A Clinical Classification of Pigmentary Disorders

1

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Introduction

Background

Human skin colour is determined by pigment located in the epidermis and the dermis. The most critical of these pigments is melanin, produced by the epidermal melanocytes. Haemoglobin plays a role, especially in lightly pigmented skin where slight variations in perfusion are clearly visible as erythema. Other pigments such as bilirubin and beta-carotene also play a minor role in physiological and pathological pigmentation [1]. Occasionally certain metals (e.g. iron, silver, gold), drugs and deposits of drug-melanin complexes can cause altered skin pigmentation. Areas of skin indentation can sometimes appear 'hyperpigmented' as an optical illusion, and skin overlying venous structures can appear bluish in colour due to the Tyndall effect.

Melanocytes are located in the basal layer of the epidermis, and their main function is melanin synthesis (melanogenesis). This takes place in specialized organelles called melanosomes, with tyrosinase being the key enzyme in the melanin biosynthetic pathway. Mature melanosomes are transferred to the surrounding keratinocytes. There is on average one melanocyte for each 36 keratinocytes, this is referred to as the multicellular epidermal melanin unit [2]. The ratio of melanocytes to basal cells is 1:4 to 1:9 depending on the region of the body but irrespective of ethnic origin. It is the number and size of mature melanosomes, and not the number of melanocytes, that results in the variations in skin colour seen among different ethnicities [3, 4].

There are two main types of melanin that influence the colour of the human skin: eumelanins that are brown-black and phaeomelanins that are yellow-orange. These melanins are found in different proportions in different populations. In most of the Caucasians, the Indians and the Africans, the predominant pigment is eumelanin. In the Mongoloids and the red-headed Caucasians, the predominant pigment is phaeomelanin [5].

The main influence on melanin synthesis is genetics [6]. The inherent genetic coding expressed by the melanocyte is the most important determinant in a given person's general pigmentation. Other factors that can stimulate or inhibit skin pigmentation include exposure to UV light, hormonal influences (i.e. MSH, ACTH) and biochemical substances (e.g. melatonin, β-lipoprotein).

In different pigmentary disorders, melanin synthesis, transfer, deposition or degradation may be defective.

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Definitions

The pigmentary disorders include those where there is a lightening in skin colour, a darkening in skin colour, a mixed pattern of lightening and darkening in skin colour, or the development of an unusual skin colour. The vast majority of pigmentary disorders are due to quantitative or qualitative defects in the synthesis, transfer, deposition and degradation of melanin. Abnormal skin colour can also result from disturbances in both endogenous and exogenous pigments. On broad terms, changes of skin colour can be called dyschromias. However, in this chapter, we use the terms hypopigmentation, hyperpigmentation and mixed type of pigmentation (hyper- and hypopigmentation) as the main categories of pigmentary disorders.

Hypopigmentation refers to any form of reduced pigmentation, whereas hypomelanosis refers specifically to a decrease in melanin content. Hypomelanosis may be due to decreased melanin production or defective melanosome function despite a normal number of epidermal melanocytes (melanopaenic hypomelanosis), or it may be due to a decreased number of epidermal melanocytes (melanocytopenic hypomelanosis). *Depigmentation* or leukoderma describes total loss of pigmentation resulting in a whitish appearance of the lesional skin. It is almost always due to a deficiency in melanin [7].

Hyperpigmentation on the other hand refers to any form of increased pigmentation, with hypermelanosis or melanoderma specifically referring to an increase in melanin content. Epidermal melanin excess produces a brownish skin colour and may be due to increased melanin production by a quantitatively normal melanocyte density in the epidermis (melanotic hypermelanosis), or it may be due to an increased number of epidermal melanocytes (melanocytic hypermelanosis). Dermal melanin excess produces a blue-grey skin colour and may be due to production of melanin by ectopic dermal melanocytes (dermal melanocytosis) or due to an abnormal transfer of melanin from epidermal cells to the dermis (pigmentary incontinence) [8].

Abnormal skin colour may also result from disturbances in non-melanin pigments [8]. Examples of this include:

- Variations in the haemoglobin content within the skin (e.g. anaemia) or localized vascular disorders (e.g. Bier spots and naevus anaemicus) causing the skin to appear pale (hypopigmented).
- Haemosiderin deposition resulting in a red-brown discolouration, a common sequel of chronic venous insufficiency.
- Xanthoderma resulting in a yellow-orange skin discolouration and most commonly due to jaundice and carotenoderma.
- Heavy metals (e.g. iron, silver, gold) and traumatic, aesthetic or medical tattoos.
- Increased epidermal thickness leading to diffuse, patchy or reticulated light to dark brown hyperpigmentation.
- Chronic avoidance of washing inducing hyperpigmented, and often keratotic, papules and plaques (e.g. retention hyperkeratosis).
- Abnormal colouration of the sweat (i.e. chromhidrosis or pseudo-chromhidrosis).

Approaching the Patient

History

When taking a history from a patient presenting with a pigmentary disorder, it is important to determine the age of onset of the skin changes. For changes that are present from birth or develop in the first 1 to 2 years of life, the skin disorder is likely to be congenital and represent a genodermatosis, whereas pigmentation changes that develop after this time are more typically acquired, and the aetiology is more varied [1].

For pigmentary disorders presenting at any age, it is important to elicit the following information:

- Was the pigmentation preceded by injury, inflammation or pruritus?
- What was the evolution/development of the pigmentation?

Table 1.1 Acquired hyperpigmented dermatoses with prominent involvement of sun-exposed skin

Acquired brachial cutaneous dyschromatosis
Ashy dermatosis
Carcinoid syndrome
Chronic liver disease
Chronic renal insufficiency
Drug-induced hyperpigmentation – photoallergic and phototoxic drug reactions, heavy metals (including silver and gold), drugs (including amiodarone, chlorpromazine and related phenothiazines, hydroxychloroquine, minocycline, phenytoin)
Ephelides
Endocrine disorders – acromegaly, Addison's disease
Erythromelanosis follicularis faciei et colli
Erythrose peribuccale of Brocq
Haemochromatosis
Lichen planus pigmentosus
Linea fusca
Melasma
Nutritional deficiencies – vitamin B12, vitamin B3, vitamin C, folic acid
Ochronosis – alkaptonuria, exogenous ochronosis
Phytophotodermatitis
Poikiloderma of Civatte
Porphyrias – hereditary coproporphyria, porphyria cutanea tarda, porphyria variegata
Post-inflammatory hyperpigmentation – especially acne, atopic dermatitis, cutaneous lupus, dermatomyositis, infections (including chikungunya), physical or chemical injuries
Riehl's melanosis

- Is the pigmentation persistent and stable, or is it transient and intermittent?
- Is the pigmentation related to sun exposure? (Table 1.1.)
- Is the pigmentation symptomatic?
- Is there pathology involving other organs?
  - For pigmentation that develops within the first 1 to 2 years of life (i.e. congenital disorders), specifically consider musculoskeletal, cardiac, ocular, neurodevelopmental and endocrine anomalies.
  - For pigmentation that develops after the first 1 to 2 years of life (i.e. acquired disorders), specifically consider neoplastic (including melanoma), endocrine, nutritional, metabolic and autoimmune disorders.
- Is there a family history of similar pigmentation?
- Is there a history of parental consanguinity?

Table 1.2 Physiological pigmentation in skin of colour

Familial periorbital hyperpigmentation
Hyperpigmentation of the tongue
Inherited patterned lentiginosis in black people
Longitudinal melanonychia (multiple)
Pigmentary demarcation lines
Pigmentation of the gingiva
Pigmented plantar and palmar macules
Transient pigmentary lines of the newborn

- Are there any offending drugs?
- Is there a relevant occupational history (e.g. contact with phenolic substances)?
- Is there a relevant travel history (e.g. to areas endemic for treponematoses, leishmaniasis, leprosy or onchocerciasis)?
- Is there a relevant sexual health history (e.g. risk factors for syphilis or HIV/AIDS)?

Examination

Examination should begin with an assessment of the patient's normal constitutive skin colour. Some lesions are more common in certain skin types (races), e.g. ashy dermatosis and progressive macular hypomelanosis in dark-skinned races. In addition, certain skin changes are considered physiological in skin of colour (Table 1.2.).

Clinical examination can then determine whether the skin changes are hypopigmented/depigmented, hyperpigmented or mixed pigmentation (hypopigmented and hyperpigmented). The specific features of the pigmentary change must then be assessed:

- Is it generalized and diffuse (i.e. contiguous)?
  - If so, is there pigmentary dilution (hypochromia), concentration (hyperchromia) or both?
- Is it circumscribed (i.e. non-contiguous)?
  - If so,
    - Is it solitary or multiple?
      - If multiple, are they widespread or localized to a certain area of the body? For example, some hyperpigmented dermatoses have predominant flexural pigmentation (Table 1.3).

Table 1.3 Hyperpigmented dermatoses with predominant flexural pigmentation

Acanthosis nigricans
Atopic dermatitis – 'dirty neck'
Confluent and reticulated papillomatosis
Dowling-Degos disease
Dyskeratosis congenita
Flexural pigmentation with multiple lentigines
Galli-Galli disease
Granular parakeratosis
Harber's syndrome
Infections – especially erythrasma
Neurofibromatosis – Crowe's sign
Post-inflammatory hyperpigmentation – especially contact dermatitis

  - What is the morphology, e.g. punctate/guttate, patchy, linear, whorled, segmental, reticulate or flagellate?
  - Is it macular (i.e. flat) or associated with textural change of the skin?
- For hyperpigmented disorders, what colour is the pigmentation?
- In the setting of circumscribed hyperpigmented lesions, it is important to assess for Darier's sign, which is positive in urticaria pigmentosa and solitary mastocytoma.

It is then important to examine the patient beyond the skin to assess whether:

- The hair colour is altered (Table 1.4.).
- The nail colour is altered (Table 1.5.).
- The oral mucosa (Table 1.6.) and/or other mucosal sites are affected [9].
- The eyes are affected.
- Dysmorphic features are present.
- Other organs are involved.

