Diploma thesis

Classification of melanocytic nevi

submitted by

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Graz, September 18th, 2017

Affirmation in lieu of an Oath

I hereby formally declare, that I have written the submitted thesis independently and without any illegitimate assistance from third parties. I confirm, that I used no other than the declared sources for the preparation of this academic work. All used sources have been indicated as such and acknowledged by means of complete references in the text.

Graz, September 18th, 2017 *Katrin Rammel eh*

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Zusammenfassung

Hintergrundinformation: Die Einteilung von melanozytären Nävi erfolgte bisher auf klinischer und histologischer Basis. Verschiedene Ansätze über die Entstehung und Entwicklung von Nävi wurden präsentiert, mit dem Ziel einer frühen Differenzierung und Erkennung von Melanomen. Die Dermatoskopie bietet hierfür als nicht-invasive, in-vivo Untersuchungsmethode wertvolle Einblicke in submakroskopische Strukturen von melanozytären Läsionen. Anhand von unterschiedlichen dermatoskopischen Mustern und Merkmalen können somit melanozytäre Läsionen besser strukturiert und eingeteilt werden.
Zielsetzung: Ziel dieser Übersichtsarbeit war es, aktuelle Studien und Reviews der letzten Jahre über die dermatoskopischen Merkmale von melanozytären Tumoren zu ermitteln und deren Ergebnisse zusammenzufassen. Dies soll sowohl Diagnose als auch Management von Nävi im klinischen Alltag erleichtern.
Methoden: Es erfolgte eine Suche nach deutschen und englischen Fachartikeln via PubMed (MEDLINE) und Journals@Ovid von Jänner 2009 bis Mai 2016. Follgende Suchterms wurden verwendet: *dermoscopy, dermatoscopy, epiluminescence microscopy, surface microscopy, digital dermoscopy, digital dermatoscopy, digital epiluminescence microscopy, digital surface microscopy, nevus, nevi, naevus, naevi, melanocytic skin lesion, pigmented skin lesion, color, colour, pattern, pigment distribution, face, facial, acral, nail, mucosa, mucosal, trunk, scalp, age, elderly, old, skin type, melanoma history, melanoma related, UV, UVR, UV irradiation, UV radiation, UV rays, ultraviolet, pregnancy, genes, genetic, BRAF* und *recurrent.* Nach Einschluss von Fachartikeln durch weitere Recherche bis Mai 2017 wurden 123 Publikationen ausgewählt und analysiert.
Ergebnisse: Innerhalb der 123 Publikationen fanden sich eine randomisiert kontrollierte Studie mit hohem Evidenzgrad (A), sowie eine Meta-Analyse und ein systematischer Review mit niedrigerem Evidenzgrad (B). Ebenso beinhaltete die Auswahl 75 prospektive und retrospektive Studien mit einem Evidenzlevel B.
Die dermatoskopische Diagnose von melanozytären Nävi basiert auf der Beurteilung folgender Kriterien: Farbe (schwarz, braun, grau, blau und rot), Struktur (globulär, retikulär, strukturlos, sternförmig und gemischte Strukturen), Pigmentverteilung (gleichmäßig, multifokal, zentral oder exzentrisch) und Gefäßstrukturen (komma-artige oder punkt-artige Gefäße). Zusätzlich beeinflussen endogene und exogene Faktoren die dermatoskopischen Merkmale

von Nävi: Alter, Körperlokalisation, Hautfarbe, Mutationen, Genetik, Melanom-Vorgeschichte, Schwangerschaft, UV-Bestrahlung und Traumata.
Konklusion: Diese Kriterien bieten nicht nur grundlegende Differenzierunsgmerkmale von melanozytären Läsionen, sondern auch einen Wissensstand über patientenbezogene Faktoren, die das Aussehen von Nävi beeinflussen. Durch Einbeziehen dieser Erkenntnisse kann das Management von von melanozytären Läsionen im klinischen Alltag optimiert werden.

Abstract

Background information: In the past, the classification of melanocytic nevi relayed mainly on clinical and histological criteria. Several models have been proposed which may explain nevus development. Categorising nevi aims at an early differentiation and diagnosis of melanoma. Dermoscopy provides a valuable *in vivo* diagnostic tool that allows the visualisation of submacroscopic structures, which are otherwise invisible for the naked eye. This allows for a dermoscopic classification of melanocytic nevi.

Objective: To review recent studies and reviews of dermoscopic imaging of melanocytic lesions that provide insights into the development of nevi and their distinct patterns, which contribute to their diagnosis and further management.

Methods: Literature search was performed via PubMed (MEDLINE) and Journals@Ovid from January 2009 to June 2016, using the following relevant terms: *dermoscopy, dermatoscopy, epiluminescence microscopy, surface microscopy, digital dermoscopy, digital dermatoscopy, digital epiluminescence microscopy, digital surface microscopy, nevus, nevi, naevus, naevi, melanocytic skin lesion, pigmented skin lesion, color, colour, pattern, pigment distribution, face, facial, acral, nail, mucosa, mucosal, trunk, scalp, age, elderly, old, skin type, melanoma history, melanoma related, UV, UVR, UV irradiation, UV radiation, UV rays, ultraviolet, pregnancy, genes, genetic, BRAF* and *recurrent.* Only German and English articles were included. Overall 123 results have been identified, including further studies during research until May 2017.

Results: From the 123 manuscripts, one randomised controlled trial of high evidence (A) and one meta-analysis and one systematic review of limited evidence (B) have been reviewed. The sample further included 75 prospective and retrospective studies from single or multiple institutions, which are graded as level of evidence B.

The results provide the following dermoscopic criteria for the diagnosis of melanocytic nevi: colour (black, brown, grey, blue and pink), pattern (globular, reticular, structureless, starburst and mixed), pigment distribution (uniform, multifocal, central and eccentric hypo-/hyperpigmentation) and vascular structures (comma-shaped and dotted vessels). In addition, the following patient related factors influence nevus morphology and illustrate distinct dermoscopic features:

age, body-site, skin-type, molecular and genetical alterations, history of melanoma, pregnancy, UV-irradiation and trauma.
Conclusion: These dermoscopic criteria may help clinicians in the diagnosis of melanocytic lesions by providing the knowledge of a basic classification of nevus morphology as well as factors influencing their dermoscopic features.

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List of Abbreviations

AMN	acquired melanocytic nevi
AMNGT	atypical melanocytic nevi of the genital type
AST	atypical Spitz tumour
CDKN2A	cyclin-dependent kinase inhibitor 2A
CMN	congenital melanocytic nevi
e.g.	exempli gratia; for example
ELM	epiluminescence microscopy
ERK	extracellular signal-regulated kinase
FAMMM	familial atypical multiple mole melanoma
i.e.	id est; that is
IRF4	interferon regulatory factor 4; previously MUM1
MAPK	mitogen-activated protein kinase
MC	mixed pattern with central globules/structureless brown area and peripheral network
MC1R	melanocortin 1 receptor
MEK	MAP-kinase/ERK-kinase
MELTUMP	melanocytic tumours of uncertain malignant potential
MP	mixed pattern with central network/structureless brown area and peripheral globules
MTAP	methylthioadenosine phosphorylase
PARP1	poly-ADP-ribose-polymerase 1
PLA2G6	phospholipase A2, group VI
RAF	rapidly accelerated fibrosarcoma oncogene; protein kinase
RAS	rat sarcoma oncogene; GTP binding protein
RCM	reflectance confocal microscopy
SAMPUS	superficial atypical melanocytic proliferation of uncertain significance
SNP	single nucleotide polymorphism
ST	skin type
STUMP	tumour of uncertain malignant potential
UV	ultraviolet

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1 Introduction

In 2009, a systematic review on the dermoscopic patterns of nevi and factors that influence their morphology has been published (1). However since then, several new articles in this field have been published and accordingly, new knowledge has been obtained.

The aim of this review is to provide a first part, the basic knowledge and general aspects regarding nevus development and nevus classification and in a second part, to review and summarise the most salient data of the literature published since 2009.

