Monogenic Pigmentary Skin Disorders: Genetics and Pathophysiology

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Key words: pigmentation, melanin, keratinocytes, skin, genetics

Abstract

For centuries skin pigmentation has played a major societal role, and genetic disorders of skin pigmentation have always evoked the curiosity of both laypersons and physicians. Normal skin pigmentation is a complex process that begins with the synthesis of melanin within the melanocytes, followed by its transfer to neighboring keratinocytes where it is translocated to the upper pole of the nucleus and degraded as the keratinocyte undergoes terminal differentiation. Mutations in various genes involved in melanocyte migration during embryogenesis, melanin synthesis and melanosomal function and transfer have been shown to cause pigmentation disorders. In the present review, we discuss normal skin pigmentation and the genetic underpinning of selected disorders of hypo- and hyperpigmentation.

IMAJ 2008;10:713–717

Variation in skin pigmentation is one of the most striking human characteristics. Differences in skin color have important evolutionary and physiological implications, especially for unclothed humans [1]. There is a close association between skin pigment level and ethnic origin, with populations living in regions of lower latitude and exposed to higher ultraviolet radiation level having higher pigment content that protects the skin from UV-induced skin damage. Human populations living in areas in which UV exposure is limited in duration and intensity adapted with lesser pigmentation, thereby facilitating UV-induced cutaneous production of vitamin D_3 [2].

Differences in skin and hair color worldwide are principally the result of differences in the melanin content of skin [3]. Melanin refers to a complex quinone/indole-quinone-derived mixture of biopolymers produced in melanocytes [4], which are dendritic neural crest-derived cells that migrate into the epidermis in the first trimester of gestation. Melanin production within the melanocyte takes place in lysosomal-like granules called melanosomes. There are two main types of melanin – red/yellow pheomelanin and brown/black eumelanin. Pigmentation differences arise from variation in the number, size, composition and distribution of melanosomes [5]. Melanins are the end products of a complex multi-step transformation process of tyrosine. The rate-limiting enzyme in melanogenesis is tyrosinase, the enzyme responsible for the hydroxylation of tyrosine to DOPA (3,4,dihydroxyphenylalanine). Following maturation in the melanocytes, the melanosomes are transported along dendrites toward neighboring keratinocytes [6]. Cytoskeletal elements play a significant role in facilitating movement of melanosomes down the melanocytes' dendrites. Melanosomes are initially at the dendrite tips after which they are captured by the keratinocytes. Retention of melanosomes at the dendrite periphery results from the combined action of at least three proteins – the motor protein myosin Va, Rab27a, a member of the Rab GTPases family of proteins, and melanophilin [7-9].

The next step involves the extrusion of the melanosomes and their incorporation in the neighboring keratinocytes. This transfer process is not fully understood but apparently involves the phagocytosis of released melanosomes by keratinocytes [10]. An important regulator of melanosome transfer is the protease-activated receptor-2 that is present on keratinocytes' membrane. Activation of PAR-2 results in increased phagocytic activity of cultured keratinocytes toward isolated melanosomes [11].

Normal skin pigmentation is a complex, multistep process

After being transferred to keratinocytes, melanosomes are translocated to the apical pole of the keratinocyte where they can absorb UV light and protect the nucleus from mutagenic damage. The trafficking of melanosomes in the keratinocytes is mediated by microtubule-associated motor proteins such as dynein [12] and, as demonstrated recently, cytoskeletal elements such as keratin and keratin-interacting proteins [13]. As the keratinocyte undergoes terminal differentiation, the recipient melanosomes are degraded so that no melanosomes are visible in the very upper part of the epidermis. The hydrolytic processes utilized by