If the individual lesions or the pattern of pigmentation change are atypical, the search for other features in history and a detailed systemic examination becomes very important to arrive at the correct diagnosis.

Bedside investigations can be useful and include:

- *Alcohol swabbing* [8]
  - While exogenous pigmentation, sweat discolouration and dirt pigmentation (terra firma-forme dermatosis) can be resistant to a regular wash with soap and water, they can be removed by alcohol swabbing. In dirt pigmentation, it is typically necessary to exert substantial shearing force when alcohol swabbing.
- *Diascopy* [7, 8, 10]
  - Diascopy can be used to identify vascular disorders. Using diascopy, non-melanotic lesions such as naevus anaemicus, Bier's spots and Woronoff's ring can be made to blend into the surrounding blanched skin. In addition, these lesions do not display the reflex vasodilatory response upon application of pressure and heat.
- *Wood's lamp examination* [3, 8, 11]
  - Wood's lamp examination can be a useful adjunct when diagnosing disorders of pigmentation. Naevus anaemicus is not accentuated by Wood's lamp, in contrast to hypomelanotic causes of hypopigmentation where the lesions are enhanced. On Wood's lamp examination, vitiligo lesions typically show chalky-white accentuation. Hypermelanosis due to epidermal pigmentation is enhanced by Wood's lamp examination, whereas it remains unchanged when it is due to dermal pigmentation. In erythrasma, corynebacteria cause a pigmented rash in skin folds that fluoresces a coral-pink colour with Wood's lamp examination. The slightly scaly hypo- or hyperpigmented rash seen over the torso in pityriasis versicolour typically emits a yellow-green glow when active. Patients with progressive macular hypomelanosis show small specs of red fluorescence in a follicular pattern inside the hypopigmented lesional skin when examined under Wood's lamp.
- *Skin scrapings and potassium hydroxide examination*
  - Under a microscope 'spaghetti- and meatball-like' structures (representing mycelia and oval yeasts, respectively) may be seen in pityriasis versicolour. In tinea nigra light to dark brown septal hyphae are typically observed.

Table 1.4 Disorders with altered hair colour

Hypopigmented/depigmented			
Circumscribed	Diffuse	Hyperpigmented	Other colours
Inherited Isolated occipital white lock Isolated white forelock Piebaldism Tuberous sclerosis Waardenburg syndrome White forelock with multiple malformations White forelock with osteopathia striata Naevoid Angora hair naevus Associated with naevus comedonicus Scalp heterochromia secondary to mosaicism Inflammatory or autoimmune Alezzandrini syndrome Alopecia areata Halo naevus Post-inflammatory (i.e. discoid lupus) Post-traumatic Vitiligo Vogt-Koyanagi-Harada syndrome	Inherited Book syndrome Down syndrome Fanconi syndrome Hallermann-Streiff syndrome Prolidase deficiency Treacher-Collins syndrome Drugs Antimalarials Tyrosine kinase inhibitors Nutritional/endocrine Chronic protein loss or deficiency (‘flag sign’) Copper deficiency Hyperthyroidism Vitamin B12 deficiency	Metabolic Porphyria cutanea tarda Drugs Dithranol (topical) Methotrexate Prostaglandin analogues, e.g. latanoprost (topical)	*Silvery hair syndromes* Chediak-Higashi syndrome Elejalde syndrome Griscelli syndrome Oculocerebral hypopigmentation syndrome, Cross type *Premature greying* Inherited Ataxia telangiectasia “Bird-headed” dwarfism Fisch syndrome Hereditary premature canities Oasthouse disease Piebaldism Progeria Prolidase deficiency Rothmund-Thomson syndrome Waardenburg syndrome Werner syndrome Inflammatory or autoimmune Sudden whitening of hair (alopecia areata) Myotonic dystrophy Vitiligo *Green* Exogenous copper deposition

Investigations

Investigations are dependent on the diagnosis suspected.

In congenital pigmentary disorders, karyotyping and molecular genetic analysis of the skin and blood may be considered, especially when the child has associated developmental delay or structural abnormalities.

Laboratory investigations may include nutritional, autoimmune, infectious, endocrine, renal, hepatic and haematologic screens.

Quantitative spectrophotometric skin colour measurements are not required for clinical diagnosis, but it is useful for monitoring and comparing improvement of various forms of treatments (refer to Chap. 3: Measurements of Skin Color).

Skin biopsy for histopathology can be a useful investigation in some, but not all disorders of pigmentation. In hypopigmented disorders, histology is most important in acquired conditions where inflammation, infection (e.g. tuberculoid leprosy), sarcoidosis, clear cell papulosis, dyschromic amyloidosis or mycosis fungoides are suspected. In hyperpigmented disorders, melanophages in the dermis suggest post-inflammatory hyperpigmentation or a lichenoid reaction pattern (which can be due to numerous causes), melanocytes in the dermis suggest conditions such as Mongolian blue spot or Hori’s naevus, and deeper naevoid cells suggest a lesion such as a blue naevus. In cases where an inflammatory cause is suspected, biopsies should be taken from an advancing edge of the lesion as well as an older lesion. In disorders with

Table 1.5 Disorders with altered nail colour

Hypopigmented/depigmented	Hyperpigmented	Other colours
True leukonychia *Completely white* (leukonychia totalis) Acquired: cirrhosis, cytotoxic drugs, infection (typhoid, leprosy, trichinosis), onychophagia Hereditary: associated with cheilitis, dental changes, keratosis pilaris, knuckle pads, hypoparathyroidism, koilonychia, LEOPARD syndrome, palmoplantar keratoderma, peeling skin, pilar cysts, pili torti, sebaceous cysts, sensorineural deafness, renal calculi *Incompletely white* (leukonychia partialis, striata, punctata) Acquired: chronic arsenic poisoning (Mee's lines), trauma Hereditary: Darier-White disease *Apparent leukonychia* Hepatic failure, cirrhosis, diabetes mellitus, CHF, hyperthyroidism, malnutrition (Terry's nails) Hypoalbuminaemia (Muehrcke's nails) Onycholysis Renal failure (half and half nails) *Pseudoleukonychia* Fungal nail infection – dermatophyte and yeast Trauma	*Longitudinal melanonychia* Physiologic causes: racial, pregnancy Local or regional causes: trauma, onychotillomania, onychophagia, carpel tunnel syndrome, subungual foreign body, radiation, fungi, bacteria, neoplasm Dermatologic causes: onychomycosis, chronic paronychia, psoriasis, lichen planus, lichen striatus, amyloidosis, chronic radiation, systemic lupus erythematosus, localized scleroderma, Bowen's disease, onychomatricoma, myxoid pseudocyst, basal cell carcinoma, subungual fibrous histiocytoma, periungual verruca, subungual linear keratosis Systemic causes: Addison's disease, Cushing's syndrome, Nelson's syndrome, hyperthyroidism, acromegaly, alkaptonuria, nutritional disorders, haemosiderosis, porphyria, hyperbilirubinaemia, graft versus host disease, AIDS Syndromes: Laugier-Hunziker, Peutz-Jeghers, Touraine Melanocytic hyperplasia: lentigo, naevus, melanoma *Transverse melanonychia* Drugs (especially chemotherapeutics) Phototherapy Radiation *Diffuse melanonychia* Drugs (especially chemotherapeutics)	*Splinter haemorrhage* Antiphospholipid syndrome Peptic ulcer disease Malignancies Oral contraceptive use Psoriasis Pregnancy Rheumatoid arthritis Systemic lupus erythematosus Subacute bacterial endocarditis Trauma *Greenish-black nails* *Pseudomonas aeruginosa* *Yellow nail* Chronic use of nail enamel Yellow nail syndrome *Exogenous pigmentation* Food colourings Industrial chemicals Nail lacquers Topical medications (e.g. potassium permanganate) *Abnormal lunula Colour* Blue/azure – Wilson disease, silver poisoning, bacterial paronychia, quinacrine, zidovudine Blue, pale – diabetes mellitus Brown black – excessive fluoride ingestion Red – heart failure, chronic obstructive pulmonary disease, collagen vascular disease, haematologic malignancy Yellow – tetracycline

Table 1.6 Disorders with altered mucosal colour

Hypopigmented/depigmented	Hyperpigmented
Aphthous ulceration	Congenital melanotic macules of the tongue
Chronic mucocutaneous candidiasis	Dowling Degos disease
Contact stomatitis – e.g. cinnamon	Drugs – especially chemotherapeutics
Dyskeratosis congenita	Endocrinopathies – e.g. Addisons disease
Darier-White disease	Exogenous material – e.g. tattoos
Howel-Evans syndrome	Familial lentiginoses – e.g. Peutz-Jeghers, Carney complex
Morsicatio buccarum (chronic cheek chewing)	Haemochromatosis
Neoplasic – oral leucoplakia, SCC, verrucous carcinoma	Hairy tongue
Nicotine stomatitis	Heavy metal poisoning – e.g. argyria
Oral submucous fibrosis	Hyperpigmentation of the tongue/gingiva (racial)
Pachyonychia congenita (leucokeratosis)	Laugier-Hunziker syndrome
Post-inflammatory hypopigmentation	Lentigines
Systemic sclerosis	Mucosal melanotic macules
Vitiligo	Neoplastic – melanocytic naevus, melanoma
White sponge nevus	Post-inflammatory hyperpigmentation: lichen planus, fixed drug eruption
	Smoker's melanosis
	Vascular anomalies – e.g. haemangioma, purpura

Table 1.7 Pigmentary disorders where histopathology is helpful in the diagnosis

Hypopigmented dermatoses	Hyperpigmented dermatoses
Amyloidosis dyschromia cutis	Acanthosis nigricans
Chronic arsenic poisoning	Blue naevus
Clear cell papulosis	Chronic arsenic poisoning
Connective tissue naevi	Colloid milium
Darier-White disease-associated hypopigmented macules	Congenital melanocytic naevus
Epidermal naevus	Dermatomyositis
Epidermodysplasia verruciformis-associated pityriasis versicolor-like lesions	Dermatosis papulosa nigra
Grover disease-associated hypopigmented macules	Dowling-Degos disease
Halo naevi	Flexural pigmentation with multiple lentigines
Leprosy – tuberculoid, borderline tuberculoid	Galli-Galli disease
Lichen sclerosus et atrophicus	Granular parakeratosis
Lichen striatus	Hori's naevus
Microcystic lymphatic malformation	Lentigo maligna
Molluscum contagiosum	Lichen planus pigmentosus
Morphea	Lichenoid drug eruption
Mucinoses	Maculopapular cutaneous mastocytosis
Mycosis fungoides	Melanoacanthoma/seborrhoeic keratosis
Pityriasis versicolour	Ochronosis – exogenous
Plane warts	Pigmented purpuric dermatosis (capillaritis)
Post-kala-azar dermal leishmaniasis	Pityriasis versicolour
Sarcoidosis	Porphyria cutanea tarda
Vitiligo	Primary cutaneous amyloidosis – macular / lichenoid
White fibrous papulosis	Siderosis (e.g. due to extravasated iron)
	Talon noir
	Tattoos – accidental (e.g. carbon)
	Tinea nigra

patchy pigmentation change, a biopsy from a comparable area of normal skin is helpful to evaluate subtle changes in pigmentation. Special stains are useful in establishing the diagnosis in some cases, e.g. clear cell papulosis. Table 1.7 provides a list of pigmentary disorders where histopathology becomes helpful in the diagnosis.

