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The etiology and molecular genetics of human pigmentation disorders

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Abstract

Pigmentation, defined as the placement of pigment in skin, hair, and eyes for coloration, is distinctive because the location, amount, and type of pigmentation provides a visual manifestation of genetic heterogeneity in pathways regulating the pigment-producing cells, melanocytes. The scope of this genetic heterogeneity in humans ranges from normal to pathological pigmentation phenotypes. Clinically normal human pigmentation encompasses a variety of skin and hair color as well as with punctate pigmentation such as melanocytic nevi (moles) or ephelides (freckles), while clinically abnormal human pigmentation exhibits markedly reduced or increased pigment levels, known as hypopigmentation and hyperpigmentation, respectively. Elucidation of the molecular genetics underlying pigmentation has revealed genes important for melanocyte development and function. Furthermore, many pigmentation disorders show additional defects in cells other than melanocytes, and identification of the genetic insults in these disorders has revealed pleiotropic genes, where a single gene is required for various functions, often in different cell types. Thus unravelling the genetics of easily visualized pigmentation disorders has identified molecular similarities between melanocytes and less visible cell types/tissues, revealing a common cellular origin and/or common genetic regulatory pathways. Herein we discuss notable human pigmentation disorders and their associated genetic alterations, focusing on the fact that the developmental genetics of pigmentation abnormalities is instructive for understanding normal pathways governing development and function of melanocytes.

Introduction

Pigmentation has long fascinated the human race, with developmental melanocyte abnormalities reported by ancient Greeks, Romans, and Egyptians.[1] The melanins responsible for mammalian pigmentation include reddish-hued pheomelanin and brown/black-colored eumelanin, and these melanins are produced by melanocytes through a process known as melanogenesis. Melanin provides coloration of hair and skin as well as photoprotection from ultraviolet radiation (UVR), and concordant with these functions, most human melanocytes are located in the epidermis or hair follicles of the skin. The epidermal and follicular melanocyte populations have distinctive anatomical distribution and proliferation. Epidermal melanocytes reside within the basal layer of the epidermis at the junction of the epidermis and dermis; these melanocytes extend dendritic processes that interact with surrounding keratinocytes and function in pigment deposition and cell

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signaling (Fig. 1A). The proliferation/regeneration of epidermal melanocytes has not yet been fully characterized. Follicular melanocytes reside within the hair follicle, and here their proliferation from stem cells and transfer of melanin into hair are synchronized with the hair cycle. Additionally, melanocytes are located within the uvea of the eye, cochlea and vestibular region of the ear, leptomeninges of the brain, and ventricular septum and valves of the heart.

Melanocytes develop from the neural crest (NC), a multipotent vertebrate cell population that emerges along the dorsal surface of the neural folds, undergoes an epithelial to mesenchymal transition, and becomes highly migratory, differentiating into a wide variety of cell types throughout the body.[2] In addition to melanocytes, NC cells give rise to neurons and glia of the peripheral nervous system (PNS), endocrine cells, and cranio-facial structures. NC cells of the trunk migrate along two primary routes: ventromedial, between the neural tube and somites, and dorsolateral, between the epidermis and somites. Embryonic melanocyte precursors, herein termed melanoblasts, are the sole progeny of dorsolaterally migrating NC cells, while ventromedially migrating NC cells give rise to melanoblasts as well as Schwann cells, adrenomedullary cells, and sensory and sympathetic neurons.[3] During later stages of embryonic development, melanoblasts migrate through the dermis into the overlying epidermis, enter into developing hair follicles, undergo extensive proliferation and initiate melanin production.[4,5]

The wide variation in basal human skin color and tanning response results from differences in amount and/or cellular distribution of melanin rather than differing melanocyte numbers.[6] Interestingly, many of the genes implicated in human hypo- and hyperpigmentation disorders also have allelic variants associated with normal phenotypic variation of basal skin color, including tyrosinase (*TYR*), tyrosinase-related protein 1 (*TYRP1*), solute carrier family 45, member 2 (*SLC45A2*), solute carrier family 24, member 5 (*SLC24A5*), solute carrier family 24 (sodium/potassium/calcium exchanger), member 4 (*SLC24A4*), oculocutaneous albinism II (*OCA2*), agouti signaling protein (*ASIP*), KIT ligand (*KITLG*), interferon regulatory factor 4 (*IRF4*), two pore segment channel 2 (*TPCN2*), and melanocortin 1 receptor (*MC1R*).[6] *MC1R* is the best characterized of these genes, and it encodes a cell surface receptor that regulates eumelanin/pheomelanin production by melanocytes. The extensive allelic variance of *MC1R* directly correlates with the presence of various red hair and fair skin phenotypes, and also includes a *MC1R* null allele, demonstrating that absence of function for this important signaling receptor still falls within the normal clinical spectrum.[7,8]

