Disorders of Hyperpigmentation

by Sarah Brooks, M.D.

GENETIC			
	Gene	**Pathophysiology**	**Clinical Features**
Dyskeratosis congenita	XLR: DKC1 gene AD: hTR, hTERT	Mutation in dyskerin protein which interacts with telomerase, or mutation in telomerase subunits	Lacy reticulated hyperpigmentation on the neck, upper arms, upper chest. Pterygium, leukoplakia, pancytopenia, mucosal squamous cell carcinoma, leukemia
Naegeli–Franceschetti–Jadassohn	AD: KRT14	Mutation in non-helical head domain of keratin 14 leading to early termination of translation	Periocular, perioral, abdominal gray-brown reticulate hyperpigmentation. Fades after puberty. Decreased sweat glands w/ heat intolerance, dental anomalies, absent dermatoglyphics.
Dermatopathia pigmentosa reticularis	(possible) AD: KRT14	Mutation in non-helical head domain of keratin 14.	Triad: reticulate hyperpigmentation of trunk and proximal extremities, non-scarring alopecia, and onychodystrophy. Does not fade after puberty.
X-Linked Reticulate pigmentary disorder	X-Linked	Unknown	Male: generalized hyperpigmentation, onset 4 mo to 5 yrs. Severe systemic manifestations (recurrent pneumonia, COPD , early death). Blonde unruly hair with a frontal upsweep, +/- low intelligence. Female: skin-limited manifestations with lacy or reticulated hyperpigmentation w/in lines of Blaschko.
Dowling-Degos disease (DDD)	AD: KRT5	Loss of function mutation (possible role of keratin 5 in melanosome uptake & organelle transport)	Reticulate hyperpigmentation, beginning in axillae and groin and spreading to other body folds. Comedone-like lesions on the back or neck, pitted perioral or facial scars.
Galli-Galli Disease	AD	Acantholytic variant of DDD.	Same as DDD
Reticulate acropigmentation of kitamura	AD, possibly KRT5	May be on a spectrum with DDD.	Atrophic lentigo-like reticulated hyperpigmented macules on the dorsal aspect hands and feet. Aggravated by sunlight. Palmoplantar pits, breaks in dermatoglyphics. Majority Japanese.
Haber's syndrome	AD		Reticulate hyperpigmentation on the trunk and proximal extremities, axillae. Facial rosacea-like eruption starting in childhood. Predominantly truncal keratotic papules, representing SK's.
Dyschromatosis Symmetrica Hereditaria	AD, DSRAD mutations	Encodes an adenosine deaminase. Unknown why mutation causes pigmentary problems.	Dorsal distal extremities with small, irregular, hypo- and hyperpigmented macules.
Dyschromatosis universalis hereditaria	Unclear	Unknown	Hyper- and hypopigmented macules on the head, neck, trunk and extremities. Isolated cases with systemic abnormalities. Majority Japanese.

DRUG-INDUCED/INGESTION		
	Drug Use	**Clinical Features/Pathology**
Bleomycin	Lymphoma and testicular carcinoma	Hyperpigmentation overlying pressure points, linear flagellate bands in areas of prior minor trauma, transverse melanonychia, sclerodermoid changes. Increased epidermal melanin, minimal dermal pigment incontinence.
5-Fluorouracil	Breast and gastrointestinal carcinomas	Hyperpigmentation of sun-exposed skin; transverse or diffuse melanonychia; lunular pigmentation.
Dactinomycin (actinomycin-D)	Wilms tumor, gestational trophoblastic neoplasia, rhabodomyosarcoma	Generalized hyperpigmentation, most prominent on the face, fades after discontinuation
Daunorubicin	Leukemia	Hyperpigmentation of sun exposed areas, transverse brown–black melanonychia
Doxorubicin	Breast cancer, sarcomas, lymphoma, ovarian cancer	Hyperpigmentation overlying the small joints of the hand and involving the palmar creases, palms, soles and oral mucosa (buccal, tongue). Increased epidermal melanin, and number or melanocytes
Arsenic	Not used medically, found in contaminated well-water	Areas of bronze hyperpigmentation ± superimposed raindrops of lightly pigmented skin which may appear up to 20 years following exposure, keratoses on the palms and soles, which may evolve into SCC. Dermal and epidermal deposition of arsenic, increased epidermal melanin synthesis
Gold	Rarely used for rheumatoid arthritis, pemphigus vulgaris	Permanent blue–gray discoloration, most prominent in sun-exposed areas, especially around the eyes. Gold particles within lysosomes in dermal macrophages, especially in perivascular and perieccrine areas
Silver	Occupational exposure, topical use of silver sulfadiazine, alternative medicine	Generalized slate-gray discoloration. Nail and sclera can also be involved. Silver granules in the basement membrane eccrine glands
Amiodarone	Cardiac arrhythmias	Slate-gray to violaceous discoloration in sun-exposed areas. Fades very gradually. Yellow–brown granules within peri-vascular dermal macrophages.
AZT (zidovudine)	HIV treatment	Hyperpigmentation of the mucous membranes and nails in up to 10% of treated patients, blue lunulae. Increased melanin within epidermal basal layer and dermal macrophages.