1.1 Basics of melanocytic nevi

1.1.1 Definition of a nevus

Melanocytic nevi are benign tumours of melanocytes, which are pigment-producing cells in the skin. Melanocytic nevi are the most common benign cutaneous neoplasms in a white population. It must be admitted that although, or maybe because melanocytic nevi are very common up to date, neither a consistent and widely accepted concept of nevogenesis nor classification system does exist (2).

1.1.2 Current concepts of nevogenesis

Over the past decades, different concepts of nevogenesis have been proposed to explain the origin and development of melanocytic nevi. In 1893, Unna (3) firstly proposed the idea, that melanocytic nevus cells arise in the epidermis and wander to the dermis during time (“drop off”, “Abtropfung”) (**Figure 1**). This process leads to different stages of development of melanocytic nevi, namely lentigo simplex, junctional, compound and dermal nevi (4). In 1951, Masson (5) firstly introduced the idea of a dual concept of the development of nevus cells, whereby he proposed that nevus cells derive from both superficial “epidermic melanoblasts” and dermal Schwann cells (**Figure 1**). Within the hypothesis that nevus cells derive from the neural crest during embryogenesis (6), Cramer (7) proposed the concept of “upward climb” (“Hochsteigerung”) (**Figure 1**). The assumption was, that nevus cells wander along extending cutaneous nerves from the spine into the dermis and finally into the epidermis. Upon their migration, the neural crest cells

gain maturation and ability for pigment production (4,7). Following the theory of Cramer, Saida (8) proposed a unifying concept of the genesis of congenital and acquired nevi, which says that both entities originate from a temporary proliferation of melanoblasts or melanocytes. It is assumed, that an early onset of proliferation of melanocyte-lineage cells during their migration from the neural crest to the skin in the embryonic or foetal stage result in large congenital nevi. To the other hand may a late start of proliferation of dermal, junctional or epidermal melanocytes result in small congenital or acquired nevi. The hypothesis can be summed up with the phrase “the later the proliferation begins, the smaller the lesions are” (8).

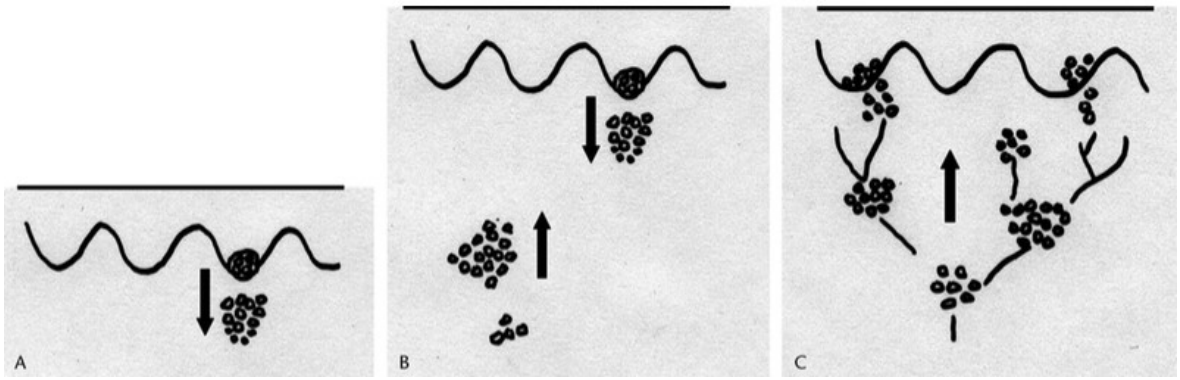

Figure 1: Different concepts of nevogenesis. A, Abtropfung (Unna, 1893). B, Dual origin (Masson, 1951). C, Hochsteigerung (Cramer, 1984) (4).

Dermoscopic studies have shown, that the patients’ predominant dermoscopic nevus pattern differs significantly between children and adults and body-sites. Based on this observation, Zalaudek proposed the hypothesis of a “dual pathway of nevogenesis”, namely the endogenous and the exogenous pathway (9,10). The former, endogenous or congenital pathway of nevogenesis, explains the common origin of nevi exhibiting the globular dermoscopic pattern as seen in congenital melanocytic nevi (CMN) and in intradermal nevi of the Unna and Miescher type. The theory indicates that CMN, globular nevi and nevi appearing in early life derive from dermal melanoblasts. They tend to persist an individuals lifetime and eventually appear as intradermal nevi of the Unna or Miescher type later on. Because of the histopathologic exhibition of dermal nevus cell nests, frequently peri-adnexal distributed, they can be classified as nevi with congenital pattern (9,11). In contrast, the exogenous or acquired pathway of nevogenesis explains the development of nevi showing a reticular pattern and appearing later in life. The hypothesis indicates that these acquired nevi originate from epidermal

melanocytes, which proliferate horizontally along the dermo-epidermal junction in response to exogenous factors as for instance ultraviolet (UV) irradiation (9,11). Reflectance confocal microscopy (RCM), an *in vivo* technique to visualize the cellular morphology of nevi, and longitudinal RCM follow-up has given new insights into nevogenesis. In fact, Pellacani (12) speculates that nevi mainly develop within the same compartment (dermal, junctional or epidermal) and maintain their overall dermoscopic pattern and RCM pattern over time. The results indicate that the endogenous pathway only applies to intradermal nevi exhibiting a dermoscopic cobblestone pattern ("Large, closely aggregated, somehow angulated globule-like structures resembling cobblestones"). In contrast, junctional nevi can initially show a globular pattern and later develop into a reticular or homogeneous pattern due to peripheral expansion of the nevus cell nests. Concordant with Cramer (7), Pellacani (12) hypothesizes that immature melanocytes accumulating and progressively expanding in the dermis give rise to nevi exhibiting the cobblestone dermoscopic pattern. Similarly, the proliferation or accumulation of more mature cells in the epidermis form epidermal nevi showing a reticular dermoscopic pattern (12).

1.1.3 Nevus classification

The classification of nevi is an evolving science and different schemes relying on different criteria have been employed. Depending on the method, nevi can be classified based on their history, morphology, genetics, location and associated melanoma risk (2).

1.1.3.1 Classification based on history and size

One method to classify nevi is based on their history. As such, two different categories can be distinguished, namely congenital (CMN) and acquired melanocytic nevi (AMN) (2,13).

1.1.3.1.1 Congenital melanocytic nevi (CMN)

CMN are present at birth or develop within the first four weeks of life (2,14). This group also includes so-called *tardive congenital melanocytic nevi* (also "congenital-nevus-like melanocytic nevi", "early onset nevi"), which develop in the first two years of postnatal life. They do not differ clinically and histologically from *"true"* CMN and therefore count to the entity of CMN (2,15). They are further said

to derive from the neural crest and occur with an incidence of 0,2 – 2,1% in neonates (16).

In 1979, Kopf et al. (17) published a classification system based on the clinical diameter of CMN in adults, whereby they can be grouped into *small* (< 1,5 cm), *medium* (1,5 – 19,9 cm) and *large* (≥ 20 cm) CMN. The latter can be further distinguished into G1 (20 – 30 cm), G2 (30 – 40 cm) and G3 (> 40 cm) nevi (16). *Giant* CMN, affecting whole parts of the body (e.g. shoulder, pelvis), are meant to be special worrisome subtypes, as evidence has shown, that a greater diameter correlates with an increased melanoma risk (2,17).

Clinically, *small* to *medium* sized CMN appear as flat homogeneous light- to dark-brown macules or plaques with sharp boarders and hypertrichosis (2). During childhood, they show an increase in size proportionally to the growth of the skin (18). Old and *large* CMN clinically often have irregular surfaces and variations in colour (2)

Histologically, CMN exhibit melanocytic infiltration into the deepest layers of the dermis, often connected to the skin adnexa and occasionally extended to the subcutaneous tissue. This deep architecture is only found in CMN up to now (2). *Giant* CMN often come along with satellite nevi, which can be disseminated on the whole integument. When also affecting the leptomeninges, the term neurocutaneous melanosis is used (2).

