Genetics of pigmentary disorders

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ABSTRACT

The molecular bases of various types of congenital pigmentary disorders have been clarified in the past ten years, as follows. (1) Disorders of melanoblast migration from the neural crest into the skin in embryo (and their disease genes), piebaldism (c-kit); Waardenburg Syndrome (WS) 1 and 3(*PAX3*); WS2(*MITF*); WS4(*SOX10; END3 / ENDRB*); dyschromatosis hereditaria symmetrica (*DSRAD*). (2) Disorders of melanosome formation in the melanocyte (and their disease gene), Hermanshy-Pudlak Syndrome (HPS)1(*HPS1*); HPS2(*ADTB3A*); HPS3(*HPS3*); HPS4(*HPS4*); HPS5(*HPS5*); HPS6(*HPS6*); Chediak-Higashi Syndrome 1 (*CHS1*). (3) Disorders of melanin synthesis in the melanosome (and their disease genes), oculocutaneous albinism(OCA)1 (*TYR*); OCA2 (*P*); OCA3 (*TRP1*); OCA4 (*MATP*). (4) Disorders of mature melanosome transfer to the tips of dendrites (and their disease genes), Griscelli syndrome (GS)1 (*MYO5A*); GS2(*RAB27A*). These disorders are explained phenotypically and discussed pathogenetically.

Key words: albinism, Chediak-Higashi syndrome, dyschromatosis, Griscelli syndrome, Hermansky-Pudlak syndrome, piebaldism, Waardenburg syndrome,

Introduction

Melanin is synthesized in the specialized organella known as melanosomes in melanocytes located in the basal layer of the epidermis and in the hairbulb. Mature melanosomes are transferred after their synthesis in the perikaryon of the melanocyte to the tips of its dendrites, and are released directly into keratinocytes. Congeital pigmentary disorders are due to various gene mutations that cause a disruption in melanogenesis, in other words, melanosome formation and its transfer in the melanocyte as well as melanocyte misdevelopment.

In 1989, we reported for the first time a pathological mutation of the tyrosinase gene of a patient with oculocutaneous albinism (OCA) (Tomita et al., 1989). Since then, various responsible genes of congenital pigmentary diseases have been reported, as shown in Table 1. In this review, pifmentary disorders are categorized as follows, (1) disorders of melanoblast migration from the neural crest into the skin in embryo (Fig.1), (2) disorders of the melanosome formation in the melanocyte (Fig.3), (3) disorders of the melanin synthesis in the melanosome (Fig.3), (4) disorders of mature melanosme transferring to the tips of the dendrites (Fig.4).

1. Disorders of melanoblast migration from the neural crest

(1) Piebaldism

Piebaldism is an autosomal dominant disease showing white patches on the midforehead, chest, abdomen, and extremities in which on melanocytes are found. In 1991, Giebel & Spritz, and Fleishman et al. clarified the responsible gene mutations in the *KIT* encoding a plasma membrane receptor for the stem-cell growth factor involving melanoblast proliferation and migration (Fig. 1). The reduction in receptors impairs the survival and migration of the neural crest-derived melanoblasts, resulting in a failure of their colonization at anatomic sites most distant from the neural crest. These involved areas are assumed to be at the low end of a gradient for the ligand of the c-kit receptor.

The steel mouse lacks steel factor, the ligand for kit, in other words, the stem-cell growth factor. Therefore, the phenotype of the steel mouse is similar to that of piebaldism, but no piebald patient with a defect of the stem-cell growth factor has been found yet.

(2) Waadenburg syndrome

Waardenburg Syndrome (WS) is an autosomal-dominant genetic disease characterized by piebaldism the same as that induced by the *c-KIT* defect, bicolored irides and sensorineural deafness. It is commonly classified into four clinical types defined by the presence of additional symptoms(s) as shown in Table 2.

Type 1 and 3 patients have a mutation of the *PAX3* transcription factor gene (Tassabehji et al., 1992; Baldwin et al., 1992) and type 2 is due to a gene mutation lf micropthalmia associated transcription factor (*MITF*) (Tassabehji et at., 1994; Tachibana et al., 1994). Type IV patients have a heterozygous gene mutation of the *SOX10* or homozygous mutations either in the Endothelin-3 (*EDN3*) or in the Endothelin B receptor (*EDNR3*) (Puffenberger et at., 1994; Mccallion & Chakravarti 2001).

Ther are epistatic relationships between *SOX10 / PAX3* and *MITF*, and between *MITF* and *c-KIT*. As shown in Fig.2, the transcription factor SOX10 / PAX3 binds to the promoter of *MITF* gene to express the MITF (Tachibana et al. 1999) which stimulates the expression of *c-KIT*. Alternatively, a defect of any one of these three transcription factors can reduce the c-KIT production, which consequently induces piebaldism.

