Review Article

Reticulate pigmentary disorders

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ABSTRACT

Reticulate pigmentary disorders is a term that is loosely defined to include a spectrum of acquired and congenital conditions with different morphologies. The presentations vary from the reticular or net like pattern to the" freckle like" hyper and hypopigmented macules that are usually restricted to the true genetic "reticulate" pigmentary disorders. There is little clarity on this topic and related terms, in major dermatology textbooks. Hence, to harmonize the different entities we feel that the term "mottled pigmentation" could be used to include reticulate pigmentary disorders (acquired and congenital), dyschromasias and the disorders with a reticular pattern. The genetic reticulate pigmentary disorders can also be classified according to the gene loci which in the majority of cases are localized to keratin 5/14. A more useful clinical method of classification is based on the regional distribution, which includes facial, truncal, acral or flexural types. In this review we will largely focus on the inherited reticulate pigmentary disorders.

Key words: Dyschromatosis, mottled pigmentation, reticulate pigmentary disorders

INTRODUCTION

The topic of reticulate pigmentation and its related terminology [Box 1] has been covered in major textbooks[1-8] but an overlapping and indiscriminate use of the terms [Box 1] leads to a lack of clarity on this important entity. Reticulate pigmentary disorders are a group of disorders which includes the inherited reticulate pigmentary disorders,[6,7] which present with hyperpigmented macules with a morphology reminiscent of "freckles" with varying pigment and size. Disorders with acquired "reticulate" or "reticular/net like'' pattern of pigmentation have a morphology that is unlike the classic "freckle like" hyperpigmentation seen in inherited reticulate pigmentary disorders. Dyschromatoses[1,3,5-8] is another term that encompasses conditions with both hyperpigmented and hypopigmented macules, many of which are small in size and irregular in shape. A third entity that often presents with reticulate or more accurately reticular pigmentation are the poikilodermatous conditions[6,7] wherein the telangiectasias are less pronounced than the fine net like pigmentation. To encompass all these entities mottled pigmentation.[1-8] could be an appropriately christened term which by definition includes all disorders with a variable hue, size and shape of pigmentation

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Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.104665

CLASSIFICATION

Till date there is no clear consensus[1-8] regarding the spectrum and definition of the term "reticulate pigmentation" even in speciality textbooks.[7] The various term used for these disorders are given in Box 1 and have been used interchangeably which makes the nosology difficult to comprehend. The true reticulate disorders classically include dyskeratosis congenita, Dowling Degos, acropigmentation of Kitamura, Naegeli Franceschetti Jadassohn (NFJ) syndrome, X linked reticulate pigmentary disorder, dyschromatosis symmetrica hereditaria and dyschromatosis universalis

How to cite this article: Sardana K, Goel K, Chugh S. Reticulate pigmentary disorders. Indian J Dermatol Venereol Leprol 2013;79:17-29.
Received: December, 2011 **Accepted:** August, 2012. **Source of Support:** Nil. **Conflict of Interest:** None declared.

Box 1: Definitions of Terminologies used in the text [3,4,8,13]

Mottled pigmentation refers to a blotchy pattern/ patchy appearance with *different* shades of color both hyper and/or hypopigmentation with the individual lesions having various sizes

Dyschromatosis is a term used for disorders with "freckle like" *hypo and hyperpigmented* macules of small size and irregular shape .

Reticular, "net like" or "lacy" in appearance refers to somewhat regularly spaced rings or partial rings with sparing of intervening skin.

Reticulate hyperpigmentation is characterized by *hyperpigmented* "ephelides like "lesions which have varying degrees of pigment and have indistinct borders and can be both congenital or acquired

Poikilodermatous conditions are characterized by atrophy, macular or reticulate pigmentation and telengietasias.

hereditaria.[8] The acquired disorders [Figure 1], [Table 1] have a pattern of reticulate pigmentation with macules of a size larger than the "freckle" like morphology of the true genetic reticulate pigmentary disorders. A minority of the acquired disorders have the classic "net like"/"reticular" pattern and include lichen planus pigmentosus, Riehl's melanosis [Figure 2], erythema ab igne [Figure 3], cutis marmorata, livedo reticularis and post inflammatory hyperpigmentation[2] amongst other conditions [Table 1]. Some of the acquired conditions [Table 1] have an admixture of hyperpigmented and hypopigmented macules which is strictly not in consonance with the definition of reticulate pigmentation [Box 1]. To encompass the differing morphology of the acquired and genetic forms of reticulate pigmentation[1-8] the umbrella term, mottled pigmentation [Box 1] is ideal and includes in addition to the true/genetic reticulate disorders, acquired reticular/reticulate conditions, poikilodermas and dyschromatoses [Figure 1 and Table 1].

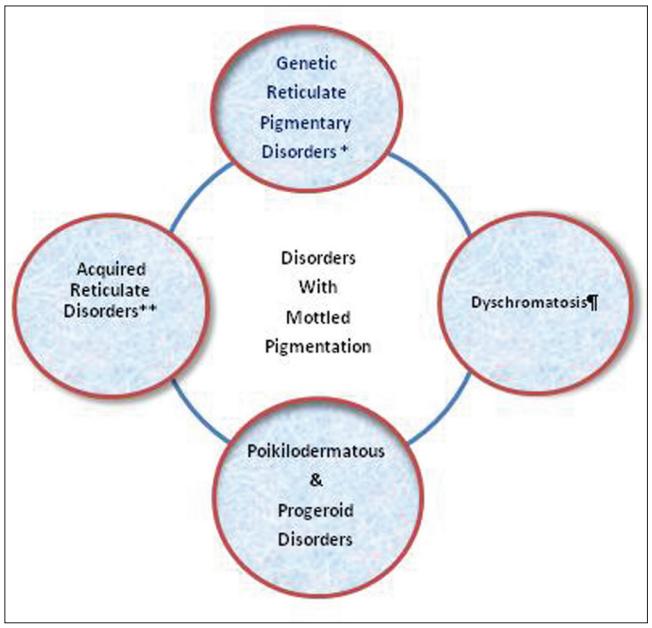

Figure 1: Spectrum of "Mottled" Pigmentary Disorders

* Hyperpigmented freckle like macules arranged in various patterns *including disorders with whorled/linear morphology*

**Includes "reticular/net like" pattern

¶ Disorders with admixture of irregular small sized hyerpigmented and hypopigmented macules

Though most of the true reticulate dermatoses are thought to be inherited, the genes responsible for their expression have not been definitively identified[2] Wherever genetic analysis has been done it has thrown up some interesting loci which can help "lump" entities[9,10] into one spectrum instead of splitting them into various types [Figure 4 a and b]. Most of the commonly seen genetic reticulate pigmentary disorders have defects localized to keratin 5 and keratin 14 gene. It has now been confirmed that NFJ/DPR [Figure 4a] are consequent to mutation of the KRT14 gene which results in haploinsufficiency and predisposes the keratinocyte to proapoptic stimuli.[5,6] Similar defects in keratin 5 predisposes to epithelial remodeling, melanosome mistargetting and plays an important role in melanosome transport.[5,6] These points to a defect in the keratinocyte melanocyte synergy which may consequentially affect the pigment regulation of melanocytes.[5,6] The similar morphology of Dowling Degos disease, acropigmentation of Kitamura and EBS with mottled pigmentation is also explained by their common gene loci [Figure 4a]. Conversely, the conventional "lumping" of DUH (dyschromatosis universalis hereditaria) and DSH (dyschromatosis symmetrica hereditaria) is not backed by genetic loci [Figure 4a] though they are morphologically similar.