The inherent visibility of pigmentation anomalies has allowed extensive characterization of the causative gene mutations as well as the normal functions of the encoded proteins (Table 1). For example, proteins that catalyze/regulate melanin production are fundamental to all pigment cells, and thus mutations in genes encoding these proteins (*TYR*, *TYRP1*, *OCA2*, *SLC45A2*) globally affect skin, hair, and eyes. In another example, mutation of genes required for melanocyte development—including paired box 3 (*PAX3*), microphthalmia-associated transcription factor (*MITF*), SRY (sex determining region Y)-box 10 (*SOX10*), endothelin receptor type B (*EDNRB*), and endothelin 3 (*EDN3*)—result in patchy hypopigmentation along with deafness, caused by absence of both cutaneous and otic melanocytes necessary for proper ear development and function. Of note, some of these mutations also affect the retinal pigmented epithelium of the eye, a structure composed of melanin-producing cells that are of neuroectodermal rather than NC developmental origin yet exhibit overlapping gene expression with cutaneous melanocytes.[9] In a third example, mutations in genes that regulate development of multiple NC cell types (*SOX10*, *EDNRB/EDN3*) cause coincident developmental defects in melanocytes and neurons/glia of the enteric nervous system. In a fourth example, mutation of genes associated with Hermansky-

Pudlak syndrome or Griscelli syndrome (see Table 1) alter subcellular trafficking of melanosomes (melanin-containing organelles) within melanocytes, as well as storage granules within hematopoietic cells, showing that these two cell types with different developmental origins share genetic pathways that regulate similar subcellular processes.

Human pigmentation disorders can be classified by phenotype, including hypo- or hyperpigmentation, congenital or acquired presentation, effects on melanocyte number (hypo- or hyperplasia), or effects on melanocyte function. However, defining the underlying genetic anomalies explains the etiology of human pigmentation disorders, thus allowing correlation of developmental genetics with clinical phenotypes. The combined description of pigmentation disorders by both phenotype and genetic alteration sheds new light on the molecular pathways regulating human pigmentation. In this review, the current knowledge of human pigmentation abnormalities and their associated genetic defects are described.

CONGENITAL PIGMENTATION ABNORMALITIES: HYPOPIGMENTATION FROM MELANOCYTE HYPOPLASIA

When a genetic insult causes the loss of melanocytes during embryonic/fetal development, congenital disorders of hypopigmentation result. These rare disorders display regions of hypopigmentation caused by a localized reduction in melanocytes (Fig. 1B), often accompanied by deafness caused by loss of cochlear melanocytes. In humans, most of these hypopigmentation disorders display dominant inheritance.

One of the best-characterized congenital hypopigmentation syndromes is Piebaldism, associated with loss of function/deletion mutations in the tyrosine kinase receptor *KIT* or in the transcription factor *SNAI2*. In Piebaldism, sharply demarcated regions of hypopigmented skin and hair occur, most frequently on the head, ventral trunk, and extremities, with a white forelock of hair being a notable phenotype. Often, small macules of hyperpigmentation occur within or at the borders of the hypopigmented regions.

The disorders collectively described as Waardenburg Syndrome (WS) display cutaneous hypopigmentation and ocular pigmentation anomalies paired with congenital hearing loss, as well as additional phenotypes in various cell types. These coincident phenotypes reflect a common NC origin for the affected cell types, along with pleiotropy of the mutated genes. Mutation of *PAX3* in WS1 and WS3 reveals the pleiotropic effects of PAX3 protein on melanocyte and craniofacial/limb development, as these WS forms display the additional phenotypes of dystopia canthorum and upper limb abnormalities. Similarly, SOX10, EDNRB, and EDN3 regulate both melanocyte and enteric ganglia development, and mutations of the genes encoding each of these proteins can cause WS4, which displays the additional phenotype of abnormal enteric ganglia formation known as Hirschsprung disease.

Identification of the heterogeneous genetic defects causing WS has resulted in many examples where distinctive clinical phenotypes of congenital hypopigmentation can be related to each other on a molecular level. For example, Tietz syndrome is associated with mutation of *MITF*, and is thus allelic with WS2 that is caused by mutation of *MITF*, even though Tietz syndrome displays the distinctive phenotypes of extensive hypopigmentation and gradual accrual of pigmentation later in life. A mild form of Yemenite deaf-blind hypopigmentation syndrome (YDBS), characterized by deafness with regional hypo- and hyperpigmentation, is associated with a missense mutation in *SOX10*,[10,11] thus demonstrating that mild YDBS and *SOX10*-associated WS2 are allelic disorders. The syndrome Peripheral demyelinating neuropathy, Central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease (PCWH), which shows neurological phenotypes combined with WS4 phenotypes, also results from deletion/mutation of *SOX10*. Similarly, the descriptively named Albinism, Black lock, Cell migration disorder of the

neurocytes of the gut, and Deafness syndrome (ABCDS) is caused by homozygosity for an *EDNRB* mutation, thus showing allelism between ABCDS and *EDNRB*-associated WS4.