UV = ultraviolet

PAR-2 = protease-activated receptor-2

Table 1. Pigmentary disorders of the skin

Hypopigmentary skin disorders	Inheritance	Gene	Locus
Piebaldism (MIM#164920)	AD	KIT	4q11-12
Waardenburg syndrome			
WS1 (MIM#193500)	AD	PAX3	2q35
WS2 (MIM#193510)	AD	MITF	3p14.2-p14.1
(MIM#602150)	AR	SNAI2	8q11
WS3 (MIM#148820)	AD,AR	PAX3	2q35
WS4 (MIM#277580)	AD	EDN3	20q13.2-q13.3
(MIM#131244)	AD	EDNRB	13q22
(MIM#602229)	AD	SOX10	22q13.1
Oculocutaneous albinism			
OCA1 (MIM#203100)	AR	TYR	11q14-q21
OCA2 (MIM#203200)	AR	OCA2	15q11.2-q12
OCA3 (MIM#203290)	AR	TYRP1	9p23
OCA4 (MIM#606574)	AR	SLC45A2	5p13.3
OA1 (MIM#300500)	XLR	GPR143	Xp22.3
Hermansky-Pudlak syndrome			
HPS1 (MIM#203300)	AR	HPS1	10q23.1-q23.
HPS2 (MIM#608233)	AR	AP3B1	5q14.1
HPS3 (MIM#203300)	AR	HPS3	3q24
HPS4 (MIM#203300)	AR	HPS4	22cen-q12.3
HPS5 (MIM#203300)	AR	HPS5	11p14
HPS6 (MIM#203300)	AR	HPS6	10q24.32
HPS7 (MIM#203300)	AR	DTNBP1	6p22.3
HPS8 (MIM#203300)	AR	BLOC1S3	19q13.32
Chediak-Higashi syndrome			
(MIM#214500)	AR	LYST	1q42.1-q42.2
Griscelli syndrome			
GS1 (MIM#214450)	AR	RAB27A	15q15-q21.1
GS2 (MIM#607624)	AR	MYO5A	15q21
GS3 (MIM#609227)	AR	MLPH	2q37.3
Hyperpigmentary skin disorders	**Inheritance**	**Gene**	**Locus**
Neurofibromatosis 1 (MIM#162200)	AD	NF1	17q11.2
McCune Albright syndrome (MIM#174800)	SO	GNAS1	20q13.3
Dyskeratosis congenital (MIM#305000)	XLR	DKC1	Xq28
Dyschromatosis symmetrica hereditaria (MIM#127400)	AD	ADAR	1q21.3
Dyschromatosis universalis hereditaria (MIM#127500)	AD	Unknown	6q24.2-q25.2
Acropigmentatio reticularis (MIM#179850)	AD	Unknown	Unknown
Naegeli-Franceschetti-Jadassohn syndrome (MIM#161000)	AD	KRT14	17q12-q21
Dowling-Degos disease (MIM#179850)	AD	KRT5	12q12-q13

* AR = autosomal recessive, AD = autosomal dominant, XLR = X-linked recessive, SO = somatic mutation

the keratinocytes in order to degrade the dense melanosomes/melanin have not yet been identified.

The genetic basis of variation in skin pigmentation

In recent years extensive work has been done to uncover the genetic basis of common hair, skin and eye variation in pigmentation. One of the major regulators of skin pigmentation is the melanocortin 1 receptor. MC1R is a G-protein coupled receptor, and binding of its agonist causes a cascade that is pivotal for the expression of numerous pigment enzymes [5]. Red hair and pale skin are associated with reduced function of MC1R, through alteration of the eumelanin to pheomelanin ratio [14]. Interestingly, a MC1R variant presumed to alter hair and skin pigmentation has recently been identified in Neanderthal remains, suggesting that reduced pigmentation might have had an evolutionary advantage in Europe [15]. Additionally, a mutation in the β-defensin gene, CBD103, causes a black coat color in domestic dogs as a result of its interaction with MC1R [16]. Another gene affecting pigmentation in humans was identified through the deciphering of the molecular basis of the golden phenotype in zebrafish, which was found to be the consequence of mutations in SLC24A5, encoding a putative cation exchanger involved in melanogenesis [17]. SLC24A5 genetic variants were found to underlie pigmentation diversity in South Asian populations [18].

Genetic mutations affecting pigment-producing cells (melanocytes), the production of melanin, its transfer to keratinocytes and its distribution and degradation therein are associated with hypo- hyperpigmentary disorders

Genetic causes of skin hypopigmentation

Inherited diseases of pigmentation were among the first traits studied in humans. As reviewed above, the skin pigmentation process involves numerous steps that offer many opportunities for genetic disruptions, and indeed, more than 120 loci have been found to affect coat pigmentation in the mouse [19]. Table 1 summarizes the genetic disorders discussed in this review and the corresponding underlying gene defects.