Clinically, the reticulate pigmentary disorders can be classified based on the extent and distribution as localized, generalized, flexural or acral [Figure 5]. This distribution pattern can serve as a useful way to diagnose the conditions which have a predilection for certain body areas. A subset [Figure 5] of reticulate pigmentary disorders (dyskeratosis congenita, Mendes de Costa syndrome and dermatopathia pigmentsosa

reticularis/NFJ syndrome) are associated with features of ectodermal dysplasia, the presence of which provides a clue to their diagnosis .The salient features of the main disorders are summarized in Tables 2 and 3[1-8,11-14] which also serves as a differential diagnosis of the reticulate pigmentary disorders.

Table 1: Disorders characterized by mixed hyper or hypopigmented macules (Mottled Pigmentation)[3-5,7,8,11-14]

1. Primary dermatoses*	Amyloidosis cutis dyschromica, atopic dermatitis, confluent and reticulated pepillomatosis, cutis marmorata, dermatoheliosis, kwashiorkor, lichen planus pigmentosus, livedoid vasculopathy, nutritional deficiencies, pigmented contact dermatitis (Riehl's melanosis) [Figure 2], porphyria (congenital erythropoietic porphyria, PCT), prurigo pigmentosa, reticular erythematous mucinosis, sarcoidosis, urticaria pigmentosa
2. Infections*	Bejel, onchocerciasis (Leopard skin), post kala-azar dermal leishmaniasis, pinta, pediculosis-corporis (Vagabonds leucoderma), pityriasis versicolor, syphilis (leukoderma syphiliticum/necklace of Venus)
3. Autoimmune disorders*	Graft vs. host disease (chronic stage), scleroderma, lupus erythematosus, dermatomyositis, mixed connective tissue disease
4. Drug induced*	
Systemic agents	Arsenic poisoning, afloqualone/ tetracycline induced photoleukomelanodermatitis of Kobori, 5-fluorouracil, thiazide diuretics
Topical agents	Betel leaves (confetti like macules), benzoyl peroxide (contact dermatitis), diphencyclopropenone, monobenzyl ether of hydroquinone, chemical leucoderma
5. Malignant disorders	poikilodermatous mycosis fungoides, poikiloderma atrophicans vasculare (atrophic parapsoriasis)
6. Genetic disorders	
Reticulate pigmentary disorders¶	Anhidrotic ectodermal dysplasia, ataxia telangiectasia, acropigmentation of Dohi, anonychia with bizarre flexural pigmentation, Blooms syndrome, Berlins syndrome, chimeras, dermatopathia pigmentosa reticularis, Dowling–Degos disease, Haber's syndrome, hidrotic ectodermal dysplasia, incontinentia pigmenti¶¶, Mendes de Costa syndrome, mitochondrial disorders, Naegeli–Franceschetti–Jadassohn syndrome, reflex sympathetic dystrophy, reticulate acropigmentation of Kitamura, unilateral dermatomal pigmentary dermatosis¶¶, X-linked reticulate pigmentary disorder, zosteriform reticulate hyperpigmentation¶¶, Ziprkowski–Margolis syndrome
Disorders with dyschromatosis	Acromelanosis albo-punctata¤, dyschromatosis symmetrica hereditaria, dyschromatosis universalis hereditaria, epidermolysis bullosa with mottled pigmentation, Chediak–Higashi syndrome, Griscelli syndrome, Wende-Bauckus/Pegum syndrome, xeroderma pigmentosum
Poikilodermatous disorders	Acrogeria, dyskeratosis congenita, Fanconi's anemia, hereditary acrokeratotic poikiloderma of Weary, progeria
7. Miscellaneous*	Erythema ab igne [Figure 3], post-inflammatory dyspigmentation, post burn and radiation damage

*Acquired causes ¶Disorders conventionally considered to be reticulate pigmentary disorders ¶¶Linear/whorled distribution ¤Other syndromes with ectodermal dysplasia include Berlins syndrome and Lucky/Winter syndrome

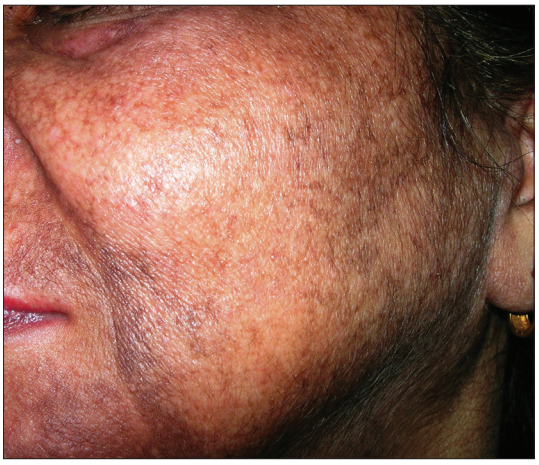

Figure 2: Reticulate pigmented macules on the face in a case of pigmented contact dermatitis (Riehl's melanosis)

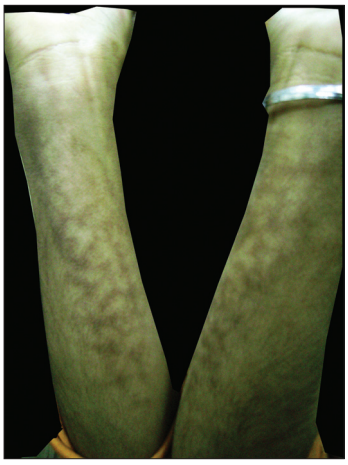

Figure 3: A case of Erythema ab igne with reticulate hyperpigmentation due to exposure to heat