Classification of Pigmentary Disorders

There are several ways that pigmentary disorders can be classified, including pathological, aetiological and clinical.

A comprehensive pathological classification based on structural and ultrastructural details is not yet possible due to non-availability of comparable histopathological, immunohistochemical and electron microscopic data of many conditions. Basic light microscopic histopathological features alone are not diagnostic of many pigmentary disorders.

A classification based on aetiology is also difficult as often times the aetiology is unknown. When the genetic cause of a pigmentary disorder is known, the disease may be categorized on a genetic basis. In the Online Mendelian Inheritance of Man (OMIM), each disease is given a six-digit code. [12]

Where exact aetiology is unknown, and the pathology is non-specific, a clinical classification based on clinical features is useful to the clinician. [13]

The classification presented in this discussion is based on clinical features. There are several classifications in journal articles and textbooks; however, many articles are not comprehensive, focusing only on the common conditions. [1, 6, 13–15]

Here, an attempt has been made to include most known disorders that are hypopigmented/depigmented, hyperpigmented and mixed pigmentation (hypopigmented and hyperpigmented). Not only pigmentation due to melanin, but also other agents causing a 'hyperpigmented appearance' (hyperchromia), are included for a clear understanding of the numerous anomalies that

afflict human skin and result in discolouration of the skin (dyschromia).

When classified by clinical features, some diseases may be listed more than once as the clinical appearance can vary in different skin types and depending on the stage of evolution/resolution of the skin disorder.

There are certain skin disorders that have been only minimally included in this classification. This includes the ichthyotic disorders, as although the scale is often dyschromic in the ichthyotic disorders the primary clinical feature is scale. Likewise, we have elected to exclude a number of skin neoplasms that display (secondary) pigmentary change. However, for completeness, these disorders have been tabulated (Table 1.8). [16]

As the main thrust of this classification is clinical, we first divide the pigmentary disorders in to whether the lesions are (Fig. 1.1):

- *Hypopigmented/depigmented*
- *Hyperpigmented*
- *Mixed pigmentation (hypopigmented and hyperpigmented)*

Each primary division is then broken down into whether the lesions have their:

- *Onset in early childhood*
  - This includes disorders that are either present at birth or develop in the first 1 to 2 years of life. The vast majority of these disorders have a genetic aetiology.
- *Onset in later childhood through to adulthood*
  - This includes disorders that typically present after the first 1 to 2 years of life. Most of these are acquired in origin; however some are genetically determined disorders manifesting many years after birth.

Within these categories, we group the pigmentary disorders on the nature of distribution and whether the skin changes are (Figs 1.2 and 1.3):

- *Generalized and diffuse (contiguous)*
  - This refers to pigmentary disorders that affect the entire skin surface confluently.
  - It includes disorders of pigmentary dilution (e.g. oculocutaneous albinism) and pigmentary concentration (e.g. melanosis diffusa congenita).
  - These disorders tend to be macular, without significant infiltration or epidermal change.
  - Within this group there may be accentuation of pigmentation in certain areas, e.g. more prominent pigmentation in the skin creases in Addison's disease.
  - This category is variably grouped according to *aetiology* or *associated extracutaneous signs/organ involvement*.
- *Circumscribed (non-contiguous)*
  - This refers to pigmentary disorders that do not affect the entire skin surface.

Table 1.8 Neoplasms with pigmentary changes or discolouration

Hypopigmented neoplastic conditions	Hyperpigmented neoplastic conditions
Arsenical keratoses and associated neoplasms with rain drop depigmentation	Acrochordons
Halo naevi	Actinic keratosis – pigmented variant
Melanoma with regression and associated leucoderma	Angiokeratoma
Microcystic lymphatic malformation	Basal cell carcinoma – pigmented variant
Mycosis fungoides – hypopigmented	Bowenoid papulosis
Porokeratosis	Chloroma/cutaneous myeloid sarcoma
Stucco keratosis	Dermatofibroma
White fibrous papulosis	Dermatosis papulosa nigra
White sponge naevus of oral mucosa	Glomus tumour
Sebaceoma	Haemangioma – deep
Xanthomas	Kaposi's sarcoma
	Lymphomatoid papulosis
	Malignant melanoma, lentigo maligna, melanosis secondary to advanced melanoma
	Mastocytoma
	Melanoacanthoma
	Melanocytic naevus
	Merkel cell carcinoma (can appear purplish or reddish in colour)
	Mycosis fungoides – pigmented variant
	Neurofibroma
	Paget's disease – pigmented variant
	Pilomatricoma (bluish in colour)
	Squamous cell carcinoma – pigmented variant
	Seborrhoeic keratosis
	Syringomas (in dark-skinned persons)
	Tumours with rapid growth and internal haemorrhage

Modified from Kumarasinghe and Hewitt [17]

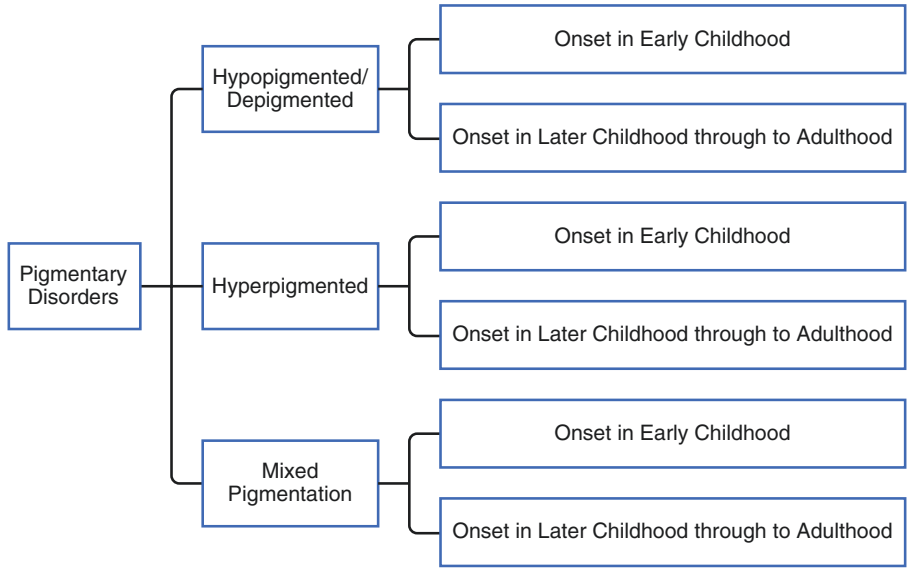

Fig. 1.1 Onset in Later Childhood though to Adulthood Clinical classification of pigmentary disorders

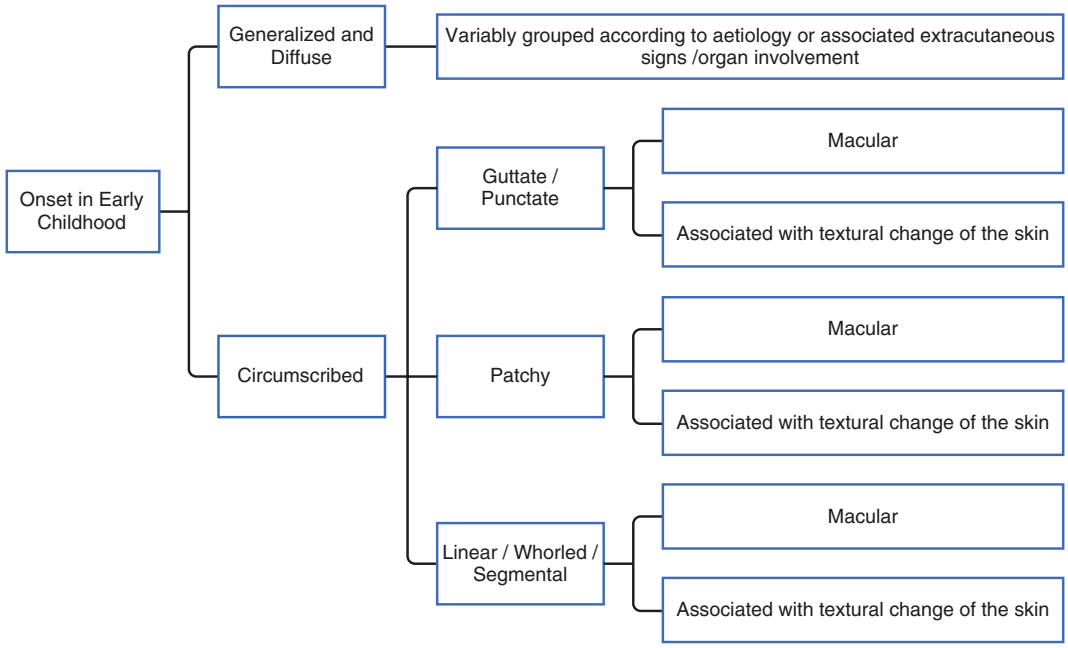

Fig. 1.2 Clinical classification of pigmentary disorders continued from Fig. 1.1

- The individual lesions are well demarcated.
- These circumscribed lesions can be widespread or localized to certain areas.
- Different morphological patterns of pigmentation are seen in circumscribed pigmentary disorders including:
  - *Guttate/punctate*: < 1cm in diameter.
  - *Patchy*: ≥1cm in diameter.
  - *Linear/whorled/segmental*: including blaschkoid, zosteriform and flagellate pigmentation.