Genetic mutations that cause defective melanoblast migration, proliferation or targeting during embryonic development result in hypopigmentation syndromes. Piebaldism is an example of a defect at this stage of development. Piebaldism is a rare autosomal dominant disorder characterized by patches of white skin and overlying hair with absence of melanocytes in hypopigmented skin areas [Figure 1]. The disease is the consequence of mutations in the KIT gene, which encodes a cell surface receptor tyrosine kinase for stem cell factor, a protein with a critical role for the normal migration of melanoblast during embryogenesis [20]. A single nucleotide polymorphism in the KIT ligand (KITLG) gene was found to be associated with fair vs. brown hair [21]. Waardenburg syndrome is also caused by abnormal melanocyte

MC1R = melanocortin 1 receptor

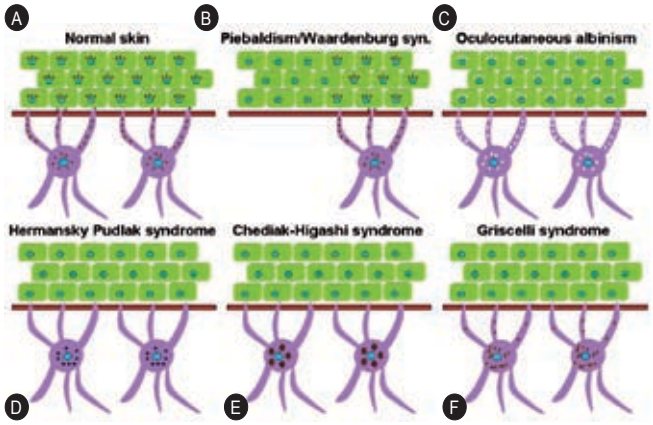

Figure 1. Pathophysiology of inherited disorders of hypopigmentation. In normal skin **[A]** melanosomes are formed within melanocytes and transported through dendrites to neighboring keratinocytes where they form a cap at the upper pole of the nucleus to protect it from the deletrious effects of ultraviolet light. Piebaldism **[B]** is characterized by patches of white skin lacking melanocytes due to impaired melanocyte migration during embryogenesis. Defects in melanin production stand at the basis of oculocutaneous albinism **[C]** demonstrated by the lack of pigment in the vesicles. Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS) and Griscelli syndrome are characterized by dysfunction of lysosomal related organelles. Impaired protein trafficking in melanocytes causes melanosomal dysfunction in HPS **[D]**, while huge intracellular lysosomes are a hallmark of CHS **[E]**. In Griscelli syndrome **[F]** impaired melanosome transport and capture by keratinocytes cause their accumulation in melanocytes.

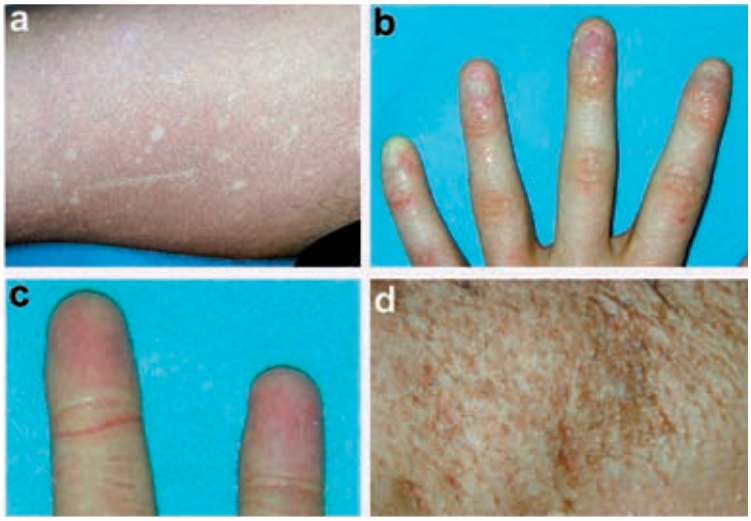

Figure 2. Disorders of hyperpigmentation. **[A]** Reticulate hyperpigmentation and **[B]** nail dystrophy in a patient with dyskeratosis congenita carrying an hemizygous mutation (p.E41K) in DKC; **[C]** absence of fingerprint in a patient with NFJS; **[D]** flexural pigmentation in DDD.

development in the embryo, and presents clinically as congenital white patches associated with sensorineural deafness. There are four subtypes of WS, with WS1 and WS3 featuring facial dysmorphism and WS4 associated with Hirschprung disease [22]. So far, mutations in six different genes have been associated with the four disease types. The WS2 gene is a microphthalmia-associated transcription factor, that mediates melanocyte survival, while the other genes have been shown to regulate MITF expression [23].