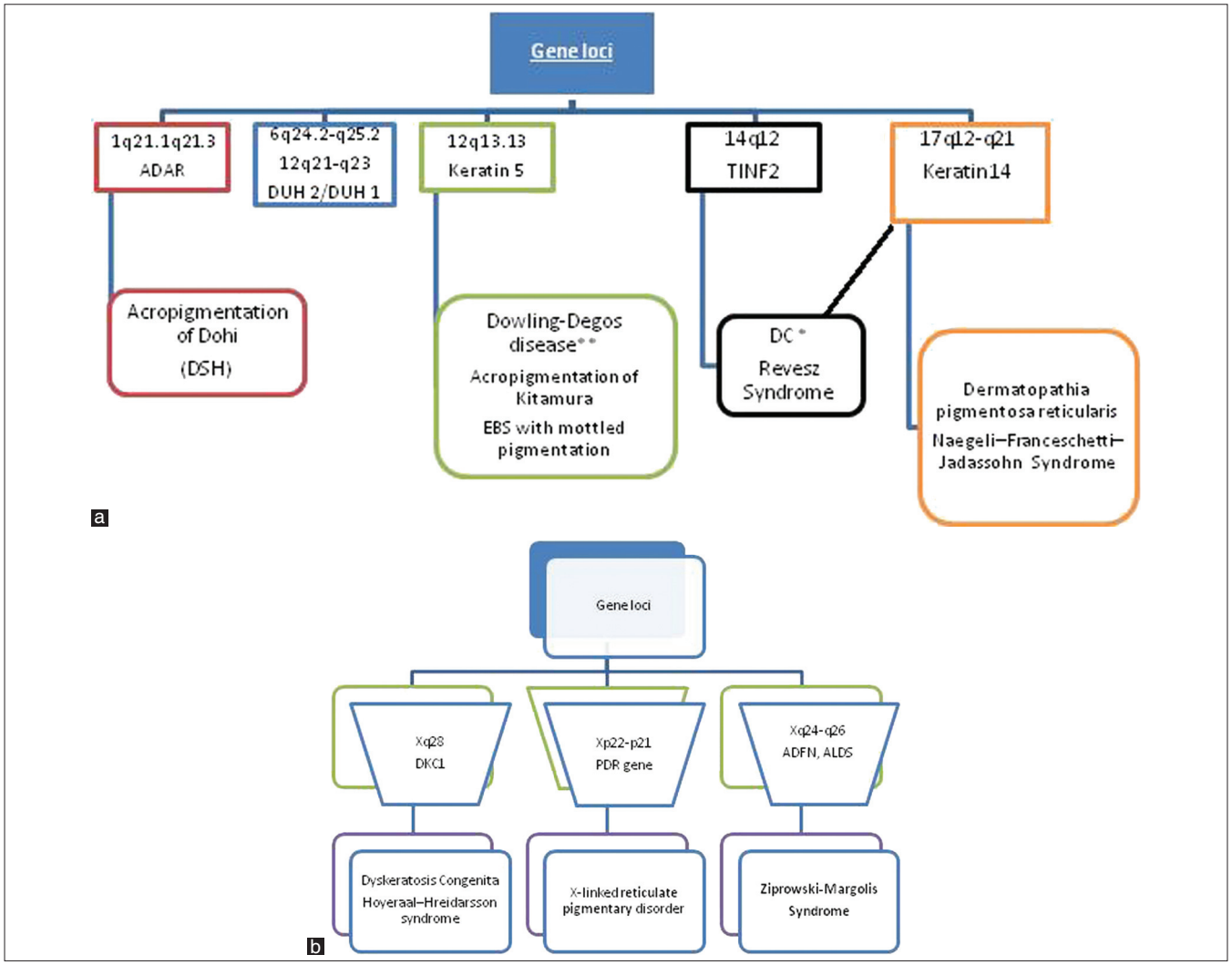

Figure 4: (a) A depiction of gene and chromosome loci in selected disorders with reticulate pigmentation[1-8] (http://www.ncbi.nlm.nih.gov/omim). (b) A depiction of gene and chromosome loci on X chromosome in selected disorders with reticulate pigmentation[1-8,12] (http://www.ncbi.nlm.nih.gov/omim)

*The other genetics loci are (DKC1,TERC,TERT,NOP10,KRT14; **Novel gene reported is 17p13.3

DUH: dyschromatosis universalis hereditaria; DC: dyskeratosis congenita

Our primary focus will be on the disorders with a genetic defect which largely fit into the classic morphology of true reticulate pigmentation and dyschromatosis.

GENETIC RETICULATE PIGMENTARY DISORDERS

Reticulate acropigmentation of Kitamura

This autosomal dominant condition has been largely reported from the Asian countries.[1,3,6,7] There are a few reports of familial cases[15] and the genetic loci [Figure 4 a] overlaps with Dowling Degos disease

Clinical features

This gradually progressive disorder has a onset in the first to second decade of life.[16] The lesions are slightly depressed, sharply demarcated black/brown macules localized to the dorsum of the hands and feet [Figure 6a].These increase in number and spread centripetally with age. The presence of small pits that cause a break in the epidermal ridge patterns [Figure 6b] on the palms and rarely on the dorsum of fingers, is a diagnostic feature.[17] Eventually the extensor aspects of the limbs, neck, upper trunk, face [Figure 7] and eyelids are affected. It can rarely involve the flexures and the palms and soles. Uncommonly disseminated hypo- or depigmented macules and papules have also been reported.[18]

Histologically, hyperpigmented lesions show epidermal atrophy, elongation and increased melanin in of