1.1.3.1.1.1 Neurocutaneous melanosis

Neurocutaneous melanosis is the appearance of one *large* or more than three *small* CMN followed by the development of leptomeningeal melanocytosis or leptomeningeal melanoma (19,20). The most relevant risk factor for neurocutaneous melanosis is having a high count (> 20) of satellite nevi (21). It can be detected already without having developed any neurological symptoms by magnetic resonance imaging of the brain (22). However, when symptoms do occur, the prognosis is very poor (23,24). Neurological symptoms often begin within the first two to three postnatal years (rarely in the 2nd or 3rd decade of life) and are characterized by signs of increased intracranial pressure and spinal compression, as well as psychomotoric retardation (23,25).

1.1.3.1.1.2 Nevus spilus

Nevus spilus (or *speckled lentiginous nevus*) is a special type of CMN (26), characterized by a café au lait spot sprinkled with small dark papules (2). Isolated cases have been reported on developing melanoma on nevi spili (27), however, their overall potential for malignant transformation is considered low (2).

1.1.3.1.2 Acquired melanocytic nevi (AMN)

AMN tend to occur multiple on a single individual. A high number of nevi (i.e. >50) is a known risk factor for melanoma development. In general, AMN are light- to dark-brown macules or papules with sharp regular boarders, which occur after the second postnatal life. Their diameter varies from 2 mm to average 5-6 mm. In contrast to CMN, which are classified based on their diameter and their time of development, AMN are subtyped by their clinical and histopathological characteristics (2). Basically, AMN run through different stages of growth with different clinical and histopathological characteristics (2). Traditionally, it was thought that AMN progress from entirely intra-epidermal (junctional) through both epidermal and dermal (compound) to entirely intradermal (dermal) (3,14). However, more recent insights into the development of nevi challenge this concept and postulate little migration of melanocytes between the epidermis and dermis (2).

1.1.3.1.2.1 Stages of development:

1) *Lentigo simplex* is identified as the initial state of the development of AMN. Clinically, Lentigo simplex appears as a medium- to dark-brown round-oval macula with a small diameter of few millimetres. The histological pattern shows an elongation of the rete ridges and melanocytic hyperplasia in the basal layer (2).
2) *A Junction nevus* clinically exhibits a regular round or oval macula with medium- to dark-brown pigmentation. Histologically, melanocytic nests are found on the dermo-epidermal junction, predominantly in the peaks of the rete ridges (2).
3) *A Compound nevus* appears as a round to oval, flat papule with light- to dark-brown pigmentation. In addition to the nests in the junction zone, compound nevi also show melanocytic nests and strands in the dermis

histologically. These deep dermal cell structures frequently have small nuclei and lose the ability to produce pigment (2).

4) *Dermal melanocytic nevi* are nodes with regular surfaces, sharp borders and without pigmentation. Histologically all of the melanocytic cell structures are located in the dermis and no epidermal nests are found. The cells have lost their pigmentation (2).

1.1.3.2 Classification based on clinical-histopathological characteristics

Ackerman and Magana-Garcia (14) proposed a concept based on clinical and histopathological factors, which subtypes nevi into flat, exophytic and endopyhtic nevi. The four main subtypes are Unna's (exophytic), Miescher's (endophytic), Clark`s (flat) and Spitz nevi, whereby the latter form a separate category (14,28). It has to be noted that the terms "exophytic" and "endophytic" do not describe the clinical appearance of nevi, but the histopathological arrangement of melanocytes within the skin (28).

1.1.3.2.1 Unna type

Nests, strands or cords of melanocytes located in a thickened papillary dermis characterize the intradermal nevus of the Unna type. Clinically, Unna's nevi have an exophytic character, whereby they often stay unrecognized when compound or junctional. Usually, Unna's nevi do not appear as a risk factor for developing melanoma, as an association with melanoma is very rare (14). A further histopathologic subtype constitutes the category of blue nevi.

1.1.3.2.2 Miescher type

Basically, the intradermal nevus of the Miescher type appears as a dome-shaped, skin-coloured to brown papule, typically located in the face. Histopathologically, the Miescher's nevus is characterized by mostly endophytically distributed melanocytes in the deep reticular dermis. An association with melanoma does exist, but is still rare (14).

1.1.3.2.3 Clark nevi

Clark nevi clinically appear as flat nevi, varying in their clinical appearance regarding symmetry, border, colour and size (29). Histological examination shows melanocytes in the dermo-epidermal junction zone and in the papillary dermis (28) Concerning the exact definition of atypical or dysplastic nevi (Clark nevi), still no international concordance has been found up to now, whereby distinguishing them from common nevi or melanomas represents a matter of concern. The former description ("atypical") represents the clinical definition, whereas the latter ("dysplastic") substitutes the histological nomenclature. Even though there is still no international agreement on the clinical characteristics because of overlapping some ABCD-features for melanoma diagnostic, some main histological criteria like basal lentiginous melanocytic hyperplasia, cellular atypia and stromal fibrosis are already accepted (2). On dermoscopy, Clark nevi can be classified by their dermoscopic pattern (reticular, globular, homogeneous, reticular-globular, reticular-homogeneous, globular-homogeneous and unclassified without a specific pattern) and their pigment distribution (uniform pigmentation, multifocal hypo- or hyperpigmentation and central or eccentric hypo- or hyperpigmentation). Thus, the most common dermoscopic features are described to be the reticular pattern, followed by a reticular-homogeneous and globular-homogeneous pattern with pigmentation variants of multifocal hypo- or hyperpigmentation followed by central hypo- or hyperpigmentation. As melanomas often show eccentric peripheral hyperpigmentation, Clark nevi showing this feature are regarded to be the most relevant melanoma simulators in the morphologic spectrum of dysplastic nevi (30).

1.1.3.2.4 Spitz nevi

Spitz nevi (formerly "juvenile melanoma) are benign melanocytic proliferations showing signs of atypia (31) and clinically presenting as rapid-growing red to brown hemispheric papules or nodes with a smooth surface. They are predominantly found in children and adolescents, commonly located in the face (2,29).

On dermoscopy, Spitz nevi exhibit central hypopigmentation and peripheral dots, globules and streaks. Histological examination shows symmetrical sharply bordered tumours with melanocytic nests vertically orientated in the dermo-epidermal junction (2).

Different subtypes of Spitz nevi can be determined: classic Spitz nevus, atypical Spitz nevus (32) and pigmented spindle cell tumour of Reed (33). Atypical Spitz nevi are predominantly observed in childhood and adolescence (2) and often misdiagnosed for melanoma (32) because of their ambiguous clinical appearance (2). Pigmented spindle cell tumours of Reed predominantly occur on the thighs of young women and are characterized by black papules or nodes showing a starburst pattern under dermoscopy (2).

1.1.3.2.5 Blue nevi

Blue nevi exhibit a bluish, sometimes mixed blue-brown or white clinical appearance with a smooth surface usually papular or nodular (16). They predominantly occur in children and adolescents with an estimated incidence of 1-2% in the white population. Their main histologic characteristic is the occurrence of dendritic melanocytes in the dermal layer. Up to now, two types of blue nevi can be distinguished: the common blue nevus (diameter <10 mm) and the cellular type (diameter ≤30 mm) (16,34). Dermoscopically, blue nevi mostly show a steel-blue homogeneous colour (35). However, in blue nevi any other dermoscopic pattern and structure is absent while different colour variations have also been described (35). While small and common blue nevi do not need any further management, especially rapidly growing blue nevi of the cellular type can lead to be misdiagnosed for melanoma (16).

While these categories refer to the most common types of nevi, it should be noted that there is a much longer list of specific histopathological variants of nevi that has been described. However, the description of each variant would cover an own book.

1.1.3.3 Classification based on dermoscopy

Dermoscopy is an *in vivo* technique allowing visualization of submacroscopic pigmented features, which are not visible to the naked eye (11,1). As the most dermoscopic features correlate well with histopathological criteria (36), dermoscopy provides a valuable method for clinicians to identify the need to biopsy a lesion (37–39). Thus, dermoscopy has given new insights concerning the morphological features of nevi and enables to categorize different nevus types regarding their dermoscopic pattern, colour and pigment distribution (13,1).