Unlike the patchy hypopigmentation typical of piebaldism and WS, mutations affecting melanin production or melanosome maturation and transport usually cause diseases characterized by either globally reduced or absent pigmentation of the skin, hair and eyes, with normal number of melanocytes in the epidermis [Figure 1]. To date there are four known types of oculo-cutaneous albinism that are inherited in an autosomal recessive manner and caused by dysfunction of four different proteins: tyrosinase, P protein, dihydroxyindol carboxylic acid oxidase, and membrane-associated transporter protein [24]; one type of ocular albinism is inherited as an X-linked recessive trait [24]. OCA1 results from loss of function mutations in the TYR gene, encoding tyrosinase, the rate-limiting enzyme in melanin production. The other disease-causing genes have a role in melanin production and the intracellular transport of tyrosinase. Interestingly, it was recently demonstrated that a common polymorphism in the OCA2 gene can explain most human eye color variation [25]. Additionally, polymorphisms in the TYR and MATP genes causing OCA1 and OCA4, respectively, have been associated with variation in skin pigmentation in the South Asian population [18].

Several disorders of pigmentation are associated with impaired biogenesis and maturation of lysosomes as well as melanosomes [Figure 1]. These disorders often present as fatal systemic diseases. Among these are Hermansky-Pudlak syndrome, Chediak-Higashi syndrome and Griscelli syndrome. HPS is a collection of eight autosomal recessive diseases, characterized clinically by diffuse hypopigmentation and platelet storage disease. Intact intracellular protein trafficking system is essential for the function of lysosome-related organelles such as the melanosomes and the platelet-dense granules. Defects in this system form the pathophysiological basis of HPS [26]. In CHS, hypopigmentation is accompanied by severe immunological defects with impaired natural killer cell function, associated lymphoproliferative disorder, bleeding tendencies and peripheral neuropathies [27]. A classic diagnostic feature of CHS is the presence of huge lysosomes and cytoplasmic granules within cells. CHS is caused by mutations in the CH1 gene, an exceedingly large cytoplasmic protein of 430 kDa. Recent studies suggest that the CH1 protein has a role in intracellular vesicle trafficking and fusion [28]. Albinism in Griscelli syndrome is due to an autosomal recessive defect in Rab27a, myosin Va or melanophilin proteins [7-9]. These three proteins are important for the melanosomes' transport along the melanocyte dendrites and their capture by keratinocytes. Consequently, melanosome uptake is impaired in Griscelli

WS = Waardenburg syndrome
MITF = microphthalmia-associated transcription factor
OCA = oculo-cutaneous albinism
MATP = membrane-associated transporter protein
HPS = Hermansky-Pudlak syndrome
CHS = Chediak-Higashi syndrome

syndrome, with concomitant accumulation of melanosomes in melanocytes.

Genetic causes of skin hyperpigmentation

In contrast to genetic disorders that result in hypopigmentation and albinism, considerably less is known about genetic disorders that result in hyperpigmentation. Café-au-lait macules are pigmented skin lesions of varying sizes, characterized by normal numbers of melanocytes and increased melanin content in the epidermis. Numerous genetic disorders such as neurofibromatosis and McCune-Albright syndrome [29] have been associated with café-au-lait macules. A full review of this topic, however, is beyond the scope of this article. For a detailed discussion, refer to Passeron et al. [29].

The study of rare inherited single-gene disorders represents a powerful investigative tool for the delineation of novel biological functions in humans

Reticulate pigmentary disorders are a group of relatively uncommon disorders with various modes of inheritance characterized by a reticulate pattern of cutaneous hyperpigmentation. The prototype for such disorders is dyskeratosis congenita, which is characterized by reticular skin pigmentation, nail dystrophy, mucosal leukoplakia and progressive bone marrow dysplasia [30]. DKC is a genetically heterogeneous disease, although many cases are the result of X-linked mutations in DKC1, encoding dyskerin, a protein involved in ribosomal RNA processing and formation of the telomerase complex [31]. The pathophysiology of hyperpigmentation in DKC remains to be established [Figure 2A and B).