These variable congenital hypopigmentation phenotypes arising from perturbation of the same gene may reflect mutation of different functional domains in the encoded protein. For example, mutations that alter the nuclear localization signal of MITF (missense or in-frame deletion) are associated with the more severe Tietz syndrome, and are suggested to confer a dominant negative phenotype whereby mutant MITF sequesters normal protein in the cytoplasm; conversely, *MITF* null alleles are proposed to lead to haploinsufficiency, thus resulting in the milder phenotypes of WS2.[12,13] Similarly, mutations affecting SOX10 C-terminal domains have been proposed to allow escape from nonsense-mediated decay, creating mutant proteins with dominant negative effects that cause the severe PCWH phenotypes, while N-terminal domain mutations are proposed to result in null alleles associated with the milder WS2 and WS4 phenotypes.[14]

However, functional domains defined by protein secondary structure do not fully correlate with the phenotypic variability associated with mutation of a single pigmentation gene. Exceptions exist to the correlations of SOX10 mutation location with PCWH or WS phenotypes, and recent work on *SOX10* missense mutations suggests SOX10 subcellular localization may be relevant to mutation effects.[15,16]. Also, WS-associated *PAX3* mutations can be categorized into two groups based upon their effect on nuclear localization and mobility, yet these categories show no clear correlation with protein functional domains or DNA binding activity.[17]

CONGENITAL PIGMENTATION ABNORMALITIES: HYPOPIGMENTATION FROM ALTERED MELANOCYTE FUNCTION

Mutation in a gene that regulates melanin production or distribution does not change melanocyte number, but instead causes reduction and/or altered distribution of melanin pigment (Fig. 1C). These mutations lead to rare, recessively inherited hypopigmentation disorders where normal numbers of melanocytes are retained, but show severe defects in the location or amount of melanin. Some of these disorders also show defects attributable to altered distribution/trafficking of cytoplasmic organelles other than melanosomes, thus revealing pleiotropy of the mutated genes.

The best known of these types of hypopigmentation disorders are oculocutaneous albinisms (OCAs), in which defective melanin production causes severe reduction to complete absence of all skin, hair, and eye pigmentation. Additional ocular phenotypes may include nystagmus, reduced visual acuity, and misrouting of optic nerves. The various OCA forms are classified based upon their associated genetic mutations. OCA1A and OCA1B are caused by mutation of the melanogenic enzyme *TYR*, with the A form displaying a complete lack of TYR protein function, and the B form showing reduced function. The essential role of TYR in melanin synthesis explains why OCA1 displays the most severe phenotypes of all OCAs. OCA2 is caused by mutation/deletion of the *OCA2* gene, encoding a membrane protein proposed to transport TYR, with patients retaining some brown pigment. OCA3 is caused by mutation of the gene encoding the melanogenic enzyme TYRP1, with patients showing reddish hair and freckling. OCA4 is caused by mutation in the gene encoding the transporter protein SLC45A2, with patients retaining modest amounts of brown pigment, similar to OCA2.

Hermansky-Pudlak syndrome (HPS) is a genetically heterogeneous disorder (Table 1), in which cutaneous hypopigmentation results from abnormal melanosome formation, movement, or transfer to keratinocytes. Additionally, HPS patients exhibit phenotypes caused by defects in cytoplasmic organelles in other cell types, including platelet-dense

granules, leading to bleeding defects, and lysosomes, leading to phenotypes of pulmonary fibrosis or colitis.[18,19] HPS-associated loci encode components of the BLOC-1, -2, or -3 protein complexes, which regulate organelle movement, or components of the AP1 protein complex, which regulates protein sorting.

A disorder with phenotypic similarity to HPS is Chediak-Higashi syndrome (CHS), where patients exhibit hypopigmentation of hair and eyes, bleeding disorders, susceptibility to infection and, in later disease stages, distinctive lymphoma and neurological defects. CHS is caused by mutation of lysosomal trafficking regulator (*LYST*), and shows subcellular phenotypes of enlarged organelles, including melanosomes (which show clumping in hairs), and giant granules in eosinophils, basophils, and monocytes. A decrease in platelet dense bodies is also present. While the cellular function of LYST protein is unclear, these mutant phenotypes suggest LYST regulates organelle size and/or organelle trafficking.[18]

Another disorder involving hypopigmentation as a result of abnormal melanosome trafficking is Griscelli syndrome (GS). Patients with GS manifest cutaneous hypopigmentation, neurological defects, immunological defects, and overactive histiocytes and lymphocytes. GS has been associated with mutation of 3 genes, myosin VA (*MYO5A*), RAB27A, member RAS oncogene family (*RAB27A*), and melanophilin (*MLPH*), whose protein products direct transport of melanosomes from microtubules to actin at the cell periphery in melanocytes, and also regulate organelle trafficking in immune cells.

