Disorders of Hypopigmentation

by Gina Chacon, MD, and Meredith Hancock, MD

Vitiligo

Heterogeneous group of disorders with various genetic backgrounds, exogenous and intrinsic triggers
Functional melanocytes absent
Clinical: amelanotic macules and patches with surrounding nl skin. Discrete margins, convex borders. Usually asymptomatic. Predilection for face (periorificial), dorsal hands, nipples, axillae, umbilicus, sacral, anogenital areas. + isomorphic Koebner phenomenon.
Localized:
- Focal: not clearly segmental
- Unilateral/segmental: do not cross midline, children (15-30%) > adults (5-10%)
- Mucosal: only mucous membranes

Generalized: (90% of cases)
- Vulgaris/non-segmental: widely-distributed, scattered
- Acrofacial
- Mixed

Universal: complete depigmentation
Associated (adults): adult-onset AI-DM, AI-thyroid , LE, RA, Addison's disease, pernicious anemia; +/- halo nevi, AA, lichen sclerosis
APCED (**a**utoimmune **p**olyendocrinopathy **c**andidiasis **e**ctodermal **d**ystrophy) syndrome: AR, *AIRE* gene, predisposed to vitiligo and AI destruction of endocrine cells. Failure to delete autoreactive T cells → AI disease

HEREDITARY HYPOMELANOSIS

Disease	Genetics / Pathophysiology / Histology	Clinical Features
Oculocutaneous Albinism (OCA) Diffuse pigmentary dilution 40% of cases are OCA1(A + B) 50% of cases are OCA2 Melanocytes present	**OCA1A** AR, *TYR* gene no tyrosinase activity (tyrosinase negative)	At birth white hair, milky white skin, blue-gray eyes; with age hair may yellow slightly, skin remains white, melanocytic nevi remain amelanotic Extreme UV light sensitivity, high risk for skin cancers (SCC especially) Reduced visual acuity most severe in OCA1A, some legally blind
	OCA1B AR, *TYR* gene ↓ tyrosinase activity (tyrosinase positive)	Yellow OCA: little to no pigment at birth. Hair becomes yellow with age (pheomelanin requires less tyrosinase) Minimal pigment OCA, platinum OCA, temperature-sensitive OCA: little to no pigment at birth. Develop some pigment in by 2nd decade. Burn without tanning. Amelanotic or pigmented melanocytic nevi possible. Temperature-sensitive: in puberty, arm hairs → light reddish-brown, leg hairs → dark-brown. Mutated tyrosinase loses activity at 35˚C (like Siamese cat)
	OCA2 AR, *OCA2* gene (prev *P*) Transmembrane transporter, role in organelle pH regulation, tyrosinase trafficking/processing tyrosinase positive	Broad clinical spectrum. Mild to mod pigmentary dilution. Little to no ability to tan. Pigmented melanocytic nevi/lentigines develop in sun-exposed skin. Brown OCA phenotype: African descent, light brown hair and skin, irides gray to tan at birth, do not sunburn. 1% of pts with PWS/AS also have OCA2; del + mutation 15q (with *OCA2/P* gene)
	OCA3 AR, *TYRP1* gene (melanocyte specific) Eumelanin synthesis via tyrosinase stabilization	Rufous OCA: skin type III–V, red–bronze skin, ginger-red hair, blue/brown irides
	OCA4 *SLC45A2* gene (prev *MATP*) Transmembrane transporter role in tyrosinase processing and intracellular trafficking of proteins to melanosome	Most common in Japanese (25% of pts), China (10-20%), India (~10%), < 5 % in Caucasians Variable phenotype; hair from white to yellow-brown, +/- increased pigment in hair/skin with age
	OA1	Severe decrease in visual acuity, hypopigmentation of the retina, +macromelanosomes in the eyes and skin; skin is normally pigmented overall
Piebaldism	AD, *KIT* proto-oncogene → tyrosine kinase transmembrane receptors on melanocytes; functional receptor required for nl melanocyte migration (from neural crest and postnatally); Histo: no melanocytes in amelanotic skin/hair follicles; hyperpigmented areas with abundance of melanosomes	Present at birth. Leukoderma favors central anterior trunk, mid-extremities, central forehead, midfrontal scalp (→ white forelock in up to 90% pts; absence does not exclude dx); distinctly irregular in shape, well-circumscribed, milk-white; nl pigment and hyperpigmented areas within leukoderma. Poliosis of eyebrows, eyelashes common. Must exclude Waardenburg syndrome via eye exam, hearing exam
Waardenburg Syndrome (WS) Absence or minimal numbers of melanocytes	**WS1** AD, *PAX3* gene	White forelock is most frequent pigment abnormality (20-60% pts) Leukoderma similar to Piebaldism Heterochromia irides (partial/extorial or complete) in ≥ 20% Synophrys (confluent, bushy eyebrows), broad nasal root Dystopia canthorum. Hearing impairment in up to 37% (unilat/bilat)
	WS2 AD, *MITF* gene, (also *SOX10*)	Similar to WS1 (except no dystopia canthorum), deafness more common
	WS3 (Klein-Waardenburg) AD, *PAX3* gene	Similar to WS1, with upper limb abnormalities (hypoplasia, syndactyly) Dystopia canthorum
	WS4 (Shah-Waardenburg) AD, *EDNRB* or *SOX10* gene	Similar to WS1 (except no dystopia canthorum or broad nasal root) Hirschsprung disease Rarely CNS dysfunction, neonatal hypotonia, arthrogryposis (related to *SOX10*)
Tiez Syndrome	AD, *MITF* gene (allelic to WS2)	Diffuse pigmentary dilution of skin/hair, deafness, hypoplasia of eyebrows. Blue eyes without nystagmus or photophobia.