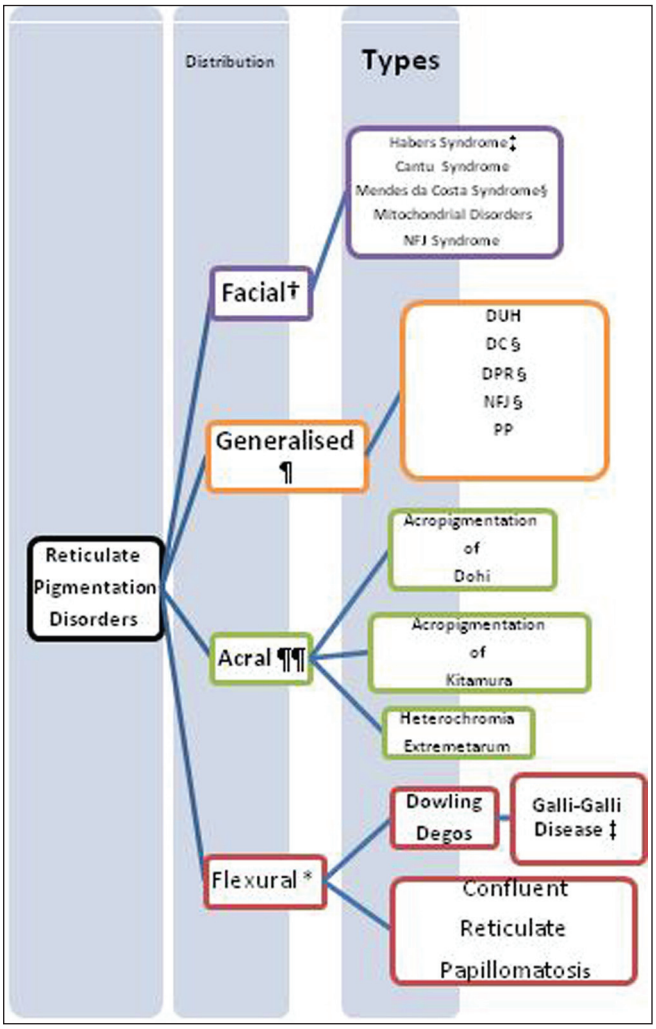

Figure 5: A depiction of the regional distribution of reticulate pigmentary disorders

DUH: Dyschromatosis universalis hereditaria; DC: Dyskertosis congenita

†Other conditions include progeria and progeroid disorders

¶Dyschromatosis universalis hereditaria (DUH), dyskeratosis congenita (DC), dermatopathia pigmentosa reticularis (DPR), Naegeli–Franceschetti–Jadasssohn (NFJ), prurigo pigmentosa (PP). Other entities include EBS with mottled pigmentation, Fanconi anemia, X linked reticulate pigmentary disorder, Berlins syndrome, Revesz syndrome, xeroderma pigmentosa, Werners syndrome and metageria

¶¶Other entities include Acrogeria, mandibuloacral dysplasia and acromelanosis progressiva.

*Other rare condition are dyschromatosis ptychotropica, anonychia with flexural pigmentation.

‡Variants of Dowling Degos: Haber's syndrome(rosacea like), Galli Galli disease (Suprabasal acantholysis), pigmentatio reticularis faciei et colli

§Ectodermal dysplasia with skin hair nail or eccrine defects (includes Berlins syndrome, Revesz syndrome, Lucky/Winter syndrome, acromelanosis albo-punctata)

rete ridges, and increased numbers of DOPA-positive melanocytes.[2,19]

Treatment and prognosis

There is very little that can change the course of the pigmentation. Treatment with 20% azelaic acid resulted in remarkable reduction of hyperpigmentation in one patient.[20]

Acropigmentation symmetrica of Dohi (dyschromatosis symmetrica hereditaria, DSH)

This autosomal dominant disorder[21] commonly described in Asians has an onset during childhood. There is a pathological mutation of the double-stranded RNA-specific adenosine deaminase gene (ADAR1 or DSRAD) and the location is at the 1q21.1-q21.2[22] [Figure 4a]. This enzyme plays an important role in post-transcriptional modification of the messenger RNA (RNA editing).[22] Impaired RNA editing affects the differentiation of melanoblasts during melanogenesis into hyper and hypoactive melanocytes.[22] Consequentially, the affected melanoblasts are those that emigrate the farthest, namely the hands and feet, thus accounting for the distribution of the disorder.[22]

Clinical features

The lesions begin in the first to second decade and are classically non progressive .The skin findings are characterized by hypo- and hyper-pigmented macules on the dorsal and ventral aspects of the hands [Figure 8] and feet, which may extend to the proximal portions of the limbs (knees and elbows). Similar lesions (freckle-like macules) can be found on the face.[3,5-7,13]

The histology of the lesions shows either increased or decreased basilar pigmentation in the hyperpigmented or hypopigmented lesions respectively. Occasional pigment incontinence is seen in hypopigmented lesions.[2]

Treatment and prognosis

Surgical therapy with transplantation of thin split-thickness skin autografts has been tried.[23] Q-switched ruby, Q-switched Nd:YAG, Q-switched alexandrite, and the 510 mm pulsed dye lasers have been used to treat hyperpigmented macules especially on face.[13]

Dyschromatosis universalis hereditaria (DUH)

Dyschromatosis universalis symmetrica hereditaria was originally believed to have a localized acral form, dyschromatosis symmetrica hereditaria (reticulated acropigmentation of Dohi).[13,14] A recent study though has clarified that genetically it is different from dyschromatosis symmetrica hereditaria (DSH) with the defect localized to 12q21-q23 loci[22,24] [Figure 4a]. It has an autosomal dominant pattern of inheritance and has been reported from Japan and India.[5,7]

Table 2: Genetic diseases with reticulate hyperpigmentation[3-5,7,8,11-14]

Disease	Inheritance (gene defect)	Distribution	Special features	Associated findings
Acropigmentation of Kitamura	AD	Acral	Pigmented atrophic macules	Palmar pits
Acropigmentation of Dohi (Dyschromatosis symmetrica hereditaria) (DSH)	AD (few cases AR) Males commonly affected	Acral	Hypopigmented and hyperpigmented macules without atrophy	Freckle like macules on the face
Dermatopathia pigmentosa reticularis	AD	Generalized with mucosal involvement	Hypopigmented macules, alopecia, onychodystrophy	Sweating disorders; loss of dermatoglyphics; acral non scarring blisters palmar/ plantar hyper keratoses
Dyschromatosis universalis hereditaria	AD	Generalized	Reticulate pigmentation involving the whole body.	Nail: pterygium, pigmentation of the palm, soles and mucosa, rarely ocular, developmental defects
Naegeli–Franceschetti–Jadasssohn	AD	Generalized (Face, neck, flexures)	Onset in early childhood, fading of pigmentation reported in adolescence	Keratoderma; enamel hypoplasia; hypohidrosis; heat intolerance, nail dystrophy
Mendes da Costa syndrome	XLR	Generalized including face and limbs	Blistering with hypopigmented macules	Microcephaly; mental retardation; atrichia; short conical fingers
Epidermolysis bullosa with mottled pigmentation	AD	Trunk, proximal extremities	Mechanobullous disorder which leads to pigmentation	Keratoderma; carious teeth; photosensitivity
X-linked reticulate pigmentary disorder (PDR) Old name: X-linked cutaneous amyloidosis	XLR	Brown pigmentation along the lines of Blaschko in females and reticulate pigmentation in males	Coarse silver colored hair, unswept eyebrows, hypohidrosis and amyloid deposition in adults	Gastrointestinal disorders, failure to thrive and early death. Other defects include corneal dystrophy severe photophobia or chronic respiratory disease.
Dowling–Degos disease	AD	Flexural then generalized	Onset delayed, worsens in hot weather	Perioral pits; keratoses; epidermal cysts
Anonychia with flexural pigmentation	AD	Flexural	Hypopigmented macules	Sparse hair; hypohidrosis; decreased dermatoglyphics; absent/rudimentary nails
Dyschromatosis ptychotropica	Single report	Neck, inguinal and axillary regions.	Reticulate hyper and hypopigmentation	Epileptic encephalopathy, severe intellectual disability, optic atrophy, progressive cerebellar and supratentorial atrophy (Progressive encephalopathy with edema and hypsarrythmia (PEHO) syndrome)

