration and chemotaxis are observed. Moreover, neurological abnormalities (mainly cerebellous ones) occur in the patients who reach adulthood.

Chediak-Higashi syndrome is characterized by the presence of giant melanosomes in melanocytes and giant inclusion bodies in most granulated cells. The absence of natural killer cell cytotoxicity and the decrease of neutrophil and monocyte migration and chemotaxis are also noted.

Chediak-Higashi syndrome results from mutations in the CHS1 gene also called LYST (1q42.1-q42.2). In mouse, mutations in the CHS1 gene result in the beige phenotype. Chediak-Higashi syndrome 1 encodes a very large cytoplasmic protein of unknown function. We know, however, that the product of the CHS1 gene is required for sorting endosomal resident proteins into late multivesicular endosomes by a mechanism involving microtubules.54 It has been recently demonstrated that the product of CHS1 gene interacts with proteins important in vesicular transport and signal transduction (the SNARE complex, HRS, 14-3-3, and casein kinase II). On the basis of protein interactions, CHS1 appears to function as an adapter protein that may juxtapose proteins that mediate intracellular membrane fusion reactions.55

Hypomelanosis related to a defect of melanosomes transport

The fourth group involves defects in melanosomes transport. Phenotypically, pigimentary and extrapigimentary manifestations are observed. Griscelli-Prunieras syndromes 1 to 3 (GS1-3) are described (Table 4).

Griscelli-Prunieras syndrome

Griscelli-Prunieras syndrome is a very rare autosomal recessive disorder associating hypopigmentation and neurological (GS1) or immunological (GS2) abnormalities. In GS3, only hypopigmentation is observed. The skin phenotype is common with the 3 types of GS and is characterized by a silvery gray ear and a relative skin hypopigmentation. Ultrastructural analyses show the accumulation of melanosomes in melanocytes.

Besides pigimentary abnormalities, patients with GS1 present neurological defects including developmental delay, hypotonia, and mental retardation. Griscelli-Prunieras syndrome 1 results from mutations in the MYO5A gene (15q21). In mouse, mutations in the MYO5A gene result in the dilute phenotype. MYO5A encodes myosin 5a, a molecular motor that forms with rab27a, and melanophilin, a molecular complex that allows the transport of the melanosomes on the actin fibbers and the docking of the melanosomes at the extremities of the dendrites tips.56

Griscelli-Prunieras syndrome 2 associates hypopigmentation and immunological abnormalities. Severe pyogenic infections with hemophagocytic syndrome are constant. Griscelli-Prunieras syndrome 2 results from mutations in the RAB27A gene (4p13). In mouse, mutations in the RAB27A gene result in the ashen phenotype. RAB27A encodes the rab27a protein, which is a small GTPase that is part of an essential complex for the melanosomes transport (see previous sections).57

Griscelli-Prunieras syndrome 3 expression is restricted to the characteristic hypopigmentation of GS. Griscelli-Prunieras syndrome 3 results from mutation in the MLPH gene (2q37). In mouse, mutations in the MLPH gene result in the leiden phenotype. MLPH encodes melanophilin, the third known protein involved in the molecular complex that allows the transport of the melanosomes on the actin fibbers and the docking of the melanosomes at the extremities of the dendrites tips (see previous sections).58 Moreover, GS3 phenotype can also result from the deletion of the MYO5A F-exon, an exon with a tissue-restricted expression pattern.58

Table 4  Hypomelanosis related to a defect of melanosomes transport

<table>
<thead>
<tr>
<th>Disorder type</th>
<th>Inheritance</th>
<th>Mouse phenotype</th>
<th>Gene (function[s])</th>
<th>Mapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1</td>
<td>AR</td>
<td>Dilute</td>
<td>MYO5A (molecular motor, forms a complex that allows the transport of the melanosomes on the actin fibbers and the docking of the melanosomes at the extremities of the dendrites tips)</td>
<td>15q21</td>
</tr>
<tr>
<td>GS2</td>
<td>AR</td>
<td>Ashen</td>
<td>RAB27A (GTPase, forms a complex that allows the transport of the melanosomes on the actin fibbers and the docking of the melanosomes at the extremities of the dendrites tips)</td>
<td>4p13</td>
</tr>
<tr>
<td>GS3</td>
<td>AR</td>
<td>Leaden</td>
<td>MLPH (forms a complex that allows the transport of the melanosomes on the actin fibbers and the docking of the melanosomes at the extremities of the dendrites tips)</td>
<td>2q37</td>
</tr>
</tbody>
</table>

Deletion of the MYO5A F-exon | 15q21 |
Hypomelanosis related to a defect of survival of melanocytes

Vitiligo

Vitiligo is an acquired cutaneous disorder of pigmentation, with a 1% to 2% incidence worldwide, without predilection for sex or race. The clinical presentation is characterized by well-circumscribed, white cutaneous macules with absence of melanocytes. Strong evidences suggest that vitiligo is an autoimmune disorder, and association with other autoimmune disorders (especially thyroid) is relatively frequent. Familial clustering is not uncommon in a nonmendelian pattern indicative of polygenic multifactorial inheritance.