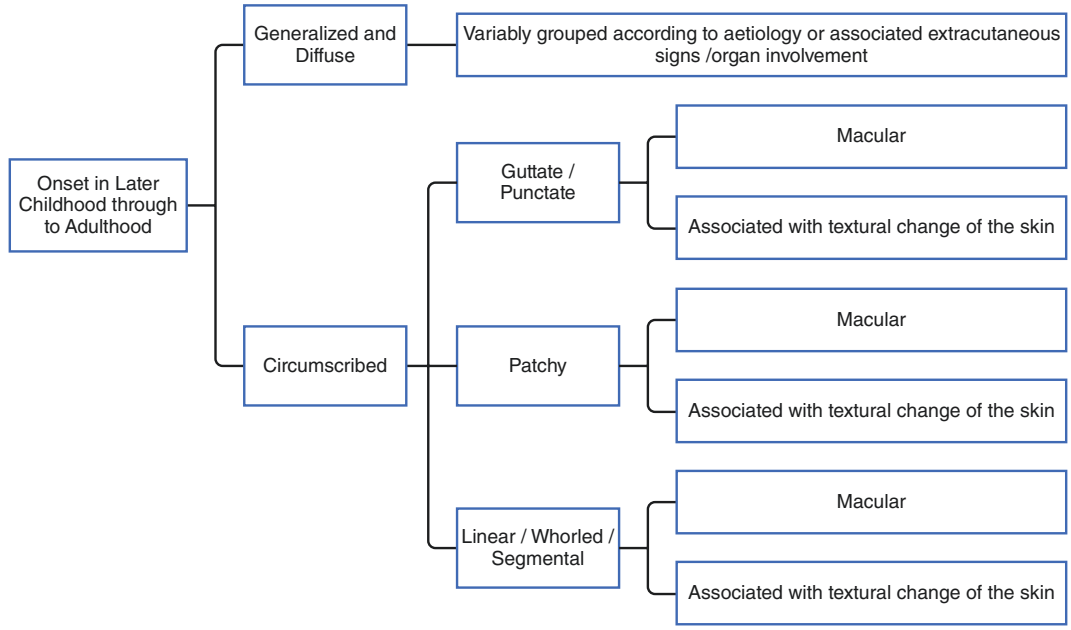

Fig. 1.3 Clinical classification of pigmentary disorders continued from Fig. 1.1

– These patterns of pigmentation can then be further categorized based on whether they are:
  - *Macular*: flat with no associated textural change of the skin.
  - *Associated with textural change of the skin*: including papular change/infiltration, epidermal atrophy, skin induration and scale.

Finally, in the hyperpigmented and mixed pigmentation groups, we variably group the circumscribed lesions into subcategories based on further clinical features including:

- *Reticulate* – this includes skin disorders showing hyperpigmented and/or hypopigmented macules leading to a blotchy appearance, as well as skin disorders characterized by a lacy or net-like pattern of hyperpigmentation. [16, 18]
- *Flagellate* – figurate dermatoses characterized by a parallel linear or curvilinear arrangement simulating the marks of whiplashes.
- *Grey-blue hypermelanosis* (*dermal hypermelanosis, ceruloderma*) – skin disorders characterized by collections of dermal melanocytes and clinically appearing as grey-blue lesions.
- *Red-brown hypermelanosis* (*haemosiderosis*) – skin disorders characterized by haemosiderin or iron deposition in the dermis resulting in a red-brown discolouration of the skin.
- *Poikiloderma* – skin disorders characterized by hypopigmentation, hyperpigmentation, telangiectasia and skin atrophy.

Key	
ʘ	Dermatoses that are more common/conspicuous in skin of colour
*	Non-melanin pigmentation

Hypopigmented/Depigmented

Onset in Early Childhood [3, 7, 12, 15, 19, 20]

Generalized and Diffuse Hypopigmentary Disorders (Pigment Dilution/ Hypochromia)

Affecting Eyes, Skin and Hair

In isolation

- Oculocutaneous albinism, types IA, IB, II-VII [OMIM # 203100, 606952, 203200, 203290, 606574, 615312, 113750, 615179]

- Histidinaemia (*syn. histidine ammonia-lyase deficiency*) [OMIM #235800]

Associated with bleeding diathesis

- Hermansky-Pudlak syndrome, types 1–10 [OMIM # 203300, 608233, 606118, 606682, 607521, 607522, 614076, 614077, 614171, 617050]

Associated with deafness

- ABCD syndrome (*syn. albinism, black lock, cell migration disorder of the neurocytes of the gut and deafness*) [OMIM #600501]
- Tietze syndrome (*syn. albinism-deafness of Tietze*) [OMIM #103500]

Associated with immunological disease

- Chediak-Higashi syndrome [OMIM #214500]

Associated with neurological disease and/or intellectual disability

- Angelman syndrome [OMIM #105830]
- Homocystinuria (*syn. methylenetetrahydrofolate reductase deficiency*) [OMIM #236200]
- Infantile nephropathic cystinosis [OMIM #219800]
- Oculocerebral hypopigmentation syndrome of Preus [OMIM #257790]
- Oculocerebral syndrome with hypopigmentation (*syn. Cross syndrome, Kramer syndrome*) [OMIM #257800]
- Phenylketonuria (*syn. phenylalanine hydroxylase deficiency*) [OMIM #261600]
- Prader-Willi syndrome [OMIM #176270]

Affecting the Skin and Hair

In isolation

- Griscelli syndrome, type 3 [OMIM #609227]

Associated with cardiorespiratory disease

- Selenium deficiency (e.g. due to total parenteral nutrition)

Associated with defects in other ectodermal structures

- Ectodermal dysplasias (including Hypohidrotic ectodermal dysplasia and Ectrodactyly ectodermal dysplasia)

Associated with immunological disease

- Griscelli syndrome, type 2 [OMIM #607624]

Associated with neurological disease and/or intellectual disability

- Copper deficiency (e.g. in premature or severely malnourished infants)
- Elejalde disease (*syn. neuroectodermal melanolysosomal disease*) [OMIM #256710]
- Griscelli syndrome, type 1 [OMIM #214450]
- Menkes disease (*syn. kinky hair disease, steely hair disease*) [OMIM #309400]

Affecting the Skin

Endocrinopathies

- Hypogonadism
- Hypothyroidism *
- Hypopituitarism
- Pernicious anaemia (B12 deficiency)

Variations in the haemoglobin content and vascular disorders

- Anaemia *
- Cutaneous oedema *
- Vasoconstriction *

Metabolic

- Infantile sialic acid storage disease [OMIM #269920]

Nutritional

- Protein-energy malnutrition – marasmus and kwashiorkor ⊙

Circumscribed Hypopigmentary Disorders

Depigmented

Guttate/punctate

- Vitiligo ponctue

Patchy

- *In isolation*
  - Piebald trait (*syn. piebaldism*) [OMIM #172800]
  - Vitiligo
- *Associated with deafness*
  - Albinism-deafness syndrome (*syn. Ziprkowski-Margolis Syndrome; Woolf syndrome*) [OMIM #300700]

  - Ermine phenotype (*syn. Pigmentary Disorder with Hearing Loss*) (includes Black locks with albinism and deafness syndrome, BADS) [OMIM #227010]
  - Waardenburg syndrome, types 1, 2a–2e, 3 and 4a–4c [OMIM #193500, 193510, 600193, 606662, 608890, 148820, 277580, 613265, 613266]
- *Associated with neurological disease and/or intellectual disability*
  - Piebald trait with neurologic defects [OMIM #172850]

Linear/whorled/segmental

- Vitiligo: segmental, blaschkoid and koebnerized

Hypopigmented

Guttate/punctate

- *Macular*
  - Cole disease (*syn. guttate hypopigmentation and punctate palmoplantar keratoderma*) [OMIM #615522]
  - Post-inflammatory hypopigmentation[⊙] – especially herpes virus infection (HSV, VZV) and guttate psoriasis
  - Tuberous sclerosis, types 1 and 2: confetti-like hypomelanotic macules [OMIM #191100, 613254]
- *Associated with textural change of the skin*
  - Clear cell papulosis of the skin [*]
  - Cutaneous papular mucinosis of infancy [*]
  - Infection – especially molluscum contagiosum[*], plane warts[*] and pityriasis versicolour
  - Microcystic lymphatic malformation (*syn. lymphangioma circumscriptum*)
  - Mucopolysaccharidosis, type 2: ivory-white reticulate pebbling (*syn. Hunter syndrome*) [OMIM #309900] [*]

Patchy

- *Macular*
  - Naevus depigmentosus (*syn. achromic naevus, hypopigmented naevus*):
    - Isolated naevus depigmentosus
    - Systematized naevus depigmentosus
    - Naevus depigmentosus-associated syndromes:
      - Ataxia telangiectasia [OMIM #208900]
      - Capillary malformations arteriovenous malformations (CM-AVMs): hypoemic halos [OMIM #608354]
      - Fanconi anaemia [OMIM #227650]
      - Neurofibromatosis, type 1: oval spots [OMIM #162200]
      - Phakomatosis pigmentovascularis, type I
      - Proteus syndrome [OMIM #176920]
      - Trisomy 13 – phylloid hypomelanosis
      - Tuberous sclerosis, types 1 and 2: ash-leaf and polygonal macules [OMIM #191100, 613254]
  - Naevus anaemicus [*]
    - Isolated naevus anaemicus
    - Naevus anaemicus-associated syndromes [*] –
      - Neurofibromatosis, type 1 [OMIM #162200]
      - Phakomatosis pigmentovascularis, types II, III and IV
  - Post-inflammatory hypopigmentation[⊙] – especially eczema (including molluscum contagiosum-associated perilesional eczema), neonatal lupus erythematosus, pityriasis alba and psoriasis
- *Associated with textural change of the skin*
  - Apert syndrome: hypopigmentation and hyperkeratosis of plantar surfaces [OMIM #101200]
  - Infection – especially pityriasis versicolour and leprosy