Clinical features

It has onset in early childhood and is characterized by mottled pigmentation which originates from the hands and can progress to involve the trunk, extremities and the face. The lesions are characterized by hyperpigmented macules admixed with hypopigmented lesions [Figure 9] and can also involve the palms, soles and oral mucosa.[1,3,5-7,13,14] The nail are hyperpigmented dystrophic with pterygium formation being the classic finding. Various associations that have been reported[7,25] include coxa valga, nerve compression, small stature, high-tone deafness, photosensitivity and neurosensory hearing defect.

Treatment and prognosis

As the condition is non-progressive, counseling seems to be the best available option. Targeting the pigmented lesion with the Q-switched alexandrite laser is an option[26] but recurrence is inevitable.

Unilateral dermatomal pigmentary dermatosis (UDPD)

It is a segmental form of dyschromatosis which has been included under the same spectrum as DUH and DSH. In UDPD, the distribution is segmental. It is differentiated from segmental neurofibromatosis and partial unilateral lentiginosis by the mottled hyperpigmentation and hypopigmentation.[27]

Table 3: Selected genetic poikilodermas[7]

Disease	Inheritance	Distribution / Clinical findings	Poikiloderma	Associated findings
Hereditary acrokeratotic poikiloderma	AD	Acral bullae with acral keratoses. Begins as vesicopustules followed by widespread eczematous dermatitis (seen between 6 months-5 years). Keratotic papules on the hands, feet, elbows and knees are seen subsequently	Diffuse poikiloderma with striate and reticulate atrophy (spares face, scalp and ears)	Eczematous dermatoses may be associated
Kindler syndrome	AR	Acral bullae Acral Keratoses+/- Spontaneous blistering in the neonatal period Photosensitivity and palmoplantar hyperkeratosis can also be seen	Widespread poikiloderma with progressive atrophy	Marked skin atrophy, webbing of digits.
Hereditary sclerosing poikiloderma	AD	Starts in the first year of life apparent by the age of 4 years.	Poikiloderma involves the whole body but spares the upper chest.	Reticulated or linear sclerotic and hyperkeratotic bands primarily located in the flexural areas.
Navajo syndrome	AR	Seen in Navajo Indians, associated with papular exanthemas	Pigmentation is acral initially and then evolves to spread over trunk	Pachyonychia, recurrent pulmonary infections,
Rothmund–Thomson syndrome	AR	Bullae seen on the photoexposed skin, acral Keratoses+/-	Photodistributed erythema followed by mottled pigmentation	Photosensitivity; cataracts; alopecia; nail and dental defects; warty keratoses over bony prominences

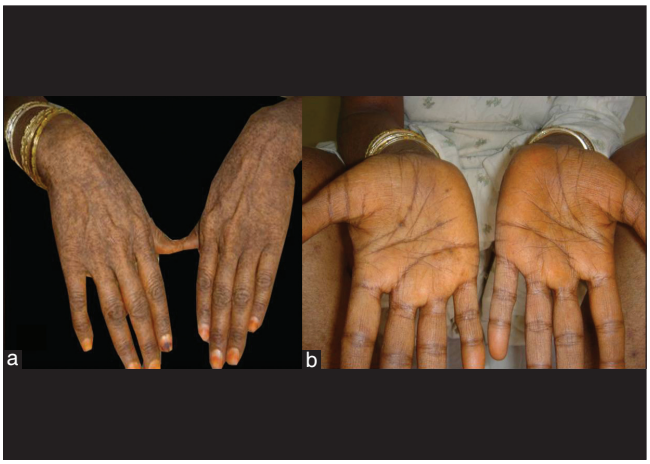

Figure 6: (a) and (b) Reticulate acropigmentation of Kitamura with depressed hyperpigmented macules on dorsa of bilateral hands and palmar pits with breaks in the epidermal ridge pattern

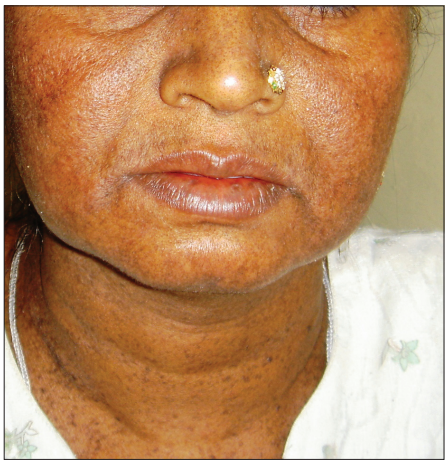

Figure 7: "Freckle like" hyperpigmented macules involving the face and the neck, in a case of reticulate acropigmentation of Kitamura

Dermatopathia pigmentosa reticularis

It is an autosomal dominant disorder that classically has a generalized distribution. The diagnostic triad is of reticulate hyperpigmentation, noncicatricial alopecia of the scalp, eyebrows, axillae, and onychodystrophy.[1,3,5,7,14,28] Genetic analysis has revealed a close association with NFJ syndrome and EBS with mottled pigmentation[28] [Figure 4a].