Several candidate genes have been proposed for vitiligo but none was really convincing. Two large genomewide screens for generalized vitiligo showed significant linkage of an oligogenic autoimmune susceptibility locus, termed AIS1 (1p31.3-p32.2). In an extended study with a cohort of 102 multiplex families, the localization of AIS1 was confirmed and 2 new susceptibility loci have been found. AIS2 is located at 89.4 cM on chromosome 7 and AIS3 at 54.2 cM on chromosome 8. In addition, the locus SLEV1 at 4.3 cM on chromosome 17 was confirmed.

Others hypomelanosis

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a dominantly inherited disease of high penetrance (for more details, see The Phakomatoses by BR Korf). This disease is characterized by the presence of hamartoma, which can affect mainly all the organs. Skin, central nervous system, eyes, heart, and kidney are the most frequently affected. Furthermore, malignant tumors (affecting mainly brain and kidney) and pigmentary disorders can be observed. Hypomelanotic macules are observed in 50% to 100% of the cases. Present at birth or occurring in the first year of life, they are typically described as white ash leaf-shaped macules. Oval or confetti-shaped hypomelanotic macules and white hair are also frequently seen. Hypopigmented iris spots and leaf-shaped lesions of ocular fundus have been also reported. Ultrastructural analyses of hypomelanotic macules show the decrease of the number of melanosomes within melanocytes and keratinocytes. Moreover, the size and the pigmentation of the melanosomes are decreased compared to normal skin, and dendrites are less developed.

Tuberous sclerosis complex results from mutation in the TSC-1 gene (9q34) and TSC-2 gene (16p13.3) encoding for hamartin and tuberin, respectively. The exact function of these proteins is still unknown; however, hamartin and tuberin interact directly with each other, and the complex may function together to regulate specific cellular processes.

Pigmentary mosaicism (hypomelanosis of Ito)

The hypomelanosis of Ito not only can involve the pigmentary system but also the brain, eyes, and bones. The cutaneous manifestations are characterized by unilateral or bilateral macular hypopigmented whorls, streaks, and patches after the Blaschko lines (cf Fig. 2). These hypomelanotic lesions are present at birth or usually appear in the first year of life. Light and electron microscopy shows a fewer melanocytes and melanosomes.

Numerous cellular mosaicisms with various cytogenetic abnormalities have been described. Constitutional autosomal or X-autosome translocations are reported. In fact, hypomelanosis of Ito does not represent a distinct entity but is rather a symptom of many different states of genetic mosaicism. The most common accepted explanation is the presence of 2 cellular clones, in particular, melanocytes. The first clone is normal and the other one could present genetic abnormalities that have occurred in an early stage of the embryological development, before the migration of the melanocytes. The migration of theses 2 cell clones is done on 2 well-defined and distinct ways that explains the Blaschko’s lines. Such a mechanism is also involved in hypermelanotic mosaicism. The linear whorled nevoid hypermelanosis is the phenotypic hyperpigmented counterpart of hypomelanosis of Ito. Chromosomal mosaicism has been already detected in this sporadic condition.

Hypermelanosis

Cafe au lait macules

Cafe au lait macules present as uniformly pigmented macules or patches with sharp margins. Size varies from small confetti macules to large irregular plaques of numerous centimeters. Cafe au lait macules are often present at birth. In normal individuals, only 1 or 2 lesions are usually observed. Light microscopy examination reveals increased epidermal melanin with normal number of melanocytes. Ultrastructural examination shows increased pigment. Giant pigment granules (macromelanosomes) that are a feature of cafe au lait macules of the neurofibromatosis are absent in sporadic cafe au lait macules. Numerous
disorders can be associated with the presence of multiple cafe au lait macules. The most common are neurofibromatosis and McCune-Albright’s syndrome.

Neurofibromatosis

Neurofibromatosis (NF) is an autosomal dominant disorder with a variable expressivity among families (for more details, see The Phakomatoses by BR Korf). It affects approximately 1 in 3000 individuals. Neurofibromatosis is characterized by the presence of more than 6 cafe au lait spots, “freckles” (in real, small-size cafe au lait spots) in the axillary or inguinal regions, neurofibromas, Lisch nodules in the eyes, and bony defects (cf Fig. 3). Other manifestations, including mental retardation, hypertension, pheochromocytoma, renal artery stenosis, meningioma, glioma, acoustic or optic neuromas, and central nervous system tumors could be also observed.