CONGENITAL HYPERPIGMENTATION ABNORMALITIES: MELANOCYTIC HYPERPIGMENTATION

Normal human epidermis exhibits an orderly 3-dimensional cellular arrangement (Fig. 1A), in which individual melanocytes are widely spaced apart from one another along the epidermal basal layer. In this arrangement, melanocytes are able to communicate with nearby keratinocytes and likely other cell types as well, including Langerhans cells, fibroblasts, vascular cells, and nerve endings.[20,21] This structural and functional grouping of a single melanocyte with a large number of surrounding keratinocytes has long been appreciated, and is called the epidermal melanin unit (EMU), with the average EMU melanocyte to nucleated keratinocyte ratio maintained at 1:36, regardless of regional variations in melanocyte density.[22] Alteration of the signaling that directs the precise architecture of the EMU can cause regional, benign overgrowth of melanocytes (known as melanocytic hyperpigmentation), resulting in sharply demarcated spots of pigment. The presence of moderate numbers of these hyperpigmented spots at birth or in early childhood is very common, thus obscuring somewhat the boundary between normal and pathological human hyperpigmentation. Nevertheless, abnormal congenital hyperpigmentation is typically defined as presentation of significantly greater amounts of hyperpigmentation than that of the general population at or soon after birth.[23,24] Below, we first introduce various forms of common melanocytic lesions, and then describe notable examples of congenital hyperpigmentation that illustrate phenotype-genotype correlations.

Common forms of melanocytic hyperpigmentation—The most common melanocytic hyperpigmented lesions are: lentigines, dark brown to black, flat hyperpigmented regions 2–20mm in diameter, caused by expansion of the epidermis into elongated rete ridges along with a corresponding increase in melanocytes along the dermal-epidermal border; nevocellular or melanocytic nevi, pigmented spots consisting of benign overgrowth of melanocytes that have lost their dendritic form and are organized in defined nests (Fig. 1D); and dysplastic (atypical, Clark) nevi, pigmented spots distinct from melanocytic nevi by their larger size, irregular border, and variable pigmentation.[25] Clinical distinction of these lesions from other melanocytic proliferations, including melanoma, the

cancerous growth of melanocytes, is difficult and often requires application of specialized technology or histological analysis.[24,26,27] The molecular genetics regulating these various benign melanocyte overgrowths are not well understood, however genetic factors clearly influence their morphology, frequency, and location.[28–32] Furthermore, numerous melanocytic nevi correlates with increased melanoma risk,[33,34] suggesting the genetic alterations that lead to benign melanocytic hyperplasia relate to melanomagenesis.

Congenital forms of melanocytic hyperpigmentation—Congenital melanocytic nevi (CMN) are distinguished from melanocytic nevi by their presence at or soon after birth and their deep histological location, including involvement of vascular and other neighboring areas.[35] CMN are categorized by size, ranging from small (<1cM) to extremely large (>20cM), and their size appears to directly correlate with melanoma risk.[36] Genetic factors that influence CMN are unknown, although heritability has been suggested for large CMN, also known as giant pigmented hairy nevus (GPHN).

Lentigo simplex (LS) is characterized by extensive lentigines in skin, nails, or mucous membranes in newborns or early childhood. The genetics of LS are not well understood, however it appears genetically distinct from melanocytic nevi or solar lentigo (see below).[37] Causative gene mutations for LS have been identified in phenotypically complex disorders, where LS occurs in combination with other abnormalities of NC-derived tissues, such as LEOPARD syndrome (multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness). Mutations in the RAS/MAPK signal transduction pathway genes protein tyrosine phosphatase, non-receptor type 11 (*PTPN11*), v-raf-1 murine leukemia viral oncogene homolog 1 (*RAF1*), and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) are associated with LEOPARD syndrome; however, mutations in these three genes are also associated with Noonan syndrome, a phenotypically variable disorder characterized primarily by craniofacial and cardiac anomalies with infrequent hyperpigmentation. [38–41] In Leopard syndrome, LS is often preceded by café-au-lait spots, light brown, ovoid, hyperpigmented spots <1cm–30 cm in diameter that typically retain normal melanocyte number rather than being melanocytic; in Noonan syndrome, café-au-lait spots are the most common form of hyperpigmentation. The molecular genetics underlying these phenotypic differences in melanocytes (and other tissues) remains unclear, however recent biochemical studies have begun to associate mutations in distinct protein domains of PTPN11 with various phenotypes.[42–44] In another disorder, dyschromatosis symmetrica hereditaria, patchy hyper- and hypopigmentation (including lentigines) on dorsal extremities is caused by mutation of the adenosine deaminase, RNA specific (*ADAR*) gene; how mutation of this ubiquitous protein, which contributes to RNA editing, leads to coincident yet opposite pigmentation anomalies remains to be determined.