Clinical features

The hyperpigmentation is generalized, and is most prominent on the trunk and proximal extremities. The presence of small "confetti" like macules gives rise to a characteristic reticulate pattern. The nails show onychodystrophy and loss of nails, with formation of pterygium [Figure 10a] during the second year of life. There is progressive alopecia

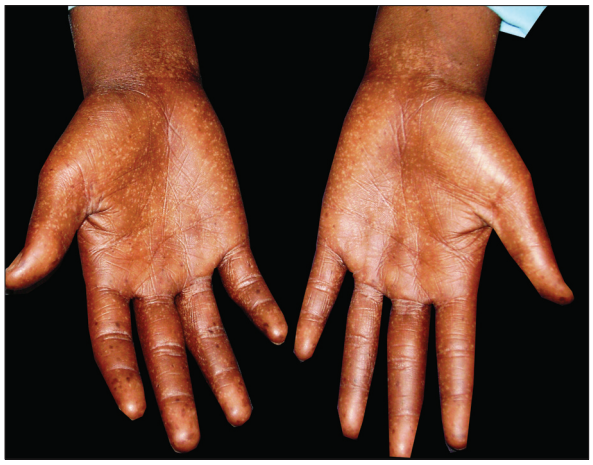

Figure 8: Freckle like hypo and hyperpigmented macules on the palms in a case of dyschromatosis symmetrica hereditaria (DSH)

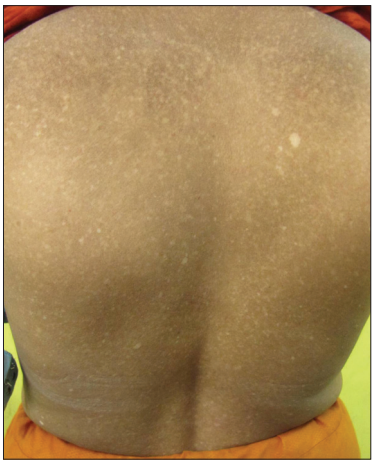

Figure 9: Truncal involvement with hypo and hyperpigmented macules in a case of dyschromatosis universalis hereditaria (DUH)

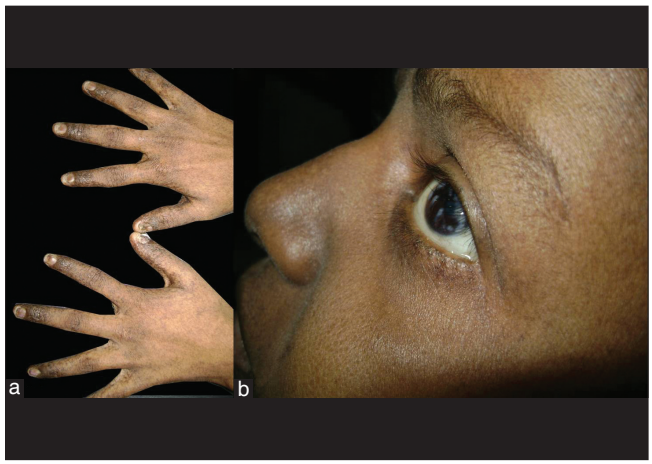

Figure 10: (a) A patient of dermatopathia pigmentosa reticularis with reticulate pigmentation over dorsum of both hands and associated dystrophy of finger nails with thin lusterless nails. (b) Also seen are fine punctuate corneal opacities and brown pigmentation of bulbar conjunctiva

involving the scalp, eyelashes, eyebrows and axilla. Other features include hypohidrosis or hyperhidrosis, punctuate palmoplantar keratoses, absent dermatoglyphics, and non-scarring acral blisters.[14] Fine punctate spots on the cornea and brown pigmentation of the bulbar conjunctiva have been also reported [Figure 10b].

A very close differential is NFJ syndrome[28,14] [Table 2]. DPR has marked alopecia, absence of dermatoglyphics, hyperhidrosis and pigmentation of the mucosa with onychodystrophy. NFJ on the contrary manifests with dental defects with little or no nail dystrophy. Also there is a tendency of fading of pigment by adolescence. Recent genetic analysis reveals that they are probably manifestations of the same genotypical defect [Figure 4a].

Histology reveals clumps of melanin-laden melanophages seen in the papillary dermis in a patchy distribution without overlying epidermal hyperpigmentation.[2]

Treatment and prognosis

There is no known treatment for the pigmentary disorder.[7] The associated keratoderma though has been successfully treated with etretinate.[29]

Dowling-Degos disease and its variants

Syn: Dark dot disease, reticular pigment anomaly of flexures

This is a progressive, disorder of pigmentation, characterized by flexural, pigmented reticulate macules and comedone-like papules on the back and neck.[1,3,5,7,14] It is inherited as an autosomal dominant trait[1,2] and the gene defect is believed to be localized to kertain.[5,30] It is usually sporadic though some affected families have been reported.

As the localization of the gene [Figure 4a] overlaps with a related condition it is also referred to as Dowling Degos – Kitamura disease.[7,10]

Clinical features

The onset is delayed with an onset in early adulthood (30–40 years). The macules gradually become confluent in a "lacelike" or reticulate pattern. Reticulate pigmentation of the flexures is seen which is gradually progressive and symmetrical. The initial sites affected are the groins and the axillae [Figure 11a] and the pigmentation insidiously progresses to involve the neck, inframammary creases, trunk, proximal arms and the antecubital fossae. Acneiform perioral pits [Figure 11b] and comedones are the hallmark of the disease. There are also comedolike, hyperkeratotic follicular papules on the neck and axillae and epidermal

cysts.[1,3,5,7,14] The hyperkeratotic papules are thought to arise in areas of friction. Other associated findings include hidradenitis suppurativa,[31] keratoacanthoma[32] and squamous cell carcinoma.[31] Hypopigmented macules on the trunk can be seen as a association in some cases.[18]

Histologically, the characteristic finding is of an atrophic epidermis with long, narrow, branched rete ridges that intertwine at their bases ("antler-like" appearance).[33] Increased melanin in the basal membrane and dilated follicles with cysts can also be seen.

Treatment and prognosis

There is no effective therapy. Many topical medications including azelaic acid, retinoic acid, hydroquinone and corticosteroids, as well as systemic retinoids, have been tried with minimal improvement.[1,3,6,7] However, there is a single report of the use of the Er:YAG laser with pulse energy of 1,000 and 1,200 mJ, which after three consecutive passes led to favorable results.[34] Probably the atrophic lesions could respond with the use of fractional lasers.

Variants of Dowling Degos disease [Figure 5]

Haber's syndrome is a disorder characterized by pigmented keratotic papules on the axilla, neck, and torso with pitted scars on the face and persistent facial erythema.[35] Galli–Galli disease is essentially an acantholytic variant of DDD.[36] Pigmentatio reticularis faciei et colli is possibly a variant of DDD which presents with hyperpigmentation of the face and neck with multiple epidermoid cysts.[37]

Dyskeratosis congenita

Syn: Zinsser-Cole-Engman syndrome

This disorder is commonly a X-linked recessive disorder[38] though AD[39] and AR[40] inheritance have also been reported [Figure 4b] The defective genes include dyskerin, *TERC*, *TERT*, *NHP2*, and *NOP10*. The genetic defect in the X-linked form is located on Xq28 (*DKC1* gene for dyskerin).[41] Autosomal-dominant inheritance is often associated with mutations in htr (*hterc*).[39]

Clinical features

There is a lacy reticulate telangiectatic hyperpigmentation interspersed with areas of hypopigmentation [Figure 12a] seen on the face, neck, trunk and upper thighs.[38] Atrophy and cyanosis of the dorsal aspects of the hands and feet with hyperkeratosis and hyperhidrosis of palms and soles may also be present. The mucosa shows leukokeratosis which may involve the pharynx, anorectal and urogenital mucosae. The nails are dystrophic with pterygium formation [Figure 12b] and the hair is thin, lusterless and sparse.