Up to now, 4 main dermoscopic patterns have been identified to subtype melanocytic nevi, namely the globular, reticular, starburst and homogeneous blue pattern (11,13,1,40). Therefore, each pattern correlates with a certain subjacent histopathological feature (1,41,42). For further classification, mixed patterns have been identified such as central globular and peripherally structureless (MC) as well as peripheral globules with a central structureless area (MP) (11). In addition, pigmented nevi almost generally show either 1 or 2 of the colours black, brown, grey and blue. Each colour allows assessment of the location of melanocytic cells in the skin (13,43,1,44). Concerning the pigmentation distribution of nevi, 4 types have been identified: uniform, multifocal, eccentric (eccentric foci of hypo- or hyperpigmentation) and central (central area of hypo- or hyperpigmentation) (1,13,30,45).

1.1.3.4 Classification based on molecular alterations

Twin and family studies have tried to investigate heritability and genetic modifications in nevus morphology. Recent examinations illustrate the involvement of the MAPK (mitogen-activated protein kinase) pathway in the growth control of melanocytic cells (46). MAPK belongs to the entity of ERK (extracellular signal-regulated kinase), whose activation plays a decisive role in signalling cell proliferation (RAS-RAF-MEK-ERK- pathway; **Figure 2**) (47). Therefore, MAPK-activation via somatic mutations in RAS (rat sarcoma oncogene; GTP binding protein)- and RAF (rapidly accelerated fibrosarcoma oncogene; protein kinase)-genes are commonly observed in both nevi and melanomas, influencing cell proliferation, migration and differentiation (2,48). Additionally, it has been monitored, that different types of nevi tend to ground on various genetic alterations. Mutations in the BRAF- gene mainly appear in melanomas and sun exposed acquired nevi (especially dysplastic/Clark nevi and small nevi with congenital-like features). Blue nevi, Spitz nevi and intermediate to large CMN tend to be based on mutations of NRAS- or HRAS- genes (11,49–52). Concerning the former, BRAF mutations are particularly associated with intermittent UV exposure and mainly (92 %) take place in a single codon ($BRAF^{V600E}$) (53). It has further been observed that the majority (82%) of benign melanocytic nevi exhibit $BRAF^{V600E}$ mutations (54). In addition, Michaloglou (55) showed that an overexpression of oncogenic $BRAF^{V600E}$ causes growth arrest in melanocytic cells. After reaching the end of growth, melanocytic nevi display four hallmarks of cell

senescence induced by oncogenes, namely: (almost-) total and stable proliferative arrest, activated $BRAF^{V600E}$ expression, up-regulation of a tumour suppressor ($p16^{INK4A}$) and the occurrence of senescence-associated β- galactosidase (55,56). Recently, also somatic mutations in the GNAQ- gene have been found in blue nevi (57). These genes (BRAF, NRAS, HRAS, GNAQ) lead to the activation of MAPK and thus to the development of melanocytic neoplasia (2).

Previously, twin studies found a linkage between nevus counts and mutations in the CDKN2A (cyclin-dependent kinase inhibitor 2A) gene (58). The CDKN2A gene encodes for the expression of tumour suppressor genes like $p16^{INK4A}$, whose inactivation because of CDKN2A mutations leads to uncontrolled cell proliferation. However, CDKN2A mutations are associated with a high risk of developing melanoma and FAMMM syndrome (familial atypical multiple mole melanoma syndrome), which is characterized by numerous melanocytic nevi (>50) and personal or family history of melanoma (59).

Genes encoding proteins responsible for human pigmentation can also be affected by alterations. It has been found that MC1R (melanocortin 1 receptor) gene mutation carriers are associated with fair skin and/or red hair (60). Further, individuals additionally carrying CDKN2A mutations are linked with an increased risk for melanoma (61).

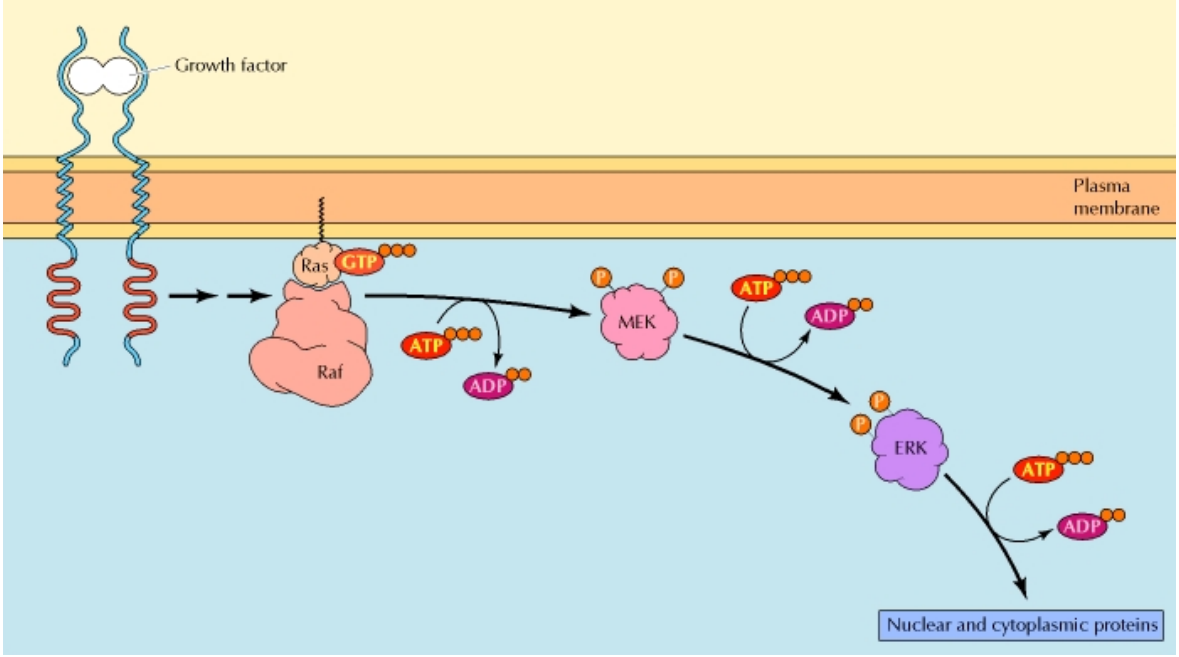

Figure 2: RAS-RAF-MEK-ERK-pathway. Stimulated growth factor receptors induce RAS-activation, which interacts with RAF then. Phosphorylation of RAF leads to MEK (MAP-kinase/ERK-kinase)- activation, which further phosphorylates and activates ERK. The activation of ERK leads to phosphorylation of numerous nuclear and cytoplasmatic proteins as well as transcription factors responsible for cell proliferation (60,61).

1.1.3.5 Classification based on location

Any of the subtypes mentioned before may occur on body areas, which are commonly referred to as special body sites. These body areas include the scalp, face, ear, breast milk line, flexures, palms and soles, nails and genitalia. Thereby the term “special” derives from histopathology as nevi from these body sites may exhibit marked atypia and carry therefore the risk of over-diagnosis of melanoma (i.e. melanoma simulators). Vice versa, early melanomas from this body sites may show bland features upon histopathology and may be misclassified as nevi (i.e. carry the risk of under-diagnosis) (13,1). Because of a typical structure of the skin in special body sites, these nevi show peculiar dermoscopic features (**Table 1**).

Table 1: Dermoscopic features of nevi based on special body sites (13,1,62)

Special body site	***Dermoscopic feature***
Face	Structureless brown-grey, with hypopigmented hair follicles*
Acral	Parallel furrow pattern
Nails	Parallel bandlike pattern, regular lines of uniform colour and width
Milk line	Prominent pigment network, large (cobblestone-like) globules, dark irregular dots when involving the nipple
Mucosa	Globular mixed pattern consisting of gray-blue globules or/and prominent network structures or/and homogeneous blue-gray pigmentation

* this feature is only seen in facial nevi of young age

1.1.3.6 Classification based on special features

Nevi exhibiting peculiar clinical features, such as white or red-eczematous halo, targetoid appearance or special clinical history like trauma or biopsy, are summed up under this category.