Linear/whorled/segmental

- *Macular*
  - Hypomelanosis of Ito [OMIM #300337]
  - Linear and figurated hypopigmented naevus (*syn. linear and whorled naevoid hypomelanosis*)
  - Menkes disease – female carrier (*syn. kinky hair disease, steely hair disease*) [OMIM #309400]

  - Naevus depigmentosus (*syn. achromic naevus, hypopigmented naevus*) – linear, blaschkoid or segmental
  - Pigmentary demarcation lines
  - Post-inflammatory hypopigmentation[⊙] – especially herpes zoster infection, lichen striatus
- *Associated with textural change of the skin*
  - Conradi-Hunermann-Happle syndrome: atrophoderma vermiculatum following Blaschko's lines (*syn. X-linked dominant chondrodysplasia punctata*) [OMIM #302960] [*]
  - Epidermal naevus/comedonal naevus [*]
  - Focal dermal hypoplasia (*syn. Goltz syndrome*) [OMIM #305600]
  - Microphthalmia with linear skin defect syndrome (*syn. MIDAS syndrome – microphthalmia, dermal aplasia, sclerocornea*) [OMIM #309801] [*]
  - Lichen striatus (in darker skin types) [*⊙]
  - Infection – especially plane warts (koebnerized)[*]

Onset in Later Childhood Through to Adulthood [3, 7, 10–16, 19–22]

Generalized and Diffuse Hypopigmentary Disorders (Pigment Dilution/ Hypochromia)

Depigmented

- Drug-induced depigmentation
  - Programmed death-1 (PD-1) inhibitors in patients with metastatic melanoma (pembrolizumab) [21]
- Vitiligo universalis

Hypopigmented

Endocrinopathies

- Hypogonadism (e.g. in castrated human males)
- Hypothyroidism [*]
- Hypopituitarism
- Pernicious anaemia (B12 deficiency)

Variations in the haemoglobin content and vascular disorders

- Anaemia [*]
- Cutaneous oedema [*]
- Vasoconstriction [*]

Iatrogenic

- Drug-induced hypopigmentation
  - Glutathione – topical and oral [22]
  - Tyrosine kinase inhibitors (dasatinib, imatinib, gefitinib, nilotinib, pazopanib, sorafenib, sunitinib)
- Haemodialysis

Nutritional

- Copper deficiency
- Kwashiorkor
- Selenium deficiency (e.g. due to total parenteral nutrition)

Circumscribed Hypopigmentary Disorders

Depigmented

Guttate/punctate

- Chemical leucoderma: confetti-like macules – phenol/catechol derivatives (especially monobenzyl ether of hydroquinone and hydroquinone), sulfhydryls, other (mercury, arsenic, cinnamic aldehyde, paraphenylenediamine)
- Halo naevi
- Leukoderma punctata (e.g. following PUVA, nbUVB and laser)
- Symmetrical progressive leukopathy
- Vitiligo ponctue

Patchy

- Alezzandrini syndrome
- Chemical leukoderma – phenol/catechol derivatives (especially monobenzyl ether of hydroquinone and hydroquinone), sulfhydryls, mercury, arsenic, cinnamic aldehyde, paraphenylenediamine
- Drug-induced depigmentation

  - Anti-neoplastic agents (doxorubicin, interferon-α, interferon-β, interleukin-2, survivin inhibitor)
  - Programmed death-1 (PD-1) inhibitors in patients with metastatic melanoma (pembrolizumab, ipilimumab, nivolumab) [21]
  - Topical/intralesional agents (azelaic acid, benzoyl peroxide, corticosteroids, 5-fluouracil, hydroquinone, imiquimod, tretinoin)
- Melanoma-associated leukoderma
- Vitiligo
- Vogt-Koyanagi-Harada disease

Linear/whorled/segmental

- Intralesional injection of corticosteroids: white line along lymphatic drainage
- Vitiligo: koebnerized, blaschkoid or segmental

Hypopigmented

Guttate/punctate

- *Macular*
  - Amyloidosis dyschromica cutis
  - Bier's spots *
  - Darier-White disease: hypopigmented macules (*syn. Darier disease, keratosis follicularis*) [OMIM #124200]
  - Epidermodysplasia verruciformis: pityriasis versicolour-like lesions *
  - Grover disease: hypopigmented macules (*syn. transient acantholytic dermatosis*)
  - Idiopathic guttate hypomelanosis
  - Multiple endocrine neoplasia, type 1 (MEN1): confetti-like macules [OMIM #131100]
  - Post-inflammatory hypopigmentation⊙ – especially acne vulgaris and acne excoriee, cutaneous infections, lichen planus, physical or chemical injuries, pityriasis rosea, pityriasis lichenoides chronica, (guttate) psoriasis
  - Sarcoidosis: hypopigmented variant
- *Associated with textural change of the skin*
  - Clear cell papulosis of the skin *
  - Infection – especially molluscum contagiosum*, plane warts*, pityriasis versicolour and onchocerciasis
  - Lichen sclerosus et atrophicus: guttate lesions
  - Morphea: guttate lesions
  - Mucinoses – follicular mucinosis (*alopecia mucinosa*) or papular mucinosis (*lichen myxoedematosus*) *
  - Mycosis fungoides: hypopigmented variant⊙
  - Sarcoidosis: hypopigmented variant
  - White fibrous papulosis

Patchy

- *Macular*
  - Drug-induced depigmentation – topical agents including azelaic acid, benzoyl peroxide, corticosteroids (topical, intralesional), 5-fluouracil, glutathione, imiquimod and tretinoin
  - Endocrine disorders – especially Addison's disease and thyroid disease (more typically cause hyperpigmentation)
  - Infection – especially pityriasis versicolour following treatment, late-stage pinta and pintoid dyschromia of yaws
  - Multiple endocrine neoplasia, type 1 (MEN1) [OMIM #131100]
  - Pityriasis rotunda (hypopigmented in patients with darker skin)
  - Post-inflammatory hypopigmentation⊙ – especially acne vulgaris and acne excoriee, atopic dermatitis, cutaneous lupus, dermatomyositis, drug reactions, infections, immunobullous diseases, lichen planus, lymphomatoid papulosis, mycosis fungoides, pityriasis alba, pityriasis lichenoides chronica, pityriasis rosea, physical or chemical injuries and psoriasis
  - Progressive macular hypomelanosis
  - Sarcoidosis: hypopigmented variant
  - Woronoff's ring *
- *Associated with textural change of the skin*
  - Infection – especially pityriasis versicolour, leprosy, post-kala-azar dermal leishmaniasis (PKDL), onchocerciasis, secondary syphilis and pinta
  - Lichen sclerosus et atrophicus: plaque lesions

  - Morphea: plaque lesions
  - Mucinoses – follicular mucinosis (*alopecia mucinosa*) or papular mucinosis (*lichen myxoedematosus*)*
  - Mycosis fungoides: hypopigmented variant⊙
  - Sarcoidosis: hypopigmented variant
  - Systemic sclerosis

Linear/whorled/segmental

- *Macular*
  - Intralesional injection of corticosteroids: white line along lymphatic drainage
  - Pigmentary demarcation lines
  - Post-inflammatory hypopigmentation⊙ – especially herpes zoster infection, lichen striatus
- *Associated with textural change of the skin*
  - Darier-White disease: linear variant (*syn. Darier disease, keratosis follicularis*) [OMIM #124200]
  - Incontinentia pigmenti – Stage 4 (*syn. Bloch-Sulzberger syndrome*) [OMIM #308300]
  - Infection – especially plane warts (koebnerized)*
  - Lichen sclerosus et atrophicus: linear variant
  - Linear unilateral basaloid follicular hamartoma
  - Morphea: linear lesions, en coup de sabre and segmental
  - Striae distensae

Hyperpigmented

Onset in Early Childhood [3, 12, 18–20, 23–28]

Generalized and Diffuse Hyperpigmentary Disorders (Pigment Concentration/ Hyperchromia)

- Cardiofaciocutaneous syndrome [OMIM #115150]
- Costello syndrome (*syn. faciocutaneoskeletal syndrome*) [OMIM #218040]
- Familial progressive hyperpigmentation [OMIM #614233]
- Fanconi anaemia: melanoderma [OMIM #227650]
- Folic acid deficiency (seen in infants on exclusive goats milk)
- Gaucher disease, types 1–3 [OMIM #230800, 230900, 231000]
- Gastrointestinal stromal tumour (*syn. GIST*) [OMIM #60674] [25]
- Grey baby syndrome (following chloramphenicol exposure in neonates)
- Ichthyosis-associated (e.g. ichthyosis vulgaris, X-linked ichthyosis, autosomal recessive congenital ichthyosis, bullous ichthyosiform erythroderma)
- Universal acquired melanosis (*syn. carbon baby syndrome*)
- Vitamin B12 deficiency (due to decreased levels of B12 in maternal milk or malnutrition in infancy)

Circumscribed Hyperpigmentary Disorders

Guttate/punctate

- *Macular*
  - Bannayan-Riley-Ruvalcaba syndrome: penile lentiginosis [OMIM #153480]
  - Carney complex (*syn. NAME syndrome, LAMB syndrome*) [OMIM #160980]
  - Centrofacial lentigines (*syn. centrofacial neurodysraphic lentiginosis*)
  - Congenital melanocytic naevi – small
  - Flexural pigmentation with multiple lentigines [26]
  - Gastrointestinal stromal tumour (*syn. GIST*) [OMIM #60674] [25]
  - Isolated generalized lentigines (*syn. diffuse non-syndrome lentiginosis*)
  - Inherited patterned lentiginosis in black people ⊙
  - Lentigo simplex
  - LEOPARD syndrome, types 1–3 (*syn. multiple lentigines syndrome*) [OMIM #151100, 611554, 613707]
  - Peutz-Jeghers syndrome (*syn. periorificial lentiginosis*) [OMIM #175200]