Melanocytic hyperpigmentation that occurs in the dermis rather than the epidermis is known as dermal melanocytosis (Fig. 1E). These lesions are distinctive from other melanocytic growths because their melanocytes typically retain their dendritic morphology, and their deeper, dermal location causes differential light scattering and absorption by melanin pigments, generating a characteristic blue-gray tint. [45] Dermal melanocytoses that can be considered congenital include nevus of Ito (localized on the neck/shoulders), nevus of Ota (localized on the face), and Mongolian spots. Mongolian spots are present at birth on the dorsal surface, most commonly in sacral/gluteal areas,[46] then regress in childhood, suggesting they may arise from a transient overgrowth and/or retention of melanocytes in the dermis during development. Although little is known about the molecular genetics of these congenital dermal melanocytoses, potential genetic influences on Mongolian spots are suggested by their familial inheritance and their prevalence in populations of Asian or

African descent. Additionally, the cranial nerve locations of nevus of Ota and nevus of Ito suggest they could originate from nerve-associated, medioventral pathway melanoblasts.[3]

Melanocytic hyperpigmentation is reminiscent of tumorigenic cell growth, and several disorders exist that display melanocyte overgrowth along with tumors of other cell types. These autosomal dominant disorders begin to show abnormal phenotypes during juvenile development, and are all caused by mutation of signaling pathway genes. They include: gastrointestinal stromal tumors paired with dysplastic nevi and lentigines (GIST), associated with activating mutations in the gene encoding the receptor tyrosine kinase KIT;[47,48] Peutz-Jeghers syndrome, where hyperpigmented spots on lips, oral mucosa, and fingers occur along with gastrointestinal polyps and additional tumor susceptibility, associated with mutation of the gene encoding the serine/threonine kinase STK11; Carney Complex, exhibiting mucosal membrane lentigines (and additional pigmentatary abnormalities) along with cardiac, endocrine, cutaneous, and neural myxomatous tumors, caused by mutation in the protein kinase A regulatory subunit-1-alpha gene (*PRKAR1A*);[49] and neurofibromatosis (NF), where benign and malignant tumor growth arises in conjunction with axial freckling and melanocytic café-au-lait spots, most commonly associated with mutation of the gene neurofibromin (*NF1*), whose protein product regulates RAS signaling. NF1 mutations are also associated with neurofibromatosis-Noonan syndrome, a syndrome exhibiting a unique combination of NF phenotypes along with defects of other NC-derived tissues (craniofacial and cardiac), short stature and motor delay.

CONGENITAL HYPERPIGMENTATION ABNORMALITIES: MELANOTIC HYPERPIGMENTATION

Congenital hyperpigmentation abnormalities that increase melanin levels without increasing melanocyte number (known as melanotic hyperpigmentation) reflect an alteration in the signalling cascades that regulate melanogenesis. These can present with pigmentation phenotypes alone, without affecting any other organ system. Of note, common café-au-lait spots (occurring in moderate numbers in approximately 2% of Caucasians) are lesions of melanotic hyperpigmentation that are not considered pathological[25] and whose histology differs from that of melanocytic café-au-lait spots of NF.[50,51] One rare disorder of melanotic hyperpigmentation is familial progressive hyperpigmentation (FPH2), characterized by general hyperpigmentation and associated with gain-of-function mutations in *KITLG*, whose protein product functions as a signaling molecule that regulates melanin production through the receptor KIT. The closely related disorder familial progressive hyper- and hypopigmentation is also associated with mutation of *KITLG*.[52] Another example is Legius syndrome, which shows phenotypes of café-au-lait molecules, occasional freckling, and craniofacial and cognitive defects. Legius syndrome is associated with mutation of sprouty-related, EVH1 domain containing 1 (*SPRED1*), which encodes a regulator of RAS signaling. Therefore, the RAS-MAPK pathway links the phenotypically distinct hyperpigmentary defects of Legius syndrome, NF1, LEOPARD syndrome, and Noonan syndrome. These four syndromes are included in the RASopathies, a varied group of human disorders that all arise from dysregulation of RAS-MAPK signaling. Additional RASopathies with occasional pigmentary anomalies include CBL-mutation associated syndrome and cardio-facio-cutaneous syndrome, caused by mutation of *KRAS, BRAF, MAP2K1* or *MAP2K2*.[53–55]

Many other congenital disorders exhibit either localized or general melanotic hyperpigmentation that arises in a reticulated pattern. These are typically seen along with other systemic disorders, and are caused by defects in ubiquitous proteins and/or basal cellular processes.[56] The presence of hyperpigmentation resulting from altered basal cell processes suggests melanocytes are a cell type with great sensitivity to such perturbations. A notable example is Fanconi Anemia, a genetically heterogeneous disorder affecting DNA repair, characterized by varied phenotypes affecting all organ systems.

ACQUIRED PIGMENTATION DISORDERS

Acquired disorders are clinically defined as those occurring after fetal stages of development. Because this review is focused on developmental genetics, examples of acquired hypo- and hyperpigmentation are briefly summarized, and emphasis is placed on heritable genetic influences on these disorders.