1.1.3.6.1 Halo nevi

Halo nevi, which are also called Sutton nevi, represent congenital or acquired melanocytic nevi surrounded by a rim of hypopigmentation/vitiligo (**Figure 3**), commonly found in children and adolescents. They are particularly located on the trunk, either single or multiple (16,29). The dermoscopic features mainly include a globular pattern with a white, scar-like depigmentation in the periphery until the

whole involution took place and grey pigmentation is left (16). Halo nevi are said to disappear over time by regression of the central part caused by T lymphocytic cells (16,29). Thus, an association with autoimmune diseases, such as vitiligo, Hashimoto thyroiditis or atopic dermatitis is suspected (16). For differential diagnosis of these regression structures, regressing melanoma needs to be ruled out (16,29).

1.1.3.6.2 Meyerson nevi

In contrast to the depigmentation of Halo nevi, Meyerson nevi are benign melanocytic nevi surrounded by an erythematous, scaly and pruritic eruption (63). Although an undergoing process of an inflammation has been confirmed, a definite aetiology of Meyerson nevi remains unclear, as some author associate these nevi with pityriasis rosea, allergic contact dermatitis or UV irradiation (64). Dermoscopic examination often shows a central blurred and unspecific pattern due to superficial and overlying crusts (**Figure 3**) (65). One or more nevi may be involved simultaneously mainly affecting young adults (66).

1.1.3.6.3 Combined nevi

The term “combined nevus” is used for nevi exhibiting two different histopathological cell populations (67), most frequently the combination between a blue nevus with a small CMN (43). However, other combinations are possible as well. Thus, dermoscopic examination can present different patterns as: blue homogeneous patterns combined with globules or a reticular network in the peripheral area (16).

1.1.3.6.4 Recurrent nevi

After incomplete removal of melanocytic nevi (e.g. after “shave biopsy”, “electronic coagulation”, “laser therapy”) (68), they may recur within 6 months (69) clinically and/or histologically mimicking melanoma (70).
Recurrent nevi clinically appear as flat, elongated and asymmetrical lesions with irregular boarders and brown to black, homogenous to spotted pigmentation (**Figure 3**). Frequently, a scar can be found within the lesion. The pathogenesis could be explained by proliferation of adnexal melanocytic residues during the process of wound healing. Histologically, recurrent nevi show intraepidermal alterations, fibrotic scar tissue and melanocytic remnants in the dermal layer,

whereas intraepidermal melanocytic proliferation does not disperse across the scar. As differentiating from melanoma can be challenging, the results of the original surgery should be involved for an exact diagnosis (2).

1.1.3.6.5 Hemosiderotic targetoid nevi

Hemosiderotic targetoid nevi are traumatised (e.g. from clothing, shaving or scratching) frequently exophytic melanocytic nevi, which show distinctive clinicopathologic features. The clinical hallmark is the appearance of a violaceous halo, which regresses within four weeks (66). Under dermoscopy, the central component includes a globular nevus pattern with vascular-haemorrhagic changes, whereas the purple rim mainly appears homogeneously red with jagged margins (**Figure 3**) (65,66). Because hemosiderotic targetoid nevi are important simulators of melanoma, precise anamnestic and clinical examinations are indicated to avoid unnecessary procedures (66).

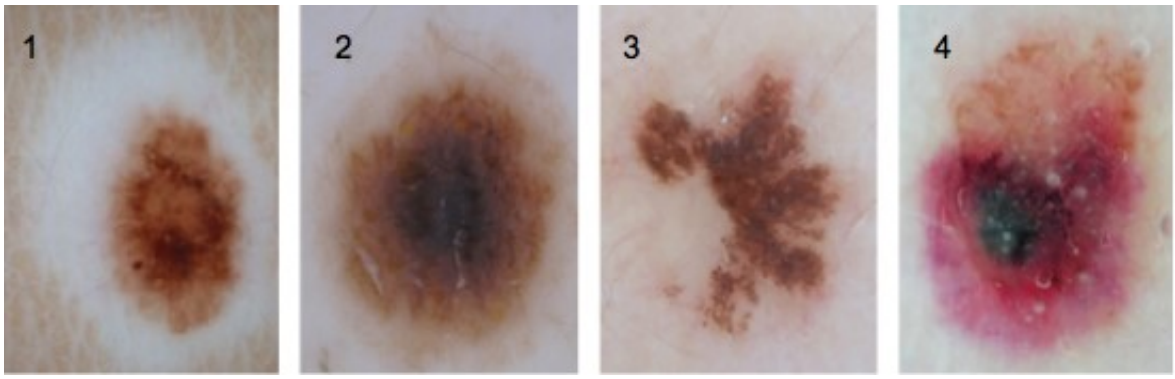

Figure 3: Nevi with special features. Dermoscopy of a (1) Halo, (2) Meyerson, (3) recurrent and (4) traumatised nevus.

1.1.3.7 Classification based on melanoma risk

The main aim of classifying nevi is related to their associated melanoma risk. As such, nevi can be precursors of melanoma, indicators for an increased risk of developing melanoma or simulators of melanoma.

1.1.3.7.1 Nevi as melanoma precursors

It is thought that 75-80% of cutaneous melanomas develop on healthy skin (71). However, almost 20-25% of melanomas are said to arise on other cutaneous lesions which can be identified as melanoma precursors (71). Nevertheless, it must be admitted that these studies relay on selection bias, as they include only excised lesions and do not take into account the great majority of nevi that have

not been excised. Tsao et al. (72) estimated the true risk of nevi progressing towards melanoma from one out of 200.000 nevi (< 40 years of age) to one out of 33.000 nevi (> 60 years of age) in the worst case. Up to now, 3 kinds of nevi are suggested to represent precursors of melanoma, namely CMN, Clark and other acquired melanocytic nevi. Another subtype of nevus that has been associated with malignant transformation are blue nevi, although the true risk of malignant transformation still needs to be defined (71).

1.1.3.7.2 CMN as melanoma precursors

Among all different subtypes, *giant* congenital nevi have the highest risk of malignant transformation. Thereby the risk increases with the clinical diameter of the nevus, being highest (5 – 15%) in congenital nevi exceeding 20 cm (2,17,73). A recent systematic review reveals that patients with *large* CMN are at a 465-fold higher risk of evolving melanoma in childhood or adolescence (74). Furthermore, melanomas arising in *large* CMN predominantly (2/3 of melanomas) develop in the dermis (75), which may result in a late diagnosis and worse prognosis (2). Instead, the risk of small congenital nevi does not seem to differ from acquired nevi. However, also *small* and *medium* sized CMN are documented to possibly undergo malignant transformation, which is particularly located in the epidermal layer and occurs during adulthood (76).

1.1.3.7.3 Nevi as melanoma indicators

A high number of nevi is the strongest and best documented risk factor for melanoma development. While there is a 4 to 5 times higher risk for patients having ≥ 50 common nevi, exhibiting ≥ 100 common nevi comes along with an even 8 to 10 fold risk of developing a melanoma (2). Melanoma patients generally have double as much common nevi as other individuals from the same age and gender. Furthermore, the existence of at least 5 atypical melanocytic nevi is said to result in a higher risk of evolving a melanoma (77). Thus, persons with multiple nevi should be kept lifelong under clinical surveillance.

1.1.3.7.4 Nevi as melanoma simulators

Some nevi may mimic melanoma from a morphological point of view, while being biologically benign (2). Among nevi, the most relevant simulators of melanoma can be summarized as follows:

I. Classic spitz nevi and atypical spitz nevi (2)
II. Recurrent nevi (2)
III. Nevi of special sites including acral nevi (palmar and plantar) as well as nevi of the milk line (genital, perianal, axillar, mammillary, umbilical) and ears or knees (2)
IV. Exogenous altered nevi (e.g. UV-irradiation) (2) or trauma-induced nevi (e.g. targetoid hemosiderotic nevi,) (66)
V. Nevi in pregnant women or in patients under immunosuppression (2)
VI. Ancient nevus, black/hyperpigmented nevus, deep penetrating nevus, combined nevus (2)
VII. Cellular blue nevus, blue nevus with peripheral satellitosis (16)
VIII. Unclassifiable melanocytic proliferations including MELTUMP (MELanocytic Tumours of Uncertain Malignant Potential), STUMP (Spitz Tumour of Uncertain Malignant Potential) or SAMPUS (Superficial Atypical Melanocytic Proliferation of Uncertain Significance) (78)

To avoid a misdiagnosis for melanoma and its' resulting therapies, the knowledge of these nevi is of particular importance (79). Up to now, melanoma simulators particularly undergo complete surgical excision (2).