  - Segmental lentiginosis (*syn. lentiginous naevus, partial unilateral lentiginosis, agminated lentigines, lentiginous mosaicism*)
  - Transient neonatal pustular melanosis (*syn. lentigines neonatorum*) ⊙
  - Xeroderma pigmentosum, groups A-G [OMIM #278700, 610651, 278720, 278730, 278740, 278760, 278780]
- *Associated with textural change of the skin*
  - Cardiofaciocutaneous syndrome: multiple pigmented naevi [OMIM #115150]
  - Congenital melanocytic naevi – small
  - Turner syndrome: multiple pigmented naevi

Patchy

- *Macular*
  - Acromelanosis progressiva
  - Bronze baby syndrome (following phototherapy)
  - Café-au-lait macules (CALM)
    - Isolated CALM
    - CALM-associated syndromes
      - Ataxia telangiectasia [OMIM #208900]
      - Bloom syndrome [OMIM #210900]
      - Familial progressive hyperpigmentation with or without hypopigmentation (*syn. FPHH; melanosis universalis hereditaria*) [OMIM #145250]
      - Fanconi anaemia [OMIM #227650]
      - Gastrointestinal stromal tumour (*syn. GIST*) [OMIM #60674] [25]
      - Legius syndrome (*syn. NF-1-like syndrome*) [OMIM #611431]
      - LEOPARD syndrome, types 1–3 (*syn. multiple lentigines syndrome*) [OMIM #151100, 611554, 613707]
      - McCune-Albright syndrome [OMIM #174800]
      - Mismatch repair cancer syndrome (*syn. constitutional mismatch repair deficiency syndrome, Turcot syndrome*) [OMIM #276300]
      - Multiple endocrine neoplasia, type 1 (MEN1) [OMIM #131100]
      - Neurofibromatosis, types I-IV and VI [OMIM #162200, 101000, 162260, 162270, 114030]
      - Neurofibromatosis, type V (*syn. segmental neurofibromatosis, mosaic-localized neurofibromatosis*)
      - Niemann-Pick disease, types A, B, C1, C2 [OMIM #257200, 607616, 257220, 607625]
      - Noonan syndrome [OMIM #163950]
      - Piebald trait (*syn. piebaldism*) [OMIM #172800]
      - Proteus syndrome [OMIM #176920]
      - Silver-Russell syndrome [OMIM #180860]
      - Tuberous sclerosis, types 1 and 2 [OMIM #191100, 613254]
      - Von Hippel-Lindau syndrome [OMIM #193300]
      - Watson syndrome (*syn. CALM with pulmonary stenosis*) [OMIM #193520]
  - Grey-blue hypermelanosis (dermal hypermelanosis, ceruloderma)
    - Mongolian spot ⊙
    - Naevus of Ito ⊙
    - Naevus of Ota ⊙ (*syn. oculodermal melanocytosis*)
    - Dermal hypermelanosis-associated syndromes –
      - GM1-gangliosidosis, type 1 [OMIM # 230500]
      - Hurler syndrome (*syn. mucopolysaccharidosis, type 1H*) [OMIM #607014]
      - Mucopolysaccharidosis, type 2 (*syn. Hunter syndrome*) [OMIM #309900]
      - Niemann-Pick disease, types A, B, C1, C2 [OMIM #257200, 607616, 257220, 607625]
      - Phakomatosis pigmentovascularis, types II, IV and V
      - Sjogren-Larsson syndrome [OMIM #270200]
      - Trisomy 20 mosaicism
  - Hyperpigmented macules on the face of young children [27]

- Maculopapular cutaneous mastocytosis (*syn. urticaria pigmentosa*) [OMIM #154800] *
- Pigmented plantar and palmar macules ⊙
- Periungual hyperpigmentation of the newborn ⊙
- Post-inflammatory hyperpigmentation⊙ – especially atopic dermatitis, cutaneous lupus, infections, physical or chemical injuries.
- Reticulate –
  - Dermatopathia pigmentosa reticularis [OMIM #125595]
  - Dyskeratosis congenita, autosomal dominant 1 [OMIM#127550]
  - Dyskeratosis congenita, autosomal recessive 1 and 5 [OMIM #224230, 615190]
  - Epidermolysis bullosa simplex with mottled pigmentation [OMIM # 131960]
  - Fanconi anaemia [OMIM #227650]
  - Naegeli syndrome (*syn. Naegeli-Franceschetti-Jadassohn syndrome*) [OMIM #161000]
  - Revesz syndrome (*syn. Dyskeratosis congenita, autosomal dominant 5*) [OMIM #268130]
- Speckled lentiginous naevus: macular (*syn. naevus spilus*)
  - Isolated speckled lentiginous naevus
  - Speckled lentiginous naevus-associated syndromes
    - Phakomatosis pigmentovascularis, types III, IV and V

- *Associated with textural change of the skin*
  - Congenital melanocytic naevus: medium and giant
  - Maculopapular cutaneous mastocytosis (*syn. urticaria pigmentosa*) [OMIM #154800] *
  - Speckled lentiginous naevus: papular (*syn. naevus spilus*)
    - Isolated speckled lentiginous naevus
    - Speckled lentiginous naevus-associated syndromes
      - Phakomatosis pigmentovascularis, types III, IV and V

Linear/whorled/segmental

- *Macular*
  - Café-au-lait macules (CALM): blaschkoid
  - Conradi-Hunermann-Happle syndrome (*syn. X-linked dominant chondrodysplasia punctata*) [OMIM #302960]
  - Human chimerism
  - Linear and figurated hyperpigmented naevus (*syn. linear and whorled naevoid hypermelanosis*)
    - Isolated linear and figurated hyperpigmented naevus
    - Linear & figurated hyperpigmented naevus-associated syndromes –
      - Cohen syndrome [OMIM #216550]
      - MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes) [OMIM #540000]
      - Pallister-Killian syndrome (*syn. Mosaic tetrasomy 12p*) [OMIM #601803]
  - Pigmentary demarcation lines ⊙
  - Reticulate
    - Incontinentia pigmenti - stage 3 (*syn. Bloch-Sulzberger syndrome*) [OMIM #308300]
    - X-linked reticulate pigmentary disorder with systemic manifestations – female carriers (*syn. familial cutaneous amyloidosis, Partington disease, X-linked cutaneous amyloidosis*) [OMIM #301220]
  - Socks line pigmentation [28]
  - Speckled lentiginous naevus: blaschkoid (*syn. naevus spilus*)
  - Transient pigmentary lines of the newborn ⊙

- *Associated with textural change of the skin*
  - Congenital melanocytic naevus: blaschkoid
  - Epidermal naevus/epidermal naevus syndrome
  - Focal dermal hypoplasia (*syn. Goltz syndrome*) [OMIM #305600]
  - Phakomatosis pigmentokeratotica

– Reticulate –
  - Castori-Paradisi epidermal naevus syndrome
  - Hong-Lee eccrine naevus

Onset in Later Childhood Through to Adulthood [3, 6, 8, 12, 18, 19, 23, 24, 29, 30]

Generalized and Diffuse Hyperpigmentary Disorders (Pigment Concentration/ Hyperchromia)

Brownish or Accentuated Dark Pigmentation

Autoimmune disorders
- Dermatomyositis
- Felty syndrome
- Primary biliary cirrhosis
- Systemic sclerosis ⊙

Chronic liver disease
Chronic renal insufficiency
Drug-induced hyperpigmentation

- ACTH administration (high dose)
- Antiretroviral therapy (e.g. zidovudine)
- Arsenic
- Busulfan ⊙
- Minocycline (diffuse type)
- Quinine and quinidine
- Tyrosine kinase inhibitors (dasatinib, imatinib, nilotinib)

Endocrine disorders
- Acromegaly
- Addison's disease
- Cushing's syndrome (inappropriate secretion of ACTH)
- Hyperthyroidism ⊙
- Nelson's syndrome

Genetic disorders
- Haemochromatosis, types 1-5
- Ichthyosis-associated (e.g. ichthyosis vulgaris, X-linked ichthyosis, autosomal recessive congenital ichthyosis, bullous ichthyosiform erythroderma)
- Multiple endocrine neoplasia syndrome, type 2B (MEN 2B) [OMIM #162300]
- Porphyria cutanea tarda, types 1–3 [OMIM #176100]
- Wilson's disease (*syn. hepatolenticular degeneration*) [OMIM #277900]

Infections and infestations
- *Diphyllobothrium latum* fish tapeworm infestation (leading to B12 deficiency)
- HIV/AIDS
- Tuberculosis

Nutritional
- Folic Acid deficiency (due to pregnancy, dialysis, drugs including methotrexate, or concurrent vitamin B12 deficiency)
- Malabsorption syndromes (resulting in multiple vitamin and trace element deficiencies)
- Vitamin B3 deficiency (*syn. Pellagra*) (due to chronic alcoholism, anorexia nervosa, malabsorption syndromes, Hartnup's syndrome, tuberculosis or drugs)
- Vitamin B12 deficiency (due to fatty stool or malabsorption syndromes, including pernicious anaemia)
- Vitamin D overdose (>100 000 IU daily over prolonged period)

Malignancy
- Carcinoid syndrome (gastric and thymic carcinoid)
- Cachectic states
- Generalized malignant acanthosis nigricans
- Hodgkin's and non-Hodgkin's lymphoma
- Lymphatic leukaemia
- Lymphosarcoma
- Mycosis fungoides
- Oat cell carcinoma of the bronchus (results in ectopic ACTH syndrome)
- Phaeochromocytoma
- POEMS syndrome
- Polyposis, skin pigmentation, alopecia and fingernail changes (*syn. Cronkhite-Canada syndrome*) [OMIM #175500]
- Primary systemic amyloidosis

Sarcoid
Tanning with UV light

Grey, Slate or Bluish Pigmentation
Cyanosis *
Drug-induced hyperpigmentation *

- Amiodarone
- Argyria (silver)
- Bismuth (bismuth)
- Chrysiasis (gold)
- Lead

Genetic disorders
- Haemochromatosis (including the Juvenile subtype)