(3) Dyschromatosis hereditaria symmetrica

Dyschromatosis symmetrica hereditaria (DSH) (also called acropigmentation symmetrica of Dohi) is an autosomal dominant disease and is characterized by a mixture of hypo- and hyperpigmented macules of various sizes on the backs of the hands and feet. This disease was first described by the Japanese dermatologist Toyama in 1910 and since then many patients have been reported not only in Japan but also from every ethnic group all over the world. Recently, we have performed a genomewide search in three families with DSH, and have determined that double-stranded RNA-specific adenosine deaminase (DSRAD), one of the RNA-editing enzymes, is th disease gene (Miyamura et al., 2003).

The reason why a low activity of DSRAD induces the peculiar skin lesions localized specifically on the dorsum of hands and feet is unknown at present. We speculate that, when melanoblasts migrate from the neural crest to the skin during development, a greater reduction in DSRAD activity might occur at anatomic sites most distant from the neural crest.

2. Disorders of melanosome formation in the melanosome

(1) Hermansky-Pudlak syndrome

Hermansky-Pudlak syndrome (HPS), inherited as an autosomal recessive trait, is clinically characterzed by a triad of features: 1) oculocutaneous albinism (OCA), 2) mild to severe bleeding diathesis, and 3) ceroid storage disease. These manifestations result from an abnormal formation of intracellular vesicles, i.e. a dysfunction of melanosomes results in OCA, and the absence of platelet dense bodies causes the bleeding diathesis. As shown in Table 3, seven responsible genes for HPS are clarified at present (Oh et al., 1996; Dell'Angelica et al., 1999; Anikster et al., 2000; Suzuki et al., 2002; Zhang et al., 2003; Li et al., 2003), and their respective proteins contribute to the biogenesis of membrane organella such as melanosomes (Fig. 3) and lysosomes. For examples, HPS2 gene, ADTB3A, encodes the beta3A subunit of AP-3. Adaptor complexes (AP) play a role in the formation of coated vesicles as well as in the selection of cargo for these vesicles.

There exist 16 mouse models of HPS in which homologs of human 7 types of HPS are included (Huizing et al., 2002; Li et al., 2003). Therefore, many other genetic types of HPS will likely be reported in the near future.

(2) Chediak-Higashi syndrome

Chediak-Higashi Syndrome (CHS) is an autosomal recessive disorder characterized by severe immune deficiency, OCA, bleeding tendencies, recurrent

pyogenic infection, progressive neurologic defects and a lymphoproliferative syndrome. OCA observed in patients with CHS is distinct from that with HPS, that is, OCA patients have dilute pigmentation and the hair is often silvery or steely gray.

The human causative gene, *CHS1 / LYST*, has been reported by Nagel et al in 1996 and shown to be homologous to the beige locus in mouse. CHS1 protein is predicted to be a cytosolic protein with a role in vesicle transport (Fig. 3), which is similar to HPS proteins because the presence of giant granules within various vesicles such as lysosomes, melanosomes, cytosolic granules and platelet dense bodies is observed in various cells of CHS patients.

3. Disorders of melanin synthesis in the melanosome,

In this section, Oculocutaneous Albinism (OCA) caused by a disturbance in melanin polymer synthesis in the melanosme is reviewed (Table 4). OCA is an autosomal recessive disorder characterized by hypomelanosis in the whole body including the skin, hair and eyes, accompanied by reduced visual acuity with nystagmus and photophobia. Though HPS, CHS and Griscelli syndrome are usually classified into the OCA group, they are reviewed in the sections describing disorders of melanosome formation and those of mature melanosome transfer in the melanocyte.

(1) OCA1A

In patients with OCA1A (tyrosinase-negative OCA), tyrosinase activity is completely lacking due to the homozygously mutated genes of tyrosinase, and melanin formation never occurs throughout the patient's life, because the first step of melanin synthesis is blocked (Fig. 3). Therefore, its phenotype is completely white hair, pinkish skin and red eyes. Since the first report by Tomita et al. in 1989, more than 90 mutations causing OCA have been reported from various research groups.

(2) OCA1B

A patient with OCA1B (yellow-mutant OCA) completely lacks detectable pigment at birth and is initially indistinguishable from patients with tyrosinase-negative OCA. However, such patients rapidly develop yellow hair pigment in the first few years of life and then continue to slowly accumulate pigment in the hair, eyes, and skin. The patients' tyrosinase activity is greatly decreased but not completely

abolished. A point mutation in the tyrosinase gene causes a small change in the tyrosinase conformation (Giebel et at., 1991) or causes the formation of a new splicing site (Matsunaga et al., 1999), which must be the cause of the great decrease in enzyme activity.