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DRUG-INDUCED/INGESTION (cont.)		
	Drug Use	**Clinical Features/Pathology**
Clofazimine	Mycobacterial infections	Violet–brown to blue–gray discoloration; diffuse reddish discoloration of the skin and conjunctivae. Dermal collections of foamy macrophages that contain diffusely distributed brownish granular pigment.
Diltiazem	Hypertension	Slate-gray to gray–brown discoloration of sun-exposed skin in patients of dark skin phenotypes; may be perifollicular or reticulate in nature. Sparse lichenoid infiltrate and numerous dermal melanophages.
Minocycline	Acne, inflammatory conditions, infectious processes	Type I: blue–black discoloration in sites of inflammation and existing scars. Intra- and extracellular iron-containing pigment within the dermis. Type II: blue–gray macules and patches that appear within previously normal skin, most commonly on the anterior legs. Melanin- and iron-containing pigment granules in the dermis and subcutis. Type III: diffuse muddy brown discoloration most prominent in sun-exposed areas. Increased melanin in the basal layer of the epidermis and in dermal macrophages without the presence of iron.
Hydroquinone	Post-inflammatory hyperpigmentation	Hyperpigmentation in areas of application due to irritant contact dermatitis or exogenous ochronosis. Yellow–brown banana-shaped fibers in papillary dermis.
Flagellate mushroom dermatitis	Those who eat or cultivate raw shiitake mushrooms	Long, flagellate streaks with petechiae or papules that are often seen on the trunk and extremities. Thermo-labile toxin is responsible for manifestations. Spongiosis and necrotic keratinocytes within the epidermis, lymphocytic dermal infiltrate.
Chlorpromazine	Psychotropic medication	Slate-gray discoloration in sun-exposed areas. Golden-brown granules in the upper dermis, electron-dense inclusion bodies.

BLASCHKOID HYPERPIGMENTATION		
	Pathogenesis	**Clinical Features**
Linear and whorled nevoid hypermelanosis	Unknown, but likely related to somatic mosaicism and melanoblast migration	Blaschkoid streaks of hyperpigmentation developing within the first year of life that persist indefinitely. Systemic abnormalities rare.
Incontinentia pigmenti, Stage III	X-linked dominant disorder, NEMO gene mutation	Gray–brown streaks and whorls along the lines of Blaschko developing within 1st year of life. Fade later in life secondary to cellular apoptosis. Systemic manifestations include conical teeth, dystrophic nails, skull abnormalities, seizures, and eye abnormalities.

OTHER DISORDERS		
	Epidemiology	**Pathogenesis/Clinical Features**
Melasma	Young females of darker skin phototypes	Hypothesized that hyperfunctional melanocytes are exposed to UVR and produce increased melanin compared to surrounding skin. Symmetric light to dark brown irregularly bordered patches in either centrofacial, malar, or mandibular distribution.
Erythema dyschromica perstans	Latin America, 2nd to 3rd decade of life, M=F	Pathogenesis unknown, but postulated to be immunologic in origin, HLADR4 found in to be associated in Mexican patients. Symmetric, circular to irregularly shaped blue-gray ('ashy' appearing) patches with erythematous borders on the trunk>extremities>face.
Post-inflammatory hyperpigmentation	No gender or age preference. Darker skin types are particularly affected.	Epidermal form is from increased production of melanin and transfer to keratinocytes in areas of inflammation. Dermal form is from damage to basement membrane, which allows pigment to seep into the dermis and become engulfed by melanophages. Dermal form appears darker secondary to Tyndall effect. Asymptomatic dark brown to gray-blue-brown macules and patches, color depends on location of melanin, with dark brown being epidermal and gray-brown dermal.

Type of Melasma	**Woods lamp**	**Response to topical treatment**
Epidermal	Accentuated	Possibly
Dermal	Blend with surrounding skin	Not Usually

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