Malignancy
- Metastatic melanoma and melanogenuria

Orange or Reddish Pigmentation *
Drug-induced hyperpigmentation
- Clofazimine
- Dihydroxyacetone (primary ingredient in sunless tanning products)

Haemosiderosis

Yellowish Pigmentation (Xanthoderma) *
Drug-induced hyperpigmentation
- Mepacrine
- Other – picric acid, dinitrophenol, trinitrotoluene, santonin, acriflavine

Hyperbilirubinaemia (icterus)
- Acute or chronic liver disease (e.g. hepatitis, decompensated cirrhosis, liver failure)

Nutritional
- Carotonaemia
- Riboflavinaemia

Circumscribed Hyperpigmentary Disorders
Guttate/punctate
- *Macular*
  - Acquired melanocytic naevi
  - Acquired pigmented macules on friction areas in red hair patients [8]
  - Agminated lentiginoses
  - Bannayan-Riley-Ruvalcaba syndrome: penile lentiginosis [OMIM #153480]
  - Carney complex (*syn. NAME syndrome, LAMB syndrome*) [OMIM #160980]
  - Cowden syndrome: penile pigmentary macules (syn. *PTEN hamartoma syndrome*) [OMIM #158350]
  - Ephelides (*syn. freckles*)
  - Eruptive lentiginosis (paraneoplastic, post-chemotherapy, post-radiotherapy, post-sunburn)
  - Genital melanosis
  - Isolated generalized lentigines
  - Inherited patterned lentiginosis in black people ⊙
  - Laugier-Hunziker syndrome
  - Lentigo simplex
  - Mismatch repair cancer syndrome: axillary freckling (*syn. constitutional mismatch repair deficiency syndrome, Turcot syndrome*) [OMIM #276300]
  - Neurofibromatosis, types I, III and IV: Crowe's sign [OMIM #162200, 162260, 162270]
  - Peutz-Jeghers syndrome (*syn. periorificial lentiginosis*) [OMIM #175200]
  - Polyposis, skin pigmentation, alopecia and fingernail changes (*syn. Cronkhite-Canada syndrome*) [OMIM #175500]
  - Post-inflammatory hyperpigmentation⊙ – especially acne, infections (including chikungunya), lichen planus, physical or chemical injuries, pityriasis rosea, pityriasis lichenoides chronica and (guttate) psoriasis
  - PUVA lentigines
  - Reticulate –
    - Dowling-Degos disease 1 (*syn. reticular pigment anomaly of the flexures*) [OMIM #179850]
    - Dowling-Degos disease 3 [OMIM #615674]
    - Dowling-Degos disease 4 [OMIM #615696]

    - Galli-Galli disease (a variant of Dowling-Degos disease)
    - Harber's syndrome
    - Reticulate acropigmentation of Kitamura – early [OMIM #615537]
  - Solar lentigines
  - Tattoos – accidental and decorative
- *Associated with textural change of the skin*
  - Acquired melanocytic naevi
  - Dermatosis papulosa nigra [*⊙]
  - Infection – especially pityriasis versicolour
  - Morphea: guttate lesions [*]

Patchy

- *Macular*
  - Acquired bilateral telangiectatic macules [29]
  - Acquired brachial cutaneous dyschromatosis (*syn. ABCD, melasma of the arms*)
  - Acrogeria (*syn. Gottron's acrogeria*) [OMIM #201200]
  - Ashy dermatosis (*syn. erythema dyschromicum perstans*) [⊙]
  - Carcinoid syndrome
  - Drug-induced hyperpigmentation – chlorpromazine and related phenothiazines, chloroquine and hydroxychloroquine, cytostatic drugs (i.e. cyclophosphamide, bleomycin, fluorouracil), imipramine and other TCAs, latanoprost/bimatoprost, mercury (topical), minocycline, oestrogen (i.e. combined oral contraceptive pill), phenytoin
  - Grey-blue hypermelanosis (dermal hypermelanosis, ceruloderma)
    - Acquired bilateral naevus of Ota-like macules (ABNOM) [⊙]
    - Acquired dermal hypermelanocytosis
    - Hori's naevus [⊙]
    - Progressive dermal melanocytosis
  - Familial periorbital hyperpigmentation [⊙]
  - Idiopathic eruptive macular pigmentation
  - Infections – especially chikungunya, erythrasma, tinea nigra
  - Lentigo maligna: large (*syn. Hutchinson's melanotic freckle*)
  - Lichen planus pigmentosus [⊙]
  - Linea fusca (*syn. brown forehead ring of Andersen, Wernoe and Haxthausen*)
  - Macular arteritis (*syn. lymphocytic thrombophilic arteritis, macular lymphocytic arteritis*)
  - Maculopapular cutaneous mastocytosis (*syn. urticaria pigmentosa*) [OMIM #154800] [*]
  - Macular pigmentation of uncertain aetiology [30]
  - Melasma (*syn. chloasma, mask of pregnancy*)
  - Mycosis fungoides: pigmented purpuric variant
  - Nutritional –
    - Folic acid deficiency (due to pregnancy, dialysis, drugs including methotrexate, or with concurrent vitamin B12 deficiency)
    - Vitamin B2 deficiency: hyperpigmentation of scrotum or vulva
    - Vitamin B3 deficiency (*syn. pellagra*): hyperpigmentation of hands, neck and feet
    - Vitamin B6 deficiency: hyperpigmentation of the scrotum or vulva
    - Vitamin B12 deficiency (due to fatty stool or malabsorption syndromes, including pernicious anaemia)
    - Vitamin C deficiency (*syn. scurvy*): melasma-like hyperpigmentation
    - Zinc deficiency: hyperpigmentation of scrotum or vulva
  - Ochronosis [*] –
    - Alkaptonuria (*syn. hereditary ochronosis, homogentisic acid oxidase deficiency*) [OMIM #203500]
    - Exogenous ochronosis (commonly due to hydroquinone)
  - Phototoxic reactions
    - Berloque dermatitis
    - Phytophotodermatitis
  - Pigmented peribuccal pigmentation of Brocq (*syn. erythrose péribuccale pigmentaire of Brocq*) [31]
  - Pigmented plantar and palmar macules [⊙]
  - Pityriasis rotunda (hyperpigmented in patients with fair skin) [32]

- Porphyrias –
  - Hereditary coproporphryia [OMIM #121300]
  - Porphyria cutanea tarda [OMIM #176100]
  - Variegate porphyria [OMIM #176200]
- Post-inflammatory hyperpigmentation[⊙] – especially acne, atopic dermatitis, cutaneous lupus, dermatomyositis, drug reactions (i.e. phototoxic drug eruption, fixed drug eruption, lichenoid drug eruption, SJS/TEN), immunobullous diseases, lichen planus, mycosis fungoides, physical or chemical injuries
- Pregnancy-associated hyperpigmentation: nipples and anogenital skin
- Red-brown hypermelanosis (haemosiderosis) [*] –
  - Diabetic dermopathy – late (*syn. shin spots, pigmented pretibial patches*)
  - Haemolytic anaemias
  - Shamberg's disease and other pigmented purpuric dermatoses
  - Sickle-cell anaemia
- Reticulate –
  - Acquired atopic hyperpigmentation (*syn. atopic dirty neck*) [33]
  - Dowling-Degos disease 1 (*syn. reticular pigment anomaly of the flexures*) [OMIM #179850]
  - Dowling-Degos disease 3 [OMIM #615674]
  - Dowling-Degos disease 4 [OMIM #615696]
  - Drug-induced reticulate pigmentation – especially diltiazem
  - Dyskeratosis congenita, X-linked [OMIM #305000]
  - Dyskeratosis congenita, autosomal dominant 1 [OMIM#127550]
  - Dyskeratosis congenita, autosomal recessive 1 & 5 [OMIM #224230, 615190]
  - Erythema ab Igne
  - Galli-Galli disease (a variant of Dowling-Degos disease) [34]
  - Harber's syndrome [35]
  - Hoyeraal-Hreidarsson syndrome (severe variant of dyskeratosis congenita, X-linked) [OMIM # 305000]
  - Lichen planus pigmentosus: reticulate pattern
  - Pigmentatio reticularis faciei et colli [36]
  - Poikiloderma of Civatte
  - Primary cutaneous amyloidosis: macular variant (rippled appearance)
  - Reticulate acropigmentation of Kitamura – early [OMIM #615537]
  - Wilson's disease (*syn. Hepatolenticular degeneration*) [OMIM #277900]
- Riehl's melanosis (*syn. pigmented cosmetic dermatitis, female facial melanosis, melanodermatitis toxica*)
- Solar lentigo: large
- Sweat discolouration [*]
  - Chromhidrosis (yellow, green, blue, brown or black)
  - Pseudo-chromhidrosis
- Talon noir [*]
- Tattoos – accidental and decorative [*]

- *Associated with textural change of the skin*
  - Acanthosis nigricans
  - Atrophoderma of Pierini and Pasini
  - Colloid milia: pigmented variant [*] (associated with exogenous ochronosis)
  - Diabetic dermopathy – late (*syn. shin spots, pigmented pretibial patches*)
  - Erythromelanosis follicularis faciei et colli [37]
  - H syndrome (*syn. hyperpigmentation and hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, low height, hormonal disturbances, haematologic illness and hyperglycaemia syndrome*) [OMIM #602782]
  - Infection – especially chikungunya, erythrasma, pityriasis versicolour, tinea nigra, secondary syphilis and onchocerciasis (*mal morado*)
  - Maculopapular cutaneous mastocytosis (*syn. urticaria pigmentosa*) [OMIM #154800] [*]
  - Melanoacanthoma/seborrhoeic keratosis
  - Morphea: plaque lesions

  - Muckle-Wells syndrome [OMIM #191900]
  - Notalgia paraesthetica
  - Reticulate –
    - Confluent and reticulated papillomatosis (*syn, Gougerot Carteaud disease*) *
    - Dirt pigmentation (*syn. dermatosis neglecta, terra firma-forme dermatosis*)*
    - Erythema ab Igne
    - Granular parakeratosis
    - Lichen planus pigmentosus – reticulate pattern
    - Pigmentatio reticularis faciei et colli [36]
    - Primary cutaneous amyloidosis: lichenoid variant (rippled appearance)
    - Prurigo pigmentosa
    - Systemic sclerosis ⊙