Dyschromatosis symmetrica hereditaria, also known as reticulate acropigmentation of Dohi, is characterized by small hyperpigmented and hypopigmented macules on the back of the hands and feet. The disease has a dominant pattern of inheritance, and is due to mutations causing haplo-insuficiency in the adenosine deaminase RNA-specific (ADAR) gene [32,33]. It has been postulated that impaired RNA editing during melanoblast migration causes their differentiation into hyper- and hypoactive melanocytes. Thus, the most affected melanocytes are those that migrate farthest, to the hands and feet [33]. Two other diseases that show some phenotypic similarity to dyschromatosis symmetrica hereditaria are dyschromatosis universalis hereditaria and acropigmentatio reticularis, also known as reticulate acropigmentation of Kitamura. In DUH the hypo- and hyperpigmented macules occur all over the body, and in reticulate acropigmentation of Kitamura the hypopigmented macules are absent and patients present with "pits" on their palms [34]. However, two diseases are not associated with mutations in ADAR in these, and their genetic basis remains to be identified [34].

Naegeli-Franceschetti-Jadassohn syndrome and dermatopathia pigmentosa reticularis are two closely related autosomal dominant ectodermal dysplasia syndromes that clinically share complete absence of dermatoglyphics (fingerprint lines) [Figure 2c], a reticulate pattern of skin hyperpigmentation, thickening of the palms and soles (palmoplantar keratoderma), abnormal sweating, and other subtle developmental anomalies of the teeth, hair and skin. Recently, these two syndromes were shown to be the result of mutations affecting the region of the KRT14 gene encoding the non-helical head domain of keratin 14 [35]. These mutations were found to result in haplo-insufficiency and to be associated with increased susceptibility of keratinocytes to pro-apoptotic stimuli [36]. Interestingly, mutations involving the central α-helical domain of keratin 14 cause a completely different clinical phenotype – EBS [37], which in some cases is also associated with mottled pigmentation [38]. Despite our understanding of the genetic basis of these disorders, the pathophysiology of the hyperpigmentation seen in epidermolysis bulosa simplex and Naegeli-Franceschetti-Jadassohn syndrome is not yet understood.

Dowling-Degos disease is another autosomal dominant disorder with variable penetrance characterized by the presence of reticulate hyperpigmentation of the flexures [Figure 2d], comedo-like lesions on the neck, and pitted perioral acneiform scars [12]. Onset is usually postpubertal. No abnormalities of hair or nails are seen. It was recently shown that DDD is caused by loss of function mutations affecting the KRT5 gene region encoding the initial part of keratin 5 [12]. Here also, the mutations result in haplo-insufficiency, ensuing in epithelial remodeling, melanosome mis-targeting and altered perinuclear organization of intermediate filaments. The fact that a mutation in KRT5 causes EBS with mottled pigmentation (EBS-MP; MIM131961) suggests that keratin 5 has an important role in melanosome transport [39]. Interestingly, DDD appears to be a genetically heterogeneous disease as a genome-wide linkage analysis in a Chinese family mapped a novel DDD-associated gene to chromosome 17p13.3, suggesting that at least another gene might be associated with the disease [40].

Conclusion

Inherited disorders of skin pigmentation beautifully illustrate how the study of relatively rare clinical entities can be illuminating, leading over the past years from clinical observations to the deciphering of the strikingly intricate machinery orchestrating the pigmentation of our skin. Despite these advances, much remains to be learned. More particularly, although the mechanisms underlying the biosynthesis of melanin are today relatively well established, the transport and degradation of melanosomes within keratinocytes are still poorly understood. The study of monogenic pigmentary disorders is likely to play a key role in the full deciphering of the mechanisms regulating a system that has played a major role in the emergence of life on the surface of the earth.

DKC = dyskeratosis congenita
DUH = dyschromatosis universalis hereditaria
EBS = epidermolysis bulosa simplex
DDD = Dowling-Degos disease

Acknowledgments. We thank Amihai Hershkovitz for his help in figure design and preparation.

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