The extracutaneous manifestations include early dental loss or extensive caries, aplastic anemia with bleeding problems and purpura, esophageal diverticuli with dysphagia, retardation of growth, hypogonadism and mental retardation.

Hoyeraal–Hreidarsson syndrome is probably a variant characterized by intrauterine growth retardation, cerebellar hypoplasia, mental retardation, microcephaly, progressive combined immune deficiency, and aplastic anemia.[42] The syndrome is genetically heterogeneous though some patients demonstrate DKC1 gene mutations and are therefore allelic to dyskeratosis congenita.

Another severe variant of DKC is Revesz syndrome[7,8,38,39] characterized by exudative retinopathy, leucoplakia,

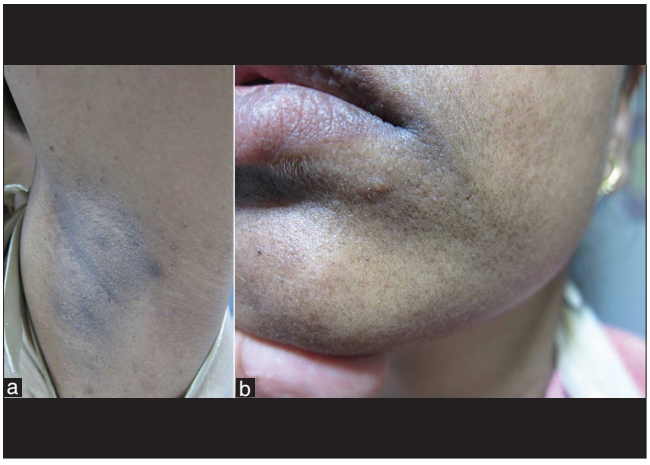

Figure 11: (a) A case of Dowling Degos with keratotic papules and hyperpigmented macules on the axilla. (b) Note the presence of perioral acneiform pits

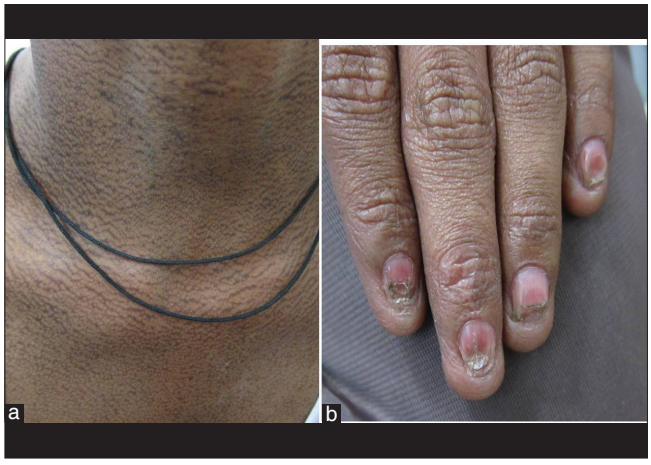

Figure 12: (a) Case of dyskeratosis congenita with lacy reticulate pigmentation of neck with associated telangiectasias. (b) Also seen is onychodystrophy of finger nails and pterygium formation

nail pits, sparse hair, CNS defects and aplastic anemia. The gene defect lies in chromosome 14q12 and TINF2 gene.

Treatment and prognosis

The disorder has a a poor prognosis and death is the rule, often in the third decade. Associated malignancies include Hodgkin's disease, oropharyngeal, esophageal, gastric, and pancreatic carcinomas, and squamous cell carcinomas. The cause of mortality includes malignant neoplasms, infection by opportunistic agents, failure of bone marrow and hematological malignancies (mainly in the second or third decade).

Fanconi anemia

Syn: Familial pancytopenia or familial panmyelophthisis

This is a autosomal-recessive condition with five complementation groups (FA-A, FA-B, FA-C, FA-D, and FA-E)[43] which affect hematopoiesis. FA-A has been localized to 16q24.3, and FA-D to 3p22.26.

Clinical features

The skin has diffused mottled pigmentation (hypopigmentation, hyperpigmentation, and café-au-lait macules).[44] The other findings include absence of the thumbs, aplasia of the radius, severe hypoplastic anemia, thrombocytopenia, retinal hemorrhage, strabismus, generalized hyperreflexia and testicular hypoplasia.

The syndrome is associated with increased risk of myelomonocytic leukemia, squamous cell carcinoma, and hepatic tumors. Human papillomavirus DNA is often found in the squamous cell carcinomas. Both cutaneous and pulmonary manifestations of associated Sweet's syndrome have been reported.

MISCELLANEOUS GENETIC RETICULATE PIGMENTARY DISORDERS

These are some of the rare conditions encountered in clinical practice and are incorporated for the sake of completion of text.[5,7,8,13,14]

Acromelanosis albo-punctata (ectodermal dysplasia)

This condition is characterized by diffuse hyperpigmentation with superimposed atrophic guttate hypomelanosis seen primarily on the dorsal aspects of the hands and flexures. Other features include keratotic follicular papules on the legs, pili torti, platynychia.

Berlin syndrome (ectodermal dysplasia)

This has been described in one family of Iranians living in Israel. The patients had generalised melanoleucoderma with ectodermal dysplasia (hypodontia, hypotrichosis), short stature, furrowing around the mouth and eyes, pokiloderma around the joints, sexual underdevelopment in male patients and mental retardation.

Lucky/Winter syndrome (ectodermal dysplasia)

This was described in two unrelated children with features of ectodermal dysplasia, generalized hyperpigmentation with superimposed guttate hypomelanosis on the flexures. Other features seen were scant lightly pigmented hair, enamel hypoplasia (single central incisor in one patient), digitalized thumb and short stature.

Ziprowski-Margolis syndrome

This X linked disorder [Figure 4b] is also known as the albinism and deafness syndrome. In this there is pigmentary dilution of the hair and skin except for the buttock and genitalia. With time pigmented macules are seen over this giving the "leopard like" appearance. Other features include deaf mutism and heterochromia irides.

Wende–Bauckus/Pegum syndrome

The disease has an onset at one year of age and presents with a background hyperpigmentation (gray–brown) which is more pronounced on the trunk than on the extremities. The superimposed white macules which are confluent on the flexures give it the "mottled" appearance.