Linear/whorled/segmental

- *Macular*
  - Becker naevus – early (*syn. hypermelanosis naeviformis*)
  - Black dermographism
  - Flagellate pigmentation
    - Chemotherapy induced: bleomycin, peplomycin, docetaxel, bendamustine
    - Idiopathic flagellate pigmentation
    - Mechanical (true flagellation): religious punishment, torture, sexual pleasure, child/partner abuse, dermatitis artefacta
    - Rheumatological disorders: adult onset Still's disease, dermatomyositis
    - Toxin-induced: shiitake mushroom ingestion, cnidarian stings, *Paederus* and other insects
    - Other pruritic dermatoses: excoriations by pruritic conditions, phytophotodermatitis, hypereosinophilic syndrome
  - Phototoxic reactions
    - Berloque dermatitis
    - Phytophotodermatitis
  - Pigmented purpuric dermatosis: linear variant *
  - Post-inflammatory hyperpigmentation⊙ – especially physical trauma and intravenous drug use ("track marks")
  - Pregnancy-associated hyperpigmentation – linea nigra
  - Progressive cribriform and zosteriform hyperpigmentation (a unilateral, late-onset variant of Linear and figurated hyperpigmented naevus) [38]
  - Neurofibromatosis, type V: CALM/freckling (*syn. segmental neurofibromatosis, mosaic-localized neurofibromatosis*)
  - Segmental lentiginosis (*syn. lentiginous naevus, partial unilateral lentiginosis, agminated lentigines, lentiginous mosaicism*)
- *Associated with textural change of the skin*
  - Becker naevus – late (*syn. hypermelanosis naeviformis*)
  - Lichen planus / Lichen planus pigmentosus – blaschkoid or zosteriform
  - Lichenoid drug eruption – blaschkoid
  - Linear atrophoderma of Moulin
  - Morphea: linear lesions, en coup de sabre
  - Neurofibromatosis, type V: CALM/freckling and neurofibromas (*syn. segmental neurofibromatosis, mosaic-localized neurofibromatosis*)
  - Striae distensae

Mixed Pigmentation (Hypopigmented and Hyperpigmented)

Onset in Early Childhood [3, 12, 19, 20]

Generalized and Diffuse Mixed Pigmentation Disorders

- Dyschromatosis universalis hereditaria, types 1–3 (*syn. DUH*) [OMIM #127500, 612715, 615402]
- Familial progressive hyperpigmentation with or without hypopigmentation (*syn. FPHH; melanosis universalis hereditaria*) (includes Westerhof syndrome) [OMIM #145250]
- Spastic paraplegia 23 (*syn. SPG23; spastic paraplegia with pigmentary abnormalities; spastic paraparesis, vitiligo, premature greying and characteristic facies; Lison syndrome*) [OMIM #270750]

- X-linked reticulate pigmentary disorder with systemic manifestations – affected males (*syn. familial cutaneous amyloidosis, Partington disease, X-linked cutaneous amyloidosis*) [OMIM #301220]

Circumscribed Mixed Pigmentation Disorders

Guttate/punctate

- *Associated with textural change of the skin*
  - Poikiloderma -
    - Xeroderma pigmentosum, groups A-G [OMIM #278700, 610651, 278720, 278730, 278740, 278760, 278780]

Patchy

- *Macular*
  - Albinism-deafness syndrome (*syn. Ziprkowski-Margolis syndrome; Woolf syndrome*) [OMIM #300700]
  - Ermine phenotype (*syn. pigmentary disorder with hearing loss*) (includes Black locks with albinism and deafness syndrome, BADS) [OMIM #227010]
  - Fanconi anaemia [OMIM #227650]
  - Piebald trait (*syn. piebaldism*) [OMIM #172800]
  - Piebald trait with neurologic defects [OMIM #172850]
  - Post-inflammatory hyper- and hypopigmentation ° – especially neonatal lupus erythematosus
  - Protein-energy malnutrition – marasmus and kwashiorkor ° (likely due to phenylalanine deficiency)
  - Reticulate –
    - Dyschromatosis symmetrica hereditaria (*syn. DSH, reticulate acropigmentation of Dohi*) [OMIM #127400]
- *Associated with textural change of the skin*
  - Poikiloderma
    - Ataxia telangiectasia [OMIM #208900]
    - Bloom syndrome [OMIM #210900]
    - Hutchinson-Gilford progeria syndrome (*syn. progeria*) [OMIM #176670]
    - Kindler syndrome (*syn. Weary-Kindler syndrome, Poikiloderma with bullae*) [OMIM # 173650]
    - Poikiloderma with neutropenia (*syn. poikiloderma with neutropenia, Clericuzio-type*) [OMIM #604173]
    - Porphyrias
      - Congenital erythropoietic porphyria (*syn. Gunther's disease*) [OMIM #263700]
      - Hepatoerythropoietic porphyria [OMIM #176100]
    - Rothmund-Thomson syndrome (*syn. hereditary congenital poikiloderma*) [OMIM #268400]
    - Sclerotylosis (*syn. Huriez syndrome*) [OMIM #181600]

Linear/whorled/segmental

- *Macular*
  - Cutis tricolour – (i) as a purely cutaneous trait; (ii) as a part of a complex malformation phenotype (Ruggieri-Happle syndrome); (iii) as a distinct type with multiple, disseminated smaller skin macules (cutis tricolour parvimaculata); (iv) in association with other skin disturbances (e.g. cutis marmorata telangiectasia congenita, ataxia-telangiectasia, phacomatosis pigmentovascularis) [39]
- *Associated with textural change of the skin*
  - Focal dermal hypoplasia (*syn. Goltz syndrome*) [OMIM #305600]

Onset in Later Childhood Through to Adulthood [3, 12, 19, 23, 24]

Generalized and Diffuse Mixed Pigmentation Disorders

Autoimmune disorders

- Systemic sclerosis: salt and pepper appearance °
- Vitiligo (trichrome)

Chronic renal insufficiency
Drug-induced hyperpigmentation

- Chronic arsenic poisoning

Endocrine disorders

- Addison's disease: with vitiligo

Genetic disorders

- Dyschromatosis universalis hereditaria, types 1–3 (*syn. DUH*) [OMIM #127500, 612715, 615402]
- X-linked reticulate pigmentary disorder with systemic manifestations – affected males (*syn. Familial cutaneous amyloidosis, Partington disease, X-linked cutaneous amyloidosis*) [OMIM #301220]

Primary cutaneous amyloidosis

- Amyloidosis cutis dyschromica (ACD) [40]

Circumscribed Mixed Pigmentation Disorders

Guttate/punctate

- *Macular*
  - Amyloidosis cutis dyschromica (ACD) [40]
  - Chronic arsenic poisoning
  - Reticulate –
    - Dowling-Degos disease 2 [OMIM #615327]

Patchy

- *Macular*
  - Dermatomyositis
  - Genital melanosis associated with localized depigmentation [41]
  - Infections – especially late-manifesting pinta, pintoid dyschromia of yaws
  - Post-inflammatory hyper- and hypopigmentation ⊙ – especially discoid lupus erythematosus, systemic lupus erythematosus
  - Protein-energy malnutrition – marasmus and kwashiorkor ⊙ (likely due to phenylalanine deficiency)
  - Reticulate
    - Dyskeratosis congenita, X-linked [OMIM #305000]
    - Dyskeratosis congenita, autosomal dominant 1 [OMIM #127550]
    - Dyskeratosis congenita, autosomal recessive 1 & 5 [OMIM #224230, 615190]
    - Hoyeraal-Hreidarsson syndrome (severe variant of dyskeratosis congenita, X-linked) [OMIM # 305000]
    - Reticulate genital pigmentation associated with localized vitiligo [42]
  - Vagabond's disease (*syn. Vagabond's leucoderma*)
  - Vitiligo: trichrome variant, quadrichrome variant
- *Associated with textural change of the skin*
  - Infections – especially pityriasis versicolour, onchocerciasis (*leopard skin*), secondary syphilis (*leucoderma syphiliticum*), pinta
  - Morphea
  - Poikiloderma
    - Cockayne syndrome A [OMIM #216400]
    - Graft versus host disease (GVHD)
    - Hartnup disease [OMIM #234500]
    - Mycosis fungoides: poikilodermic variant (*syn. poikiloderma vasculare atrophicans*) [43]
    - Poikiloderma of Civatte
    - Porphyrias
      - Hereditary coproporphryia [OMIM #121300]
      - Porphyria cutanea tarda, types 1–3 [OMIM #176100]
      - Variegate porphyria [OMIM #176200]
      - Werner syndrome (*syn. adult progeria*) [OMIM #277700]

Conclusion

The colour of human skin is mainly due to melanin and haemoglobin, but it can be altered in non-physiological conditions such as jaundice, carotenoderma and drug intake. Melanin is produced by epidermal melanocytes, where it is synthesized in specialized organelles called melanosomes. Variations in individual skin colour and between people of various ethnicities are not due to the number of melanocytes but rather are due to the number, size and type of melanosomes and the dispersion of the melanin pigment.

The pigmentary disorders include those where there is a lightening in skin colour, a darkening in

skin colour, a mixed pattern of lightening and darkening in skin colour or the development of an unusual skin colour. The vast majority of pigmentary disorders are due to quantitative or qualitative defects in the synthesis, transfer, deposition and degradation of melanin. Abnormal skin colour can also result from disturbances in both endogenous and exogenous pigments.

When approaching a patient with abnormal skin colour, it is important to perform a thorough history, examination and relevant bedside investigations (often including diascopy and Wood's lamp examination). Investigations are dependent on the diagnosis suspected, but in many cases investigations (including histopathology) are not diagnostic. For this reason, it is important to have a systematic approach for the pigmentary disorders.

In this chapter we have presented a comprehensive clinical classification of the pigmentary disorders.

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