The genotype of a 1B patient is homoalleic for the 1B allele or is heterozygotic for the 1B and 1A alleles.

(3) OCA1TS

Patients with temperature-sensitibe OCA (OCA1TS) have white hair and skin, and blue eyes at birth. At puberty, they develop progressively darker hair in the cooler areas (extremities) but retain white hair in the warmer areas (scalp and axilla) (King et al., 1991). A missense mutation in the tyrosinase gene of such patients introduces one amino acid replacement which causes the enzyme to become temperature dependent, i.e. very low activity at 35℃ and loss of activity above 35℃ (Giebel et al., 1991). The genotype of a 1TS patient is homoalleic for the 1TS allele or heterozygotic for the 1TS and 1A alleles.

(4) OCA2

In 1993, Rinchick et al reported a mutation in the human *P* gene in a case of tyrosinase-positibe OCA, which was later classified as OCA2. At present, more than 40 *P* gene mutations causing OCA2 are known. The phenotypes of OCA2 are various, that is, a patient with complete loss of melanin is indistinguishable from an OCA1A patient and a patient with brown hair resembles an OCA1B one.

The specific function of the P gene product (P protein) in the melanocyte has not been fully clarified. Lee et al. reported in 1995 that the 838 amino acid protein contains 12 transmembrane domains arranged similarly to various transporters and appears to be an integral membrane protein of melanosomes (Fig. 3). Kushimoto et al. proposed in 2003 that both P and MATP protein (the disease-responsible protein for OCA4) seem to function in directing the trafficking of melanosomal proteins (including tyrosinases) to the melanosome.

(5) OCA3

Tyrosinase-related protein 1 (TRP-1) was demonstrated to have DHICA oxidase activity which catalyzes the polymerization of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) (Fig. 3). Boissy et al. described in 1996 that a homozygous mutation for the TRP1 gene of African-American twins was responsible for the decreased

melanogenesis. And Manga et al. clarified in 1997 that Rufous OCA in African blacks is caused by mutations in the TRP1 gene. Rufous OCA is now classified as TRP-1 gene-related OCA or OCA 3. The clinical features of OCA3 are rather mild, judging from the light brown of the patient's skin compared to the dark brown skin of their parents in southern African blacks. The mild phenotype may prevent the detection of OCA3 patients, which is the reason why no OCA3 patients has been reported from other ethnic populations.

TRP-2 protein has dopachrome tautomerase activity (Fig. 3). The gene mutation of human dopachrome tautomerase or *TRP-2* gene-related OCA has not been reported yet. It would be of interest to know the clinical condition induced by a defect of the dopachrome tautomerase activity.

(6) OCA4

OCA4 has been recently classified as a new type. The mouse underwhite (*uw*) gene has been know to cause generalized hypopigmentation. The human homologue of mouse *uw* is membrane-associated transporter protein gene (*MATP*)(Fig 3). Function of MATP in human has not been clarified, but is suspected to be a sucrose transporter or to be similar to the P protein. In 2001, Newton et al reported a homozygous G to A transition in the splice acceptor sequence of exon 2 of *MATP* gene in a Turkish OCA patient, and the *MATP* gene was recognized as the fourth one causing OCA. This type of patient may be rare among Caucasians, since no other patient has been reported since the first case.

We have found 17 Japanese OCA4 patients with seven novel mutations including four missense, two deletion and one insertion mutation(s) (Tomita et al., 2003). According to our survey of Japanese patients, almost one half of OCA patients belongs to OCA1, and the other half is comprised of OCA2 (10%), OCA4 (25%) and unclassified (15%). OCA4 is therefore one of the major types in Japan. The clinical phenotype of Japanese OCA4 is various and similar to that of OCA2.

4. A disorder of mature melanosome transfer in the melanocyte

(1) Griscelli syndrome

Griscelli syndrome (GS), now classified into two types, GS1 and GS2 is caused by mutations in the gene encoding muosin VA (*MTO5A*) (Pastural et al 1997) and RAB27A (Menasche et al 2000), respectively. Both types are characterized by pigmentary dilution of the skin and hair, the presence of large clumps of pigment in the hair shaft, and an accumulation of melanosomes in melanocytes. In addition to

the partial albinism, GS1 develops primary neurologic disease without hemophagocytic of syndrome and GS2, of the other hand, shows manifestations of hemophagocytic syndrome and immune defects with or without neurologic involvement.

MY5A and RAB27A interact between melanosomes and actin filaments, resulting in melanosome transport on the actin filament for docking at the plasma membrane (Fig. 4). Therefore, an impairment of either protein blocks the transport of melanosomes from their early perinuclear maturation stages until their delivery to the surrounding keratinocytes (Westbroek et al., 2001).