1.1.4 Factors influencing the nevus morphology

The difficulties in the classification of nevi are complicated by the fact that a number of intrinsic and extrinsic factors influence the nevus patterns (11). Moreover, there is body of evidence suggesting that nevi are not stable over lifetime. In the following, these factors and their impact on nevus morphology will be discussed more in detail, based on the results of a systematic review (1).

1.1.4.1 Intrinsic factors

1.1.4.1.1 Age

Melanocytic nevi predominantly arise during childhood and adolescence (2). It is well known that the number of nevi enlarges from childhood to midlife (until fourth or fifth decade of life) and subsequently goes down. Piliouras summarized this dynamic in the phrase “we are born and we will die without naevi” (80).
While a globular or homogeneous dermoscopic nevus pattern is prevalent in prepubertal children, adults predominantly exhibit the reticular (network) nevus pattern. Around puberty (until the second decade of life) nevi often exhibit peripheral rim of globules, which has been proven to be a sign of growth. Concerning the distribution of pattern, globular nevi in prepubertal children tend to be located on the head and neck area as well as on the upper trunk. In contrast, reticular nevi in adults are mostly found on the trunk and extremities. However, a few globular nevi (especially seen in the head and neck area and on the chest) can be discovered in individuals of all ages (13,1,81–84).

1.1.4.1.2 Skin type

According to Fitzpatrick, six (I – VI) different types of skin colour can be distinguished concerning to their estimated response to ultraviolet (UV) light (potential to burn vs. ability to tan) (85). It is said, that lighter skin types (ST) display higher UV sensitivity and therefore a higher risk of developing skin cancer (86).

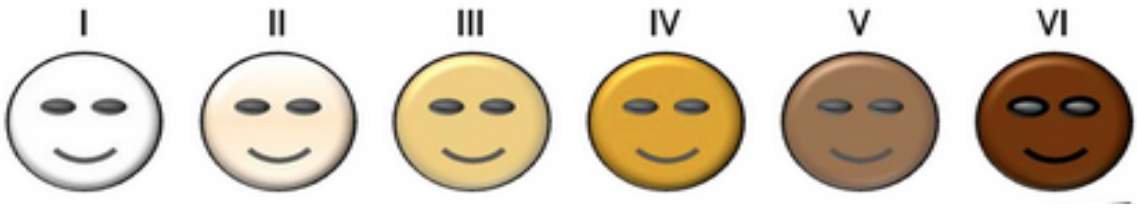

Figure 4: Fitzgerald scale for skin type-classification, modified from D’Orazio et al. 2013 (86). I: fair white skin, always burns, never tans; II: white skin, always burns, tans minimally; III: cream white skin, burns minimally, tans gradually and moderately; IV: light brown skin, burns minimally, tans well; V: brown skin, rarely burns, tans deeply; VI: dark brown/black skin, never burns, tans deeply (87)

Previous studies have investigated a different dermoscopic nevus morphology from patients with skin type I to IV (1). Whereas nevi of ST I predominantly exhibit light brown colour and central hypopigmentation, individuals having ST II to III tend

to display a light to dark brown colour with multifocal pigmentation (hypo-hyper-pigmentation). On the contrary, patients with ST IV are prone to be dark brown and centrally hyperpigmented, showing a reticular pattern (also known as black or hypermelanotic nevi) (88,89). Moreover, a study revealed, that children with darker ST significantly have a higher occurrence of small reticular nevi than their coevals with fair skin, although the globular pattern is the most frequent among children (81). On the other hand, children with a lighter skin type (FZ ST I and II) tend to significantly have more nevi than those with a darker skin type (FZ ST III and IV) (2).

1.1.4.1.3 Pregnancy

During pregnancy, melanocytic nevi show significant morphologic modifications concerning both architecture and pattern (90). Observed changes include progressive lightening, reduction of prominence and thickness of reticular pattern, increased vascularization (91) and an increase in diameter, especially on the abdomen which could be explained by the expansion of the skin (92). These modifications linearly increase with the duration of the pregnancy and represent difficulties to differentiate from melanoma (91–93).
After delivery, these transient changes disappear within 3 to 6 months and the nevi return to their former appearance. In every case of alteration, dermoscopic examination and monitoring is indicated (1,91).

1.1.4.2 Extrinsic factors

1.1.4.2.1 UV-Irradiation

As already discussed above, melanocytic nevi predominantly arise during childhood and adolescence (2). Studies have shown that the exposition to sunlight in younger ages has an impact on the evolution of melanocytic nevi (94–96). Growing up in sunny regions as well as frequent intermittent UV - expositions (e.g. during summer holidays) correlate with higher nevi counts on the sun exposed body sites (2,97).
Further studies investigated that nevi exposed to UV irradiation exhibit several reversible dermoscopic changes due to melanocytic activation (1). Beside an evolution of irregular blotches, dots or globules, both an increase in size and the development of an erythema can be observed. Additionally, darkening of pigment

as well as fading of reticular pattern are common alterations (1,98–103). It is said that these nevi return to their former dermoscopic features after discontinuation of UV exposure within 1 to 3 months (1).

1.1.5 Diagnosis and management of nevi

The diagnosis of melanocytic nevi aims at a correct classification and sub-typing as well as differentiation from melanoma (2). As an early differentiation between benign melanocytic nevus and melanoma is the most important factor regarding the prognosis, self-examination and physicians play a crucial role in the early melanoma detection.

1.1.5.1 Analytic versus comparative approach

In order to differentiate benign from malignant melanocytic lesions, various dermoscopic algorithms have been made up (e.g. ABCD criteria, 7-point checklist, Menzies' method), mainly attributed to an analytic approach (104). In 1985, Friedman et al. (105) firstly introduced a simple tool for distinguishing benign from malignant lesions with the naked eye: the "ABCD rule". As further studies have been investigated regarding the validation of these criteria, a fifth criterion concerning the macroscopic change of melanomas has been added (106). However, these criteria are also feasible for dermoscopic examination.

Table 2: ABCDE- criteria. Physical characteristics and clinical criteria of melanomas and melanocytic nevi (2,105–107)

		Melanoma	***Melanocytic nevus***
A	*asymmetry*	asymmetrical shape	symmetrical shape, round to oval
B	*borders*	border irregularity	sharp, regular borders
C	*colour*	variegated colours (black, brown, blue, red, white, grey)	uniform colour (light- to dark-brown)
D	*diameter*	> 6mm	≤ 6mm
E	*evolving*	change, enlargement, evolution	change rarely symmetrically

As dysplastic nevi exhibit various melanoma features from the ABCD criteria and therefore hardly can be differed from melanoma, the comparative approach of "the ugly duckling sign" has been formulated (108). Since a single individual shows a

predominant nevus pattern seen in more than 30% of all melanocytic nevi (109), atypical lesions deviating form this pattern should be identified (30,108,110). These “ugly ducklings” may be suspicious for melanoma (108). Thus even for non-dermatologists, the ugly duckling sign seems to be a valuable tool for melanoma detection (110).