Acquired hypopigmentation—The hypopigmentation disorder vitiligo shows regional, progressive epidermal melanocyte loss that results in severe skin depigmentation. Vitiligo is relatively common, with an estimated frequency of 1–2%, and is categorized into two clinically distinct forms: the more common symmetrical, general form (GV) and the rare, asymmetrical, segmental form. The molecular genetics of vitiligo involves multiple loci and pathways, with recent genome-wide association studies confirming the long-held hypothesis that autoimmune responses directed towards melanocytes are involved in GV progression.[57] Other suggested mechanisms contributing to vitiligo include mosaicism, sensory neuron-directed abnormalities, or region-specific, microvascular homing of cytotoxic T-cells to the skin.[58–60]

Acquired Benign Hyperpigmentation—Exposure to UVR has a strong influence on the appearance of acquired forms of benign hyperpigmentation, and is associated with formation of the common hyperpigmented lesions ephelides, melanocytic nevi, and solar lentigines (SLs). Ephelides, which are localized patches of melanotic hyperpigmentation (Fig. 1F), are also genetically influenced, as their frequency is correlated with allelic variants of MC1R.[61] Melanocytic nevi also appear to be influenced both by genetics (described in Melanocytic Hyperpigmentation section) and childhood exposure to UVR.[62–65] In contrast, SLs are defined by their appearance on sun-exposed skin, and thus clearly affected by UVR, but genetic influences on their formation are not yet known. Candidate pathways in which allelic variance could regulate SL susceptibility are: the KITL pathway, as SL formation is associated with upregulated KITL, and the fibroblast growth factor receptor 3 (FGFR3) and phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA) pathways, as SLs can harbor *FGFR3* or *PIK3CA* mutations.[37,66] In addition, rarer types of acquired, benign hyperpigmentation include: dysplastic nevus syndrome, characterized by extensive numbers of dysplastic nevi; Spitz nevi, small, symmetric, juvenile nevi that arise singly, often on the face or lower extremities, which clinically resemble melanoma, but are nonmalignant and have a distinctive mutation profile; and acquired blue nevi, a heterogenous group of blue-black dermal lesions,[45] which display gene mutation profiles distinct from those of cutaneous melanocytic nevi and Spitz nevi, including the association of some forms with mutations in guanine nucleotide binding protein (G protein), q polypeptide (*GNAQ*) and guanine nucleotide binding protein (G protein), alpha 11 (*GNA11*).[67,68]

Hormonal and inflammatory influences—Acquired hypo- or hyperpigmentation can result from a wide variety of systemic alterations. Changes in hormones can be quite influential on pigmentation, including pregnancy-related estrogen increases (causing melasma and linea nigra), hyperthyroidism, overproduction of adrenocorticotropic hormone (seen in Cushing's disease), and adrenal gland insufficiency (seen in Addison disease).[69] Other systemic alterations that can trigger hypo- or hyperpigmentation are post-inflammatory responses to various external insults, such as infection, drug response, or contact dermatitis.[70] A genetic predisposition to development of these anomalies is likely to be complex and/or multifactorial.

Animal models of human cutaneous melanocyte development and function

Mouse, chick, frog, and zebrafish animal models have been valuable tools for identifying candidate genes regulating human melanocyte development and function, because many important genes that regulate pigmentation are highly conserved among these divergent species. Striking phenotypic parallels occur when orthologous genes are mutated, and the ease of experimental manipulation afforded by animal models has often directed discovery of pathological human gene mutations as well as revealed details of gene function. Each animal has inherent advantages and disadvantages for modeling human melanocytes. For example, zebrafish reproduce rapidly and allow precise pigment cell lineage tracing, but have pigment cell types that are divergent from those of mammals. Chicken and frog models facilitate studies of melanoblasts newly emerging from the NC, but are not amenable to genomic manipulation. Mouse models are readily altered genetically, but display significantly different epidermal architecture: while melanocytes occur in human epidermis, melanocytes are absent from mouse epidermis (excepting tail and ear regions), residing solely in hair follicles, which in mouse are present at much greater density. Of note, this difference has been addressed by creation of transgenic mice in which altered growth factor expression causes retention of melanocytes in the epidermis or dermis.[71,72] While newly emerging technologies such as 3-dimensional skin models[73] or large-scale genome sequencing will facilitate direct analysis of human melanocyte function and gene expression, animal models will remain essential tools to verify functional data gathered using these new technologies, thus keeping animal models at the forefront of pigmentation research.

Conclusion

Much remains to be discovered regarding the developmental genetic pathways that govern both normal and abnormal human pigmentation. Many human pigmentation disorders have a genetic locus associated with a subset of patients, while additional, phenotypically similar patients harbor no mutations at these identified genes and in some cases map the disease locus to a novel genomic region. These genetically heterogeneous disorders that await further characterization include Piebaldism,[74] WS2,[75] YDBS,[11] Carney complex, and FPH1. For other disorders, no underlying genetic mutations are known, including: Albinism deafness syndrome, exhibiting a piebald-like pigmentation phenotype, congenital deafness and heterochromia irides,[76] dyschromatosis universalis hereditaria (DUH1, DUH2), exhibiting extensive hypo- and hyperpigmented patches, and congenital diffuse melanosis, displaying widespread dermal/epidermal hyperpigmentation and neurological abnormalities.[77,78]