Electronic-Database Information

Albinism Database, http://www.cbc.umn.edu/tad/ (for mutations and polymorphisms of tyrosinase gene, TRP1 gene, and MATP gene)

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Table 1. Genetic pigmentary disorders

1	Disorders of melanoblast migration from the neural crest into the skin in embryo
	piebaldism (*c-KIT*)
	Waadenburg Synd. (*PAX3*, *MITF*, *SOX10*, *EDN3*, *EDNRB*)
	Dyschromatosis symmmetrica Hereditaria (*DSRAD*)
2	Disordrs of the melanosome formation in the melanocyte
	Hermnsky-Pudlak Synd. (*HPS1*, *ADTB3A*, *HPS3*, *-4*, *-5, -6, -7*)
	Chediak-Higashi Synd. (*CHS1*)
3	Disorders of the melanin synthesis in the melanosome
	oculocutaneous albinism (*TYR*, *P*, *TRP1*, *MATP*)
4	Disorders of mature melanosome transferring to the tips of the dendrites
	Griscelli Synd. (*MY5A*, *RAB27A*)

Disease responsible genes are in paretheses.

Table 2. Types of Waadenburg syndrome

Type	Responsible Gene	Hereditary	Additional Symptom(s)
I	*PAX*	AD	dystonia
II	*MITF*	AD	(−)
III	*PAX3*	AD	dystopia canthorum limb abnormalities
IV＊	*SOX10*	AD	aganglionic megacolon
	EDN3 / EDNRB	AR	

All types have piebaldism, bicolored irides and deafness.

AD, autosomal dominant;　AR, autosomal recessive.

＊　Shah-Waadenburg Synd. / Hirschsprung disease Type II

Table 3. Types of Hermansky-Pudlak syndrome

Type	Responsible genes	Symptoms			
	Human (Mouse)	OCA	Bleeding Disorder	Pulmonary fibrosis	Colitis
HPS1	*HPS1* (*ep*)	+++	+++	+++	++
HPS2	*ADTB3A* (*pe*)	++	+	?	?
HPS3	*HPS3* (*coa*)	+	+	+/ -	++
HPS4	*HPS4* (*le*)	+++	+++	+++	++
HPS5	*HPS5* (*ru2*)	+	++	?	?
HPS6	*HPS6* (*ru*)	++	++	-	-
HPS7	*HPS7* (*sdy*)	+++	+++	-	?

-, absence; +, mild; ++, moderate; +++, severe; ?,unknown.

Table 4. Types of Oculocutaneous Albinism

Type	Responsble Gene	hair color at birth
OCA1	*TYR*	
OCA1A		white
OCA1B		white, blond, light brown
OCATS		light brown, brown
OCA2	*P*	white, blond, light brown
OCA3	*TRP1*	light brown
OCA4	*MATP*	white, blond, light brown

Table 5. Types of Griscelli syndrome

Type	Responsible Gene	Additional Symptoms
GS1	*MY5A*	neurologic involvement
GS2	*RAB27A*	immune defects, hemophagocytic syndrome

All types have pigmentary dilution of the skin and hair.

Legends

Figure 1. Differentiation and migration of melanocytes from the neural crest.

During the embryonic period, melanobalsts migrate from the neural crest, differnenciating to melanocytes After reaching the dermis, they migrate into the epidermis and hair bulb.

Figure 2. A cascade of genes and their products related to Waardenburg syndrome.

Transcription factors of PAX3 and SOX10 epistatically upregulate a gene expression of a transcription factor of MITF which stimulate the synthesis of c-KIT as well as tyrosinase and TRP-1. Conversely, c-Kit involves activation of MITF.

Figure 3. Melanin synthesis in the melanosome

Melanosmal proteins are transported by specialized sorting vesicles through endosomes or directly tp melanosomes. HPS and CHS proteins are components of the vesicles. Melanin is formed from tyrosine by enzymes of tyrosinase, tyrosinase-related protein 2 (TRP-2)/dopachrome tautomerase (Dct) and TRP1/DHICA oxidase in the melanosme. P protein and membrane-associated transporter protein (MATP) are suspected to be a cationic-ion and sucrose transporters, respectively. Tyrosinase, P protein, TRP1 and MATP are responsible proteins for OCA 1, 2, 3, and 4, respectively.

Figure 4. Melanosome transfer in melanocyte

Mature melanosomes around the nucleus are transported on the actin filaments to the peripheral tips of the dendrites and are delivered to the surrounding keratinocytes. RAB27A localized on the melanosome (gray part in the figure) binds to MYO5A, a vehicle for the melanosome. MYO5A has molecular motors i.e. ATPases moving along the actin filament of the cytoskeleton.