1.1.5.2 Dermoscopy of melanocytic nevi

Dermoscopy (also dermatoscopy, epiluminescence microscopy or surface microscopy) is a hand-held illuminated magnifier, which allows visualisation of submacroscopic pigmented structures (e.g. networks, dots, streaks or veils) that are associated with histopathologic correlates. Therefore, epidermal and upper dermal structures usually invisible to the naked eye can be uncovered (36,37,111). Up to now, various dermoscopic scores and algorithms have been set up to differentiate benign melanocytic nevi from melanoma. By performing pattern analysis, benign melanocytic nevi usually exhibit an orderly general appearance and symmetrical structure with sharp borders, regular pigment network thinning out at the periphery, regular streaks, clods, blue structureless areas and brown globules under dermoscopy (2,112,113). Besides, an ABCDE rule of dermoscopy has been formulated to score the following criteria for melanoma detection: (A) *asymmetry* in shape in at least one axis and *asymmetrical* different structures within the lesion in at least one axis (B) abrupt ending of the pigment pattern at the *border*, (C) ≥ 3 different *colours*, (D) ≥ 3 *different* structural components and (E) *evolution* or change within the last three months (113,114). Further algorithms have been proposed for a differentiation of benign nevi from melanoma, based on an analysis of patterns and architectural disorder: Menzies-method (115) 7-point checklist (116) and CASH algorithm (117).

1.1.5.2.1 Digital dermoscopic monitoring

Sometimes, melanocytic nevi show atypical features, which lead to uncertain differentiation whether being benign or malignant. With the objective of not missing any malignant lesion together with avoiding unnecessary excisions, dermoscopic follow-up is a valuable tool to identify any history of atypical change, which is highly suggestive for melanoma (118). Therefore, short-term follow-up with an interval of 3 months from baseline tends to be sufficient for single atypical lesions in order to detect early melanoma (119). Patients exhibiting several atypical nevi

(i.e. atypical mole syndrome, familial atypical mole and multiple melanoma syndrome) may profit from long-term digital dermoscopic monitoring of several lesions (120).

1.1.6 Aims of this review

The enormous variety of different classification modalities of melanocytic nevi may lead to disorientation in some cases. Since the latest systematic review on dermoscopic classifications systems has been conducted in 2009 (1), numerous new studies in this field have been published. The aim of this systematic review is to present the state of the since then newly acquired knowledge regarding dermoscopic nevus morphology and the factors influencing nevus features.

2 Materials und methods

This thesis has been written at the Medical University of Graz at the Departement of Dermatology and Venerology. Access to the databases was given by the licences of the Medical University of Graz.

2.1 Data Sources and search strategy

A systematic literature search of MEDLINE (via PubMed) and Journals@Ovid was performed on the 13th of June in 2016 and the following keywords were used: *dermoscopy, dermatoscopy, epiluminescence microscopy, surface microscopy, digital dermoscopy, digital dermatoscopy, digital epiluminescence microscopy, digital surface microscopy, nevus, nevi, naevus, naevi, melanocytic skin lesion, pigmented skin lesion, color, colour, pattern, pigment distribution, face, facial, acral, nail, mucosa, mucosal, trunk, scalp, age, elderly, old, skin type, melanoma history, melanoma related, UV, UVR, UV irradiation, UV radiation, UV rays, ultraviolet, pregnancy, genes, genetic, BRAF* and *recurrent.*

The keywords were connected with the builder (“AND” and “OR”) as the following schedule shows (**Table 3**).

Table 3: Schematic composition of the search terms. The terms in column 1, 3 and 5 are connected by “OR”, respectively. The three columns (1, 3 and 5) are each connected to the other by “AND”.

OR		OR		OR
“dermoscopy” “dermatoscopy “digital epiluminescence microscopy” “digital surface microscopy”	AND	“nevus” “nevi” “naevus” “naevi” “melanocytic skin lesion” “pigmented skin lesion”	AND	“color”,“colour”, “pattern”, “pigment distribution”, “face”, “facial”, “acral”, “nail”, “mucosa”, “mucosal”, “trunk”, “scalp”, “age”, “elderly”, “old”, “skintype”, “melanoma history”, “melanoma related”, “UV”, “UVR”, “UV irradiation”, “UV radiation”, “UV rays”, “ultraviolet”, “pregnancy”, “genes”, “genetic”, “BRAF”, “recurrent”

On MEDLINE, a total number of 890 results were recorded, whereas the Journals@Ovid search showed 2138 results. Additional limitations and inclusion criteria on Journals@Ovid database were selected and search restricted to “articles with abstracts”, “original articles or reports or review articles” and “clinical medicine”. Subsequently, the total of 2206 search results (Medline: n=890; Journals@Ovid: n=1316) have been accumulated. The results were sorted alphabetically by a collective chart using Microsoft® Excel® for mac version 2011. Furthermore, 407 duplicates were manually removed by going through every single title in the Excel spreadsheet. Finally, a total number of 1799 search results were registered. Because of the enormous amount of data, articles were manually categorized into 14 subgroups for further title analysis (**Table 4**). The subgrouping of results aimed to sort out irrelevant off-topic articles.

Table 4: Subtypes of the extracted data.

Title-	***Subgroup***	***Number of results***
1	Nevus	398
2	Melanoma	306
3	Lesion	258
4	Further diseases	240
5	Diagnostic in general	216
6	Dermatology in general	90
7	Dermoscopy	69
8	Basalcellcarcinoma	59
9	Treatment	47
10	Melanonychia	41
11	Telediagnostic	26
12	Syndromes	22
13	Skin cancer	21
14	Skin type	6
	In total	***1799***

All titles regarding nevi, melanomas and melanocytic lesions are sub-grouped in group 1, 2 and 3, respectively. 4 includes results concerning different dermatological pathologies. 5, 6 and 7 include titles about diagnostic tools, dermatology and dermoscopy in general, respectively. The results about basalcellcarcinoma are summarised in number 8. 9 concludes articles about various dermatological treatment modalities. 10 includes results about nail pigmentation. 11 sums up current methods in dermatological telemedicine. Various syndromes and nonmelanocytic skin cancer are summarised in 12 and 13, respectively. 14 concludes results concerning type of skin.

2.2 Data extraction

For the purpose of finding the most relevant articles concerning nevus morphology and factors that influence nevus morphology, the subgroups including “nevus”, “lesion”, “dermoscopy”, “melanonychia” and “skin type” have further been examined for title analysis. Therefore, the data of each subgroup has been copied into new Excel worksheets.

Working through each worksheet of the five subgroups, a total of 772 titles has been reviewed and categorized into either relevant or irrelevant. Overall 592 results were identified to be relevant and thus capable to analyse the abstracts. Subsequently, the relevant titles have been copied into new Excel documents for further analysis of the abstracts which revealed 318 relevant abstracts. During reading the abstracts (592), the individual year of publication has been added to each record in the Excel spreadsheets and the data according to their up-to-datedness was listed. Because the latest systematic review regarding the influencers of nevus morphology has been conducted in 2009 by Zalaudek et al. (1), the lower limit for publication year was set for the year 2009 which revealed 192 relevant abstracts for further analysis of the full text.

After exclusion of two French full-text articles and 77 irrelevant articles, 109 manuscripts remained. During further research until 1st of June in 2017, 13 additional publications have been found to be relevant. One additional study older than 2009 has been added, due to providing relevant results. Expertise of the 123 articles was given by Priv.-Doz.in Dr.in med.univ. Iris Zalaudek. The extraction flow is shown in **Table 5.** Quantitative data extraction is shown in **Figure 5**.

Table 5: Data subgroups and extraction.