Model organisms (see sidebar) will remain essential tools to aid in discovery and understanding of genes associated with human pigmentation anomalies, their allelic variance, and additional multifactorial effects. Additionally, melanocytes in model organisms and humans may harbor genetic differences associated with their anatomical location or developmental origin, and characterization of these intrinsic features may explain phenotypes of various pigmentation anomalies.[32] For example, human skin has been proposed to contain regional mosaicism that is developmentally determined and potentially associated with neuronal architecture. [22,79] Various patterns of hyperpigmented lesions have been proposed to correlate with these defined cutaneous subregions.[80] The molecular details of regional mosaicism, and how these regional differences contribute to the pathology of melanocytic hyperpigmentation remains an open field of study, which may yield many discoveries via whole genome sequence analysis or expression profiling. Furthermore, detailed sequence analysis of various melanocytic lesions will help determine the

contributions of somatic and/or germline mutations to their proliferation. Additional research also remains in the field of melanocyte stem cell research, as dermal stem cells competent to differentiate into human epidermal melanocytes were recently discovered.[81] The pathways governing proliferation of these stem cells need to be discerned, as well as the possibility that aberrations in these stem cells may play an integral role in human pigmentation anomalies.[82] Future genetic analyses will allow greater integration of both phenotypes and genotypes of melanocyte abnormalities, thus furthering understanding of melanocyte function and potentiating novel treatment of pigmentation disorders.

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Further Reading/Resources

1. Nordlund, JJ.; Boissy, RE.; Hearing, VJ.; King, RA.; Oetting, WS.; Ortonne, JP. The Pigmentary System: Physiology and Pathophysiology. Blackwell Publishing; Malden, Massachusetts: 2006.

2. The Online Metabolic and Molecular Bases of Inherited Disease

3. Online Mendelian Inheritance in Man

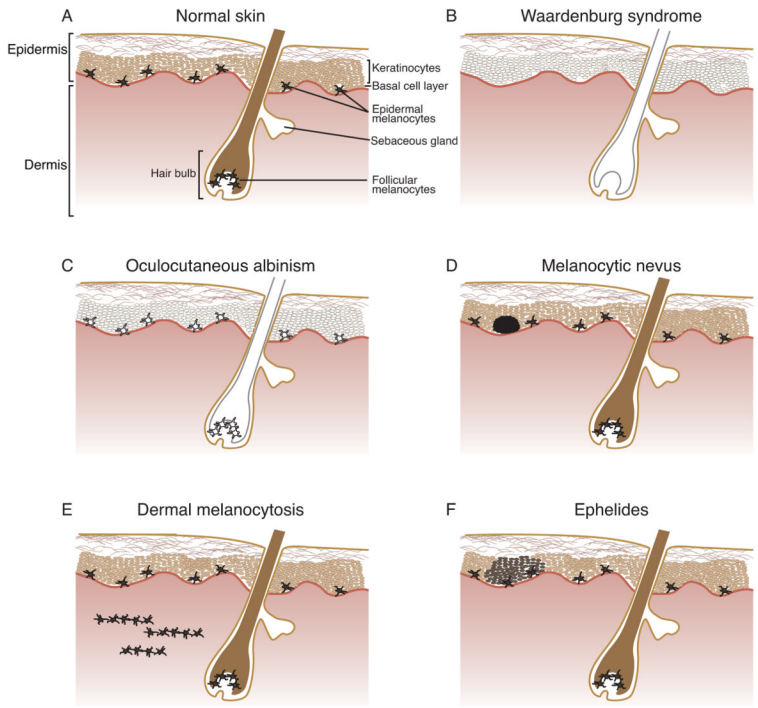

Figure 1.

Diagrammatic representation of congenital human cutaneous pigmentation abnormalities. A) Normal skin shows individual, dendritic melanocytes located at the basal cell layer of the epidermis and in the bulb of the hair follicle. Epidermal melanocytes provide pigment to surrounding interfollicular keratinocytes, and follicular melanocytes provide pigment to hair shaft keratinocytes. B) In Waardenburg syndrome, developmental anomalies in genes crucial for pigment cell development cause regionalized absence of melanocytes, resulting in areas of hypopigmented skin and hair. C) In oculocutaneous albinism, melanocytes are retained, but they contain a genetic defect that prevents them from producing normal levels of melanin. Illustrated is OCA1A, where complete absence of pigment results from loss of function of the melanogenic enzyme TYR. Other forms of oculocutaneous albinism typically show some residual pigmentation. D) Melanocytic nevi show benign overgrowth of epidermal melanocytes that have lost their dendritic form and are organized in defined nests. E) In dermal melanocytosis, melanocytes retaining dendritic morphology are found within the dermis, in a scattered array often parallel to the skin's surface. Their deeper, dermal location gives them a characteristic blue tint, with a superficial dermal location typical for nevus of Ito or nevus of Ota, and a deeper dermal location for Mongolian spots. F) In ephelides, normal numbers of melanocytes produce localized patches of increased melanin in surrounding keratinocytes. Formation of ephelides is directly correlated with UV irradiation levels.