Chédiak–Higashi syndrome (CHS) and Griscelli syndrome (GS)

Though these are characterized by pigmentary dilution of the skin, they may also have diffuse hyperpigmentation with superimposed guttate hypopigmentation in sun-exposed areas. Other findings include bleeding diathesis (CHS), neurologic abnormalities (CHS, GS1), immunodeficiency (CHS, GS2).

ACQUIRED RETICULATE PIGMENTARY DISORDERS

A detailed list is given in Table 1, but we will focus on two conditions which present primarily with a macular morphology and thus mimic the morphology of genetic reticulate disorders.

Confluent and reticulate papillomatosis (CRP)

This eponymous entity is named after two French

dermatologists, Gougerot and Carteaud,[45] and it has a variable clinical presentation. This condition is commoner in females than males.

Clinical features

The onset of the disease is around 20 years of age. The lesions are red, verrucous, minimally scaly papules, occuring in the inframammary, interscapular and epigastric regions, which coalesce to form brown plaques.[5,7,13,14,45] There is accentuation in the neck and in the axillae. With progression, the lesions acquire the characteristic reticulate appearance.

The criteria for diagnosis are.[46]

- Hyperpigmented papules and plaques involving the chest and/or back with a reticulated peripheral margin.
- No hyphae suggestive of tinea versicolor present on potassium hydroxide preparation or skin biopsy.
- Histological changes including hyperkeratosis, papillomatosis, acanthosis alternating with mild atrophy, and evidence of mild dermal inflammation and vasodilatation.

Treatment and prognosis

Topical agents include tacalcitol and calcipotriol. The treatment of choice for CRP is minocycline,[47] which is given in a dose of 100–200 mg per day for weeks to months. Other antibiotics tried include clarithromycin (500 mg daily for five weeks), erythromycin (1000 mg daily) and azithromycin (500mg daily). Isotretinoin and etretinate are also effective drugs.[48]

Prurigo pigmentosa

It is a rare inflammatory skin disease of unknown pathogenesis and is characterized by pruritic, erythematous urticarial papules, papulovesicles, or vesicles that are symmetrically localized on the trunk and nape and that resolve quickly leaving behind reticulate pigmentation.[7,49] Lesions in different stages are usually present together and disease has a waxing waning course.[49] It is seen most commonly in young Japanese women. Various causative factors have been implicated such as ethnic predisposition, environmental causes, seasonal variation, mechanical stimuli, contact allergens, drugs such as bismuth subsalicylate containing antacid, *Helicobacter pylori* infection, atopic disease etc.[50,51] A comprehensive clinico-histopathological diagnostic criteria have been given by Boer *et al*.[49]

Histopathological features range from superficial perivascular dermatitis, spongiotic dermatitis, and lichenoid dermatitis to post-inflammatory hyperpigmentation, depending on the stages of skin lesions.[49]

Various medications have been tried with variable results. Antihistamines and steroids have been found to be ineffective whereas minocycline, tetracycline and doxycycline have shown promising results.[48] Other established treatments include sulfonamides (dapsone, sulfamethoxazole), macrolide antibiotics (clarithromycin, roxythromycin), potassium iodide, and isotretinoin.[52]

CONCLUSION

A practical clinical classification based on regional distribution can help the clinician to diagnose most of the genetic reticulate disorders [Figure 5] but probably genetic analysis might be a more rational way of analyzing these conditions [Figure 4a and b]. This [Figure 4a and b] has shown that probably the reticulate disorders have variable phenotypical expressions of similar gene defects.The therapy of most of the genetic disorders is inadequate and it is practically impossible to ameliorate the defect. Presently, the clinician can at best counsel the patients about the invariably benign course of the disorder.

The acquired causes are simpler to diagnose [Table 1] and may not pose a problem as they are usually associated with the primary dermatoses in most cases. The acquired conditions are equally frustrating to treat but as they have a more dominant primary cutaneous morphology which is of primary concern, the secondary reticulate pigmentation is less of an issue.

We believe that a rational classification of these disorders [Box 1] necessitates using the overarching term "mottled pigmentation" which would include the "true/genetic" reticulate pigmentary disorders [Figures 6-12] which are different morphologically from the acquired disorders [Figures 2 and 3].

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Multiple Choice Questions

1. The term dyschromatosis includes all entitites with
   a. Hypo and hyperpigmented macules
   b. Net like pattern of pigmentation
   c. Hyperpigmented macules only in a reticular pattern
   d. Hypopigmented macules only in a reticular pattern

2. The classically described true reticulate disorders include all except
   a. Dyskeratosis Congenita
   b. Acropigmentation of Kitamura
   c. Dowling Degos disease
   d. Lichen planus pigmentosus

3. The acquired causes of reticulate hyperpigmentation include all except
   a. Lichen planus pigmentosus
   b. Dyskeratosis congenita
   c. Atopic dermatitis
   d. Erythema ab agne

4. Palmar pits are characteristically seen in
   a. Acropigmentation of Kitamura
   b. Dowling Degos disease
   c. Dyskeratosis congenita
   d. Dyschromatosis universalis hereditaria

5. The triad of Dermatopathia Pigmentosa Reticularis includes all except
   a. reticulate hyperpigmentation
   b. noncicatricial alopecia of the scalp, eyebrows, axillae
   c. palmar hyperlinearity
   d. onychodystrophy

6. Comedone like papules with acneiform pitted scarring is seen in
   a. Acropigmentation of Kitamura
   b. Dowling Degos disease
   c. Dyskeratosis congenita
   d. Dyschromatosis universalis hereditaria

7. Triad of Dyskeratosis congenita includes all of these except
   a. Reticulate telangiectatic hyperpigmentation
   b. Leukokeratosis
   c. Dystrophic nails with pterygium formation
   d. Cicatricial alopecia

8. All of these entities share common genetic loci except
   a. Dyskeratosis congenital
   b. Revesz syndrome
   c. Hoyeraal–Hreidarsson syndrome
   d. Fanconi's anemia

9. Antler like appearance is the histological feature of
   a. Acropigmentation of Kitamura
   b. Dowling Degos disease
   c. Dyskeratosis congenital
   d. Dyschromatosis universalis hereditaria

10. Most of the genetic reticulate pigmentary disorders have gene defect localized to
    a. Keratin 9 and 18
    b. Keratin 1 and 10
    c. Keratin 5 and 14
    d. Keratin 6 and 16

Answers
1. a, 2. d, 3. b, 4. a, 5. c, 6. b, 7. d, 8. d, 9. b, 10. c