The NF1 gene is mapped in 17q11.2. It encodes for a 327-kDa protein called neurofibromin, which presents homology with members of the GTPase-activating protein superfamily. Neurofibromin may be involved in the negative regulation of the protein product of the protooncogene RAS. This tumor-suppressive activity has been clearly linked to the cancer phenotype. The mechanisms inducing pigmentation troubles in NF is, however, still unknown. It has been suggested that the reduction of the neurofibromin level in the epidermis of NF1 patients could explain the pigmentation abnormalities. One clue is brought by the fact that the neurofibromin level of cultured melanocytes can be regulated by a mechanism independent of NF1 gene transcription and translation, which might influence the degradation rate of the protein. But neurofibromin has also the capacity to regulate several intracellular processes, including ERK (extracellular signal-related kinase), MAP (mitogen-activated kinase) kinase cascade, adenylly cyclase, and cytoskeletal assembly. Interestingly, ERK and cyclic adenosine monophosphate play an essential role in melanogenesis.

Watson syndrome

Pulmonic stenosis, cafe au lait spots, and dull intelligence have been observed by Watson in 15 patients of 3 families. Originally described as a distinct entity, evidences show today that Watson syndrome is allelic to NF1.

McCune-Albright syndrome

The McCune-Albright syndrome is a sporadic disease affecting 3 areas: the skeleton, the skin, and the endocrine system. It is characterized by polyostotic fibrous dysplasia, pigmented lesions, and endocrinologic abnormalities, including precocious puberty, thyrotoxicosis, pituitary gigantism, and Cushing syndrome. The involvement of the skin consists predominantly of large cafe au lait spots with irregular margins as opposed to the more regularly outlined cafe au lait spots of neurofibromatosis. This phenotype is associated with mutations in the GNAS1 gene (20q13.2).

Cafe au lait spots with leukemia or with glioma

Leukemia and cafe au lait spots starting from an early age, but with no other features of NF1, were reported in patients with inherited homoyzogous deficiency of mismatched repair (MMR). Mutation in the MLH1 gene was described in 3 patients and mutation in the MSH2 gene in the fourth one. Defects in the MSH2 gene (2p22-p21) and the MLH1 gene (3p21.3) can account for the vast majority of cases of nonpolyposis colon cancer. DNA MMR genes resemble tumor suppressor genes in that 2 hits are required to cause a phenotypic effect. In these families and the patients themselves, no cancers indicative of hereditary nonpolyposis colorectal cancer was noted. A case of an asymptomatic 4-year-old girl who died unexpectedly of hemorrhage caused by a glioma and was observed to have cafe au lait spots including multiple axillary “freckles” characteristic of NF1 was also reported.

No other abnormalities were found. Both parents had family histories of hereditary nonpolyposis colorectal cancer and were heterozygous for germ line deletions of exon 16 of the MLH1 gene; the girl was homozygous for the deletion. The relation of these mutations and the occurrence of cafe au lait spots is, however, still unknown.

Fig. 3  Cafe au lait spots in the axillary region characterized of neurofibromatosis.
Turcot syndrome

Turcot syndrome is defined by malignant tumors of the central nervous system associated with familial polyposis of the colon. Several cafe au lait spot are described. This disorder is due to mutations in either the adenomatous polyposis coli (APC) gene or in the mismatch repair genes MLH1 or PMS2.

Lentigines

The lentigo simplex is a discrete, 1- to 5-mm, tan, dark brown or black, circular or oval macule that can affect the skin and the mucosa. These lesions may be present at birth but usually develop during childhood. On histological examination, the lentigo simplex displays basal layer melanocytic proliferation in elongated epidermal rete ridges with increased epidermal melanin deposition. Although very common, the lentigines, when they are multiples, may be a marker for the presence of a multisystem disorder.

LEOPARD syndrome

LEOPARD is a rare autosomal dominant disorder with high penetrance and variable expressivity. It is an acronym for the manifestations that may occur: lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness (sensorineural). LEOPARD syndrome can be caused by mutations in the PTPN11 gene (12q24.1) and is therefore allelic to Noonan’s syndrome. Few evidences are reported concerning the pathogenesis of LEOPARD syndrome. Mutations of PTPN11 may perturb the developmental processes (especially neural crest cells).

Lentiginosis with cardiocutaneous myxomas

In most cases, the transmission of lentiginosis with cardiocutaneous myxomas is autosomal dominant with variable expressivity. Multiple and small lentigines are present at birth or develop during early infancy and usually increase in number at puberty. The distribution is diffused with predilection for the face, neck, and upper trunk (cf Fig. 4). Cardiac and subcutaneous myxomas are observed in more than half of the patients. Other manifestations could be observed, including Cushing’s syndrome from nodular adrenocortical dysplasia, hormone-secreting pituitary adenomas, bilateral myxoid mammary fibroadenomas, testicular tumors, and psammomatous melanotic schwannomas.