Table 1

Congenital pigmentation disorders with cloned and characterized genetic components.[1]

Disease	Gene	Encoded Protein Function
Piebaldism	*KIT*	Receptor tyrosine kinase; ligand is KITLG
	SNAI2	Transcription factor
Waardenburg syndrome 1	*PAX3*	Transcription factor
Waardenburg syndrome 2	*MITF*	Transcription factor
	SOX10	Transcription factor
	SNAI2	Transcription factor
Waardenburg syndrome 3	*PAX3*	Transcription factor
Waardenburg syndrome 4	*SOX10*	Transcription factor
	EDNRB	Transmembrane receptor; ligand is EDN3
	EDN3	Secreted growth factor
Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and hirschsprung disease	*SOX10*	Transcription factor
Tietz syndrome	*MITF*	Transcription factor
Yemenite deaf-blind hypopigmentation syndrome	*SOX10*	Transcription factor
Albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness syndrome	*EDNRB*	Transmembrane receptor; ligand is EDN3
Oculocutaneous albinism 1	*TYR*	Melanogenic, rate-limiting enzyme
Oculocutaneous albinism 2	*OCA2*	Melanosome membrane protein
Oculocutaneous albinism 3	*TYRP1*	Melanogenic enzyme
Oculocutaneous albinism 4	*SLC45A2*	Solute transporter
Hermansky-Pudlak syndrome	*HPS1*	Member of BLOC-3 complex; regulates lysosome-related organelle movement
	AP3B1	Member of AP3 complex; regulates protein sorting
	HPS3	Member of BLOC-2 complex; regulates lysosome-related organelle movement
	HPS4	Member of BLOC-3 complex; regulates lysosome-related organelle movement
	HPS5	Member of BLOC-2 complex; regulates lysosome-related organelle movement
	HPS6	Member of BLOC-2 complex; regulates lysosome-related organelle movement
	DTNBP1	Member of BLOC-1 complex; regulates lysosome-related organelle movement
	BLOC1S3	Member of BLOC-1 complex; regulates lysosome-related organelle movement
	PLDN	Member of BLOC-1 complex; regulates lysosome-related organelle movement
Chediak-Higashi syndrome	*LYST*	Function unknown; may regulate lysosome-related organelle size and trafficking
Griscelli syndrome	*MYO5A*	Myosin motor regulating melanosome transport

Disease	Gene	Encoded Protein Function
	RAB27A	RAS-associated protein that interacts with MLPH to regulate melanosome transport
	MLPH	Interacts with MYO5A to regulate melanosome transport
LEOPARD syndrome	*PTPN11*	MAPK signal transduction pathway
	RAF1	MAPK signal transduction pathway
	BRAF	MAPK signal transduction pathway
Noonan syndrome	*PTPN11*	Cytoplasmic protein tyrosine phosphatase; modulates RAS activity
	RAF1	Serine threonine kinase; downstream effector of RAS
	BRAF	Serine threonine kinase; downstream effector of RAS
	SHOC2	Leucine-rich protein; modulates RAS activity
	KRAS	Monomeric GTPase; modulates RAS activity
	SOS1	Guanine nucleotide exchange factor; modulates RAS activity
	NRAS	Monomeric GTPase; modulates RAS activity
Cardio-facio-cutaneous syndrome	*KRAS*	Monomeric GTPase; modulates RAS activity
	BRAF	Serine threonine kinase; downstream effector of RAS
	MAP2K1	Dual specificity kinase; acts downstream of RAS as RAF effector
	MAP2K2	Dual specificity kinase; acts downstream of RAS as RAF effector
CBL-mutation associated syndrome	*CBL*	E3 ubiquitin ligase; acts downstream of receptor tyrosine kinases
Legius syndrome	*SPRED1*	Sprouty domain protein; tyrosine kinase substrate; modulates RAS activity
Dyschromatosis symmetrica hereditaria	*ADAR*	RNA specific adenosine deaminase; regulates RNA editing
GIST with dysplastic nevi and lentigines	KIT	Receptor tyrosine kinase; ligand is KITLG
Peutz-Jeghers syndrome	*STK11*	Serine threonine kinase
Carney complex	*PRKAR1A*	Protein kinase regulatory subunit
Neurofibromatosis	*NF1*	RAS GTPase, modulates RAS activity
Neurofibromatosis-Noonan syndrome	*NF1*	RAS GTPase, modulates RAS activity
Familial progressive hyperpigmentation 2	*KITLG*	Growth factor; ligand for KIT
Familial progressive hyper- and hypopigmentation	*KITLG*	Growth factor; ligand for KIT
Fanconi anemia	Heterogeneous see OMIM #227650	Associated with mutation of at least 15 loci, which encode proteins that regulate various DNA repair processes

[1]This table is not an exhaustive list of all known congenital pigmentation disorders. For extensive descriptions of published human pigmentation disorders, see Further Reading/Resources.