DISORDERS OF MELANOSOME BIOGENESIS

Disease	Genetics / Pathophysiology / Histology	Clinical Features
Hermansky Pudlak Syndrome (HPS)	AR, 9 subtypes Most subtypes have mutations in genes encoding **b**iogenesis of **l**ysosome-related **o**rganelles **c**omplexes 1-3 (*BLOC1/2/3* genes); → involved in lysosome-related organelles (LRO), eg, melanosomes formation. Exception is HPS2, mutation in *AP3B1* gene → involved in protein sorting to lysosomes and LRO, associated with antigen presentation, secretion of lytic granules in cytotoxic T cells	Pigmentary dilution of the skin, hair, eyes; variable, depending on mutation and ethnicity (HPS1 and 3 in Puerto Ricans). ↑ pigmentation with age. Nystagmus and reduced visual acuity similar to albinism, NMSC Systemic symptoms due to organelle dysfunction: - Bleeding tendency (on EM: absence of dense bodies in platelets) - interstitial pulmonary fibrosis → cause of early death (30-50 y) - granulomatous colitis (ceroid lipofuscin accumulation in lysosomes) - renal failure, cardiomyopathy (less common) HPS2: recurrent bacterial infection due to neutropenia, abnl cytotoxic T-cell function

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Disease	Genetics / Pathophysiology / Histology	Clinical Features
DISORDERS OF MELANOSOME BIOGENESIS (cont.)		
Chédiak–Higashi Syndrome (CHS)	AR, *LYST* gene (**lys**osomal **t**rafficking regulator) → protein regulating fission/fusion of lysosome-related organelles	OCA with silvery-gray hair, photophobia, nystagmus, ocular hypopigmentation, hyper/hypopigmentation, bleeding diathesis (diminished function of platelet granules), progressive neurologic dysfunction, severe immunodeficiency. Giant LRO (including melanosomes, platelet dense granules, PMN granules); peripheral smear for screening
DISORDERS OF MELANOSOME TRANSPORT AND/OR TRANSFER		
Griscelli Syndrome (GS)	GS1 AR, MYO5A gene → myosin Va, key role in transfer of melanosomes to keratinocytes	Diffuse pigmentary dilution of skin, silvery-gray hair due to pigment clumping in melanocytes (GS1/2/3). Neurologic impairment (MYO5A also found in neurons).
	GS2 AR, *RAB27A* gene → Ras-like GTPase present in melanosomes.	Diffuse pigmentary dilution and silvery hair. Immunodeficiency, hemophagocytic syndrome (RAB27A found in hematopoetic cells). Can be treated with HSCT.
	GS3 AR, *MLPH* gene → melanophilin which links myosin Va to Rab27a	Diffuse pigmentary dilution and silvery hair
Elejalde Syndrome	Pigmentary findings of GS + severe neurologic dysfunction	
TUBEROUS SCLEROSIS COMPLEX AND PIGMENTARY MOSAICISM		
Tuberous Sclerosis Complex (TSC)	AD, *TSC1* gene → hamartin, *TSC2* gene → tuberin (both tumor suppressor genes) Normal # of melanocytes; however, ↓ size and poor melanization of melanosomes	Hamartomas of multiple organs (skin, brain, eye, heart, kidney). White hypomelanotic macules (possibly present at birth), confetti-like/guttate, lance-ovate "ash leaf"; consider in children with ≥ 3 hypomelanotic macules Triad: facial angiofibromas ("adenoma sebaceum"), seizures, mental deficits
Hypomelanosis of Ito (HI)		Hypopigmentation along Blaschko's lines, reflects mosaicism characterized by a clone of skin cells with a decreased ability to make pigment. Apparent at birth, during infancy or childhood. The characteristic pattern of streaks and whorls can occur unilaterally or bilaterally. Most common on trunk and limbs. Abnormalities of CNS, eye or musculoskeletal system.