Lentiginosis with cardiocutaneous myxomas is genetically heterogeneous. One form, called Carney’s complex type 1, is due to mutation in the PRKAR1A gene (17q22-q24). This tumor suppressor gene codes for the type 1 α-regulatory subunit of PKA (protein kinase A) and is found to be mutated in about half of the then known Carney’s complex kindreds. The second locus, at chromosome 2p16, to which most (but not all) of the remaining kindreds mapped, is found to be involved in the molecular pathogenesis of Carney’s complex tumors.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by lentiginosis of the lips, buccal mucosa, and digits and hamartomatous polyps of the gastrointestinal tract. An increased risk of various neoplasms is reported. Peutz-Jeghers syndrome is caused by a mutation in the gene mapped in 19p13.3 and encodes the serine/threonine kinase STK11. STK11 may be a tumor suppressor gene that acts as an early gatekeeper regulating the development of hamartomas that may be pathogenetic precursors of adenocarcinoma. The pathogenesis of the syndrome, especially the occurrence of the melanotic macules, is, however, still poorly understood.

Freckles

Ephelides (freckles) are small tan to dark brown macules localized on sun-exposed skin. They appear early in childhood and are associated with fair skin type and red hair. Light microscopy reveals an increased pigmentation on the basal layer without elongation of the rete ridges. Despite their late appearance, freckles are genetic in their origin. Two types of melanin are present in human skin. The black eumelanin is photoprotective, whereas the red pheomelanin may contribute to the UV-induced skin damage because of its potential to generate free radicals in response to ultraviolet radiation. Individuals with red hair have a predominance of pheomelanin in hair and skin and/or a reduced ability to produce eumelanin, which may explain why they fail to tan and are at risk from ultraviolet radiation. In mammals, the relative proportions of pheomelanin and eumelanin are regulated by melanocyte-stimulating hormone, which acts via its receptor, the melanocortin 1 receptor (MC1R) on melanocytes. The MC1R gene is mapped on 16q24.3. MC1R gene sequence is found in variants in more than 80% of individuals with red hair and/or fair skin that tan poorly, but in fewer than 20% of individuals with brown or black hair, and in less than 4% of those who showed a good tanning response. Carriers of 1 or 2 MC1R gene variants had a 3- and 11-fold increased risk of developing freckles, respectively, and nearly all individ-
uals with freckles were carriers of at least 1 MC1R gene variant. MC1R gene variants may be necessary to develop ephelides. Until recently, however, freckles as an independent trait have not been mapped to any chromosome region. A genomewide scan for linkage analysis in a multigeneration Chinese family with freckles has allowed mapping the gene for freckles to chromosome 4q32-q34. The responsible gene is not identified so far.

**Leukomelanoderma**

**Dyschromatosis symmetrica hereditaria**

Dyschromatosis symmetrica hereditaria is a very rare autosomal skin disorder. Some individuals seem to exhibit an autosomal recessive inheritance and some sporadic cases have also been reported. Dyschromatosis symmetrica hereditaria is characterized by the association of hypopigmented and hyperpigmented macules mostly on the back of the hands and feet. On the face, the lesions resemble ephelides and no hypopigmentation appears. The lesions are asymptomatic and only skin is involved. Lesions appear during infancy and early childhood and usually stabilized with age. An increase number of melanosomes in the melanocytes and the keratinocytes is described in hyperpigmented macules, whereas a low density of DOPA (dihydroxyphenylalanine)-positive melanocytes is noted in hypopigmented lesions. In some areas, there are no visible melanocytes. The dyschromatosis symmetrica hereditaria locus has recently been mapped to chromosome 1q21.3, and pathogenic mutations were identified in the DSRAD gene encoding double-stranded RNA-specific adenosine deaminase. The pathogenesis of this disorder leading to these characteristic pigmentary troubles is, however, still unknown.

**Conclusions**

There are still many pigmentary disorders for which the genetic background is completely unknown. Even if the mutation is described, the pathogenesis leading from the mutated protein to the clinical phenotype is still not understood. Up to the present time, 127 loci are known to affect pigmentation in mouse when they are mutated. The gene involved is, however, identified in only one third of the cases. It is likely that our knowledge of the genes involved in pigmentary disorders will grow drastically in the near future. The better understanding of the molecular mechanisms responsible for these pigmentary changes will bring us new therapeutic approaches for the pigmentary disorders.

**References**


