Disorders of dyschromia (hypo- and hyperpigmentation)

by Parin Pearl Rimtepathip, MD, and Janna Mieko Vassantachart, MD

Genetic conditions			
Disorder	**Gene Mutation**	**Pathophysiology**	**Clinical Features (Unique Features)**
Dyskeratosis Congenita (Zinsser-Engman-Cole syndrome)	XLR (MC): DKC 1 AD: TERT, TERC	Reduced telomerase activity and abnormally **shortened telomeres** → chromosomal instability/cellular replication dysfunction	Male > Female. **Bone marrow failure** up to 90% (increase risk of hematopoietic malignancies) + triad of abnormal skin pigmentation (poikilodermatous patches of face/neck/upper torso), onychodystrophy, **premalignant oral leukoplakia** (vs benign oral leukoplakia in Pachyonychia Congenita type I)
Dyschromatosis Symmetrica Hereditaria (Reticulate Acropigmentation of Dohi)	AD: ADAR (SDAR gene)	Heterozygous mutations in the gene encodes an RNA specific adenosine deaminase	Presents by 6-years-old with hyper/hypopigmented macules restricted to sun-exposed skin on the **dorsal aspects of bilateral extremities and face**
Naegeli-Franceschetti-Jadassohn Syndrome (NFJS)	AD: Keratin 14	Location of expression of keratin 14 - Basal keratinocytes	Allelic to DPR. Brown gray reticulated hyperpigmentation typically localized to abdomen, develops around age 2 and **improves after puberty**. Other findings: **PPK** + adermatoglyphia (no finger prints) + **dental anomalies** including early loss of teeth (not seen in DPR) + hypohidrosis + onychodystrophy
Dermatopathia Pigmentosa Reticularis (DPR)	AD: Keratin 14	Location of expression of keratin 14 - Basal keratinocytes	Allelic to NFJS. Unique features: **diffuse non-scarring alopecia** (not seen in NFJS) + onychodystrophy + adermatoglyphia + **persistent** reticulated hyperpigmentation of torso and proximal UE + No dental anomalies
Dyschromatosis Universalis Hereditaris (DUH), familial progressive hyper- and hypopigmentation	AD/AR: ABCB6	Mutation in ATP binding cassette subfamily B, member 6	Japanese. **Torso predominant with mottled appearance**, nail dystrophy, and pterygium. Rare reports of assoc with short stature, idiopathic torsion dystonia, x-linked ocular albinism, and neurosensory hearing loss
Reticular Acropigmentation of Kitamura	AD: ADAM 10	Encodes a disintegrin and metalloproteinase 10	Japanese. Slightly depressed, lentigo-like hyperpigmented macules coalescing into a reticulated pattern (hence the name) **on the dorsal hands and feet (main clue) + PPK pits** and abnormal dermatoglyphics. Histo significant for increased melanin and an increased number of melanocytes
Dowling-Degos Disease (reticular pigmented anomaly of flexures)	AD: Keratin 5 gene (also a/w EBS with mottled pigmentation)	Location of expression of Keratin 5 - Basal keratinocytes	Adult onset with **reticulated hyperpigmentation involving axilla and groin (skin folds)** + Comedone like lesions on the back or neck + Pitted perioral scars. Histo significant for increased pigmentation of basal layer and "antler-like" pattern with finger-like rete ridges. **Galli-Galli disease:** Variant of DDD in which suprabasilar acantholysis is noted on histology but presents similar clinically.
Epidermolysis Bullosa Simplex (EBS) with Mottled Pigmentation	AD: Keratin 5>14	Mutation in keratin affecting epidertmal stability	Childhood onset with **acral blisters**, mottled pigmentation on trunk and limbs. Punctate palmoplantar keratoderma, nail dystrophy.

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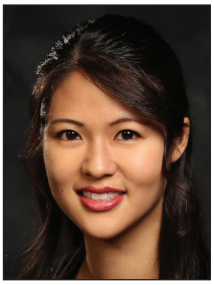

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Genetic conditions

Disorder	Gene Mutation	Pathophysiology	Clinical Features (Unique Features)
Hutchinson-Gilford Progeria	AD: LMNA gene	Mutation affects the structure and function of the cellular nuclear envelope	**Accelerated aging seen around 6-18 months**. Sclerodermatous changes, dyspigmentation, failure to thrive, atherosclerosis, angina, osteoporosis, lipodystrophy, enlarged head, micrognathia, beaked nose.
Werner Syndrome (Adult Progeria)	AR: RECQL2/ WRN gene	Encodes a DNA helicase that when mutated results in inhibitors of DNA synthesis and telomere-driven replicative senescence	**Accelerated aging seen in 3rd-4th decade**. Short stature, muscle wasting, **atherosclerosis**, osteoporosis, **diabetes** mellitus, hypogonadism, cataracts, malignancy. Cutaneous findings with premature canities, bird-like facies, sclerodermatous changes, ulcers, mottled pigmentation.
Incontinentia Pigmenti (IP)	XLD: NEMO	Mutation in nuclear factor-kB **(NF-kB)** essential modulator prevents activation of NF-kB which regulates cell proliferation, inflammation and apoptosis induced by TNF-a	Neuroectodermal disorder affecting teeth **(hypo/anodontia)**, CNS, eyes and skin. Skin manifestations follow **Blaschkoid pattern** with streaks and whorls. **Four distinct stages:** Vesicular (birth-1 mo), Verrucous (up to 2 yrs), Hyperpigmented (up to adolescence), Hypopigmented (may persist through adulthood).
Congenital Erythropoietic Porphyria (Gunther's disease)	AR: UROS XLR: GATA1	Deficiency in uroporphyrinogen III synthetase (UROS) results in a buildup of uroporphyrin I and coporphyrin I in erythrocytes, plasma, urine, and feces	**Erythrodontia** (red teeth under Wood's lamp), **red urine** at infancy, hemolysis, hypertrichosis. **Extreme photosensitivity** with blistering, scarring, dyschromia, and increased skin cancers.

Other

Disorder	Pathophysiology/ Epidemiology/Histology	Clinical Features (Unique Features)
Confluent and Reticulated Papillomatosis (CARP)	Unknown etiology, starts at puberty, F>M, blacks>whites Hyperkeratosis, acanthosis, papillomatosis	Keratotic red or brown papules that spread from intermammary region outward **Pseudoatrophoderma colli:** variant with vertically-oriented hyperpigmented papillomatous lesions with wrinkling on the neck. TOC: **Minocycline**
Kwashiorkor	Protein deficiency, normal caloric intake	Edema, potbelly, red-tinged dry hair +/- **flag sign**, superficial desquamation **(flaky paint sign)**, pallor, petechia, dyschromia
Vascular Lasers	Targets hemoglobin	Side effects, purpura, blisters, dyschromia (increased risk in darker skinned patients)
Tinea Versicolor (Pityriasis Versicolor)	Malassezia furfur overgrowth; produces azelaic acid which blocks melanin synthesis; "ziti and meatballs"	Hypo- and hyperpigmented macules and patches with fine scale in lipid-rich areas; common in summer; pale yellow fluorescence with Wood's lamp

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