NUTRITIONAL HYPOMELANOSIS		
Kwashiorkor	Severe protein deficiency	Initially, skin erythematous to red-brown color with marked desquamation → hypomelanosis and/or patchy postinflammatory hypermelanosis. Hypomelanosis starts on the face; hair is dry, lusterless, +/- red-brown color
Copper Deficiency Selenium Deficiency	Tyrosinase requires copper	Diffuse pigmentary dilution
POSTINFLAMMATORY HYPOMELANOSIS		
Secondary to Psoriasis, seborrheic dermatitis, atopic dermatitis, sarcoidosis, lichen sclerosis, lichen striatus, PLC, MF, LE Multiple factors/processes affect skin color; dysregulation caused by inflammation can alter melanosomes biogenesis, melanin production, melanosome transport/transfer to keratinocytes. Severe inflammation can lead to functional loss of melanocytes, even cell death.		
Pityriasis Alba	Reduced numbers of active melanocytes, decrease in # and size of melanosomes in affected skin	Slightly scaly, round/oval, ill-defined hypopigmented macules/patches. Children/adolescents > adults, more noticeable in darker skin, summer. Early lesions pink → white/dry/powdery with pink border Face most common site. Wood's lamp accentuates hypopigmentation
Sarcoidosis	Dermal non-caseating granulomas; melanocytes may or may not appear normal. Melanosomes appear normal but ↓ # in keratinocytes.	Circumscribed, poorly marginated papules/plaques +/- induration. Dermal nodules surrounded by hypomelanosis. Most common on extremities, asymptomatic, no secondary changes.
Hypopigmented Mycosis Fungoides (MF)	Histology consistent with MF; decreased melanosomes in keratinocytes. NI # of melanosomes in melanocytes (= defect in transfer)	Variant of early stage MF; most frequently seen in people with darker pigmentation. Hypomelanotic lesions on trunk/extremities, +/- pruritus. Erythema and infiltration usually present.
Scleroderma	Unknown	Characteristic leukoderma (sclerotic and non-sclerotic skin) is circumscribed areas of complete pigment loss with perifollicular and supravenous pigment retention. "Salt and pepper." Seen in overlap syndromes, scleromyxedema.
Lichen Sclerosis (LS)	Unknown	Genital and extragenital lesions are hypomelanotic +/- epidermal atrophy, follicular plugging, and purpura (anogenital). Extragenital LS may be guttate.
Lupus Erythematosus (DLE, SCLE)	↓ # of melanocytes, epidermal atrophy, vacuolar changes, pigment incontinence	Hypomelanosis/amelanosis associated with cutaneous atrophy/scarring. Hypomelanosis at lesion center often with a rim of hyperpigmentation. Pigment loss can be permanent in chronic scarring DLE, reversible in SCLE.

Abbreviations:
NI: normal, abnl: abnormal, **AI:** autoimmune, **LE:** lupus erythematosus, **RA:** rheumatoid arthritis, **AA:** alopecia areata, **PWS/AS:** Prader-Willi syndrome/ Angelman syndrome, **EM:** electron microscopy, **PMN:** polymorphonuclear cells, **HSCT:** hematopoietic stem cell transplant, **PLC:** pityriasis lichenoides chronica , **MF:** mycosis fungoides, **DLE:** discoid lupus erythematosus, **SCLE:** subacute cutaneous lupus erythematosus

References:
1. Bolognia, Jean, Joseph L. Jorizzo, and Julie V. Schaffer. "Chapter 66." Dermatology. 3rd ed. Philadelphia: Elsevier Saunders, 2012. 1023-041. Print. Special thanks to Erik Stratman, MD.

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