Subgroup	*Titles for analysis*	*Relevant titles*	*Relevant abstracts*	*Relevant abstracts (2009 - now)*	*Relevant publication*
Nevus	398	305	181	115	68
Lesion	258	216	97	59	32
Dermo-scopy	69	32	12	8	1
Melano-nychia	41	33	24	7	5
Skin type	6	6	4	3	3
In total	***772***	***592***	***318***	***192***	***109***

2.3 Flow-chart

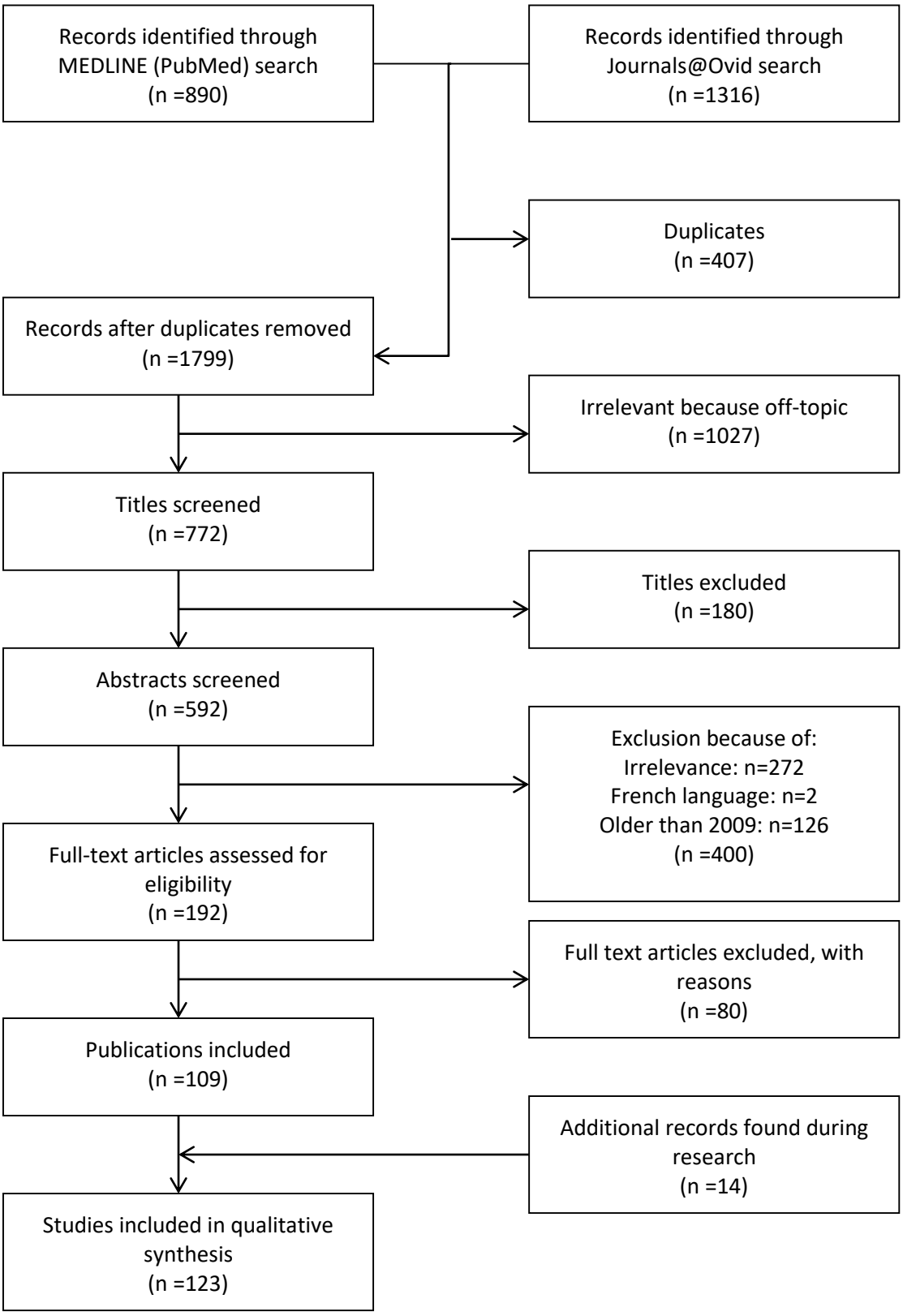

Figure 5: Flow chart of data extraction.

2.4 Evaluation of level of evidence

In the following step, the level of evidence for screening recommendations was rated for every manuscript according to the criteria arranged by Robinson et al. (**Table 6**) (121). Evidence was rated by reading of the abstract or full text analysis, whereas the manuscripts were evaluated regarding the type of publication (i.e. systematic review, meta-analysis, randomized controlled trial, observational study, clinical trial, cohort study, case-control study, guideline, usual practice, expert opinion or case series) and existent limitations (e.g. limitations of any study or review).

Table 6: Levels of evidence. Table adapted from Robinson et al. (121).

Grade of recommendation	***Quality of Evidence Screening (A, B, C)***
1	***A***
Strong recommendation; high-quality evidence	Systematic review Meta-analysis Randomized controlled trial with consistent findings All-or-none observational study
2A	***B***
Weak recommendation; limited-quality evidence	Systematic review/meta-analysis of lower-quality clinical trials or studies with inconsistent findings and limitations Lower quality clinical trial Cohort study Case-control study
2B	***C***
Weak recommendation; Low-quality evidence	Consensus guidelines Usual practice Expert opinion Case series

3 Results

3.1 Search results

Overall, 123 publications were reviewed. Of those articles, one randomized controlled trial was identified, representing a quality of evidence A (122). One meta-analysis (n=1) and one systematic review (n=1) were additionally found, graded as weak recommendations (2A) due to inconsistent findings and included studies of lower evidence and limitations (123,124). The sample included 54 prospective and 15 retrospective studies from single institutions and 3 prospective and 3 retrospective multi-institutional studies, each graded as level B supporting screening recommendation. Case reports (n=11), as well as expert reviews (n=33) and one expert opinion (n=1) were also included, representing level C for screening recommendation. The quality, which supports screening recommendation was level B (n=77; 63% of publications) (**Figure 6**); hence, current recommendations are rated as weak (2A).

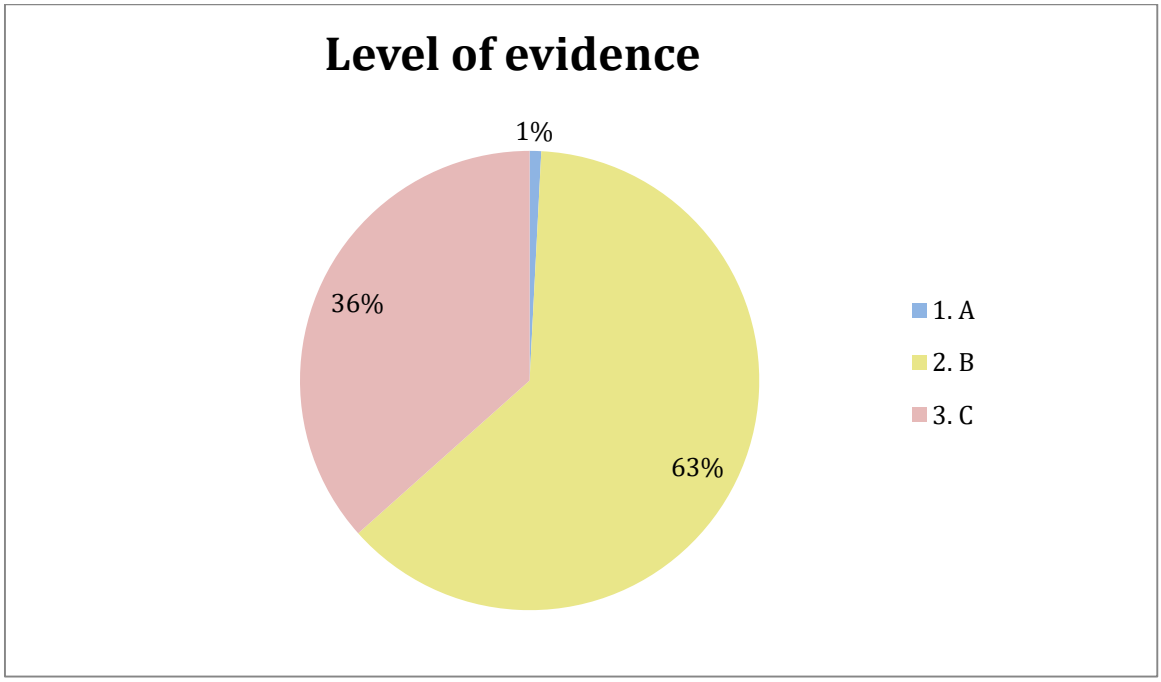

Figure 6: Distribution of level of evidence supporting screening recommendations. 1. Represents level A, 1% of the publications (n=1). 2. Represents level B, 63% of the publications (n=76). 3. Represents level C, 36% of the publications (n=45).

For the dermoscopic criteria “colour, pattern, pigment distribution, vascular structures” particularly expert reviews have been identified (level of evidence C) (**Table 7**). In contrast, evidence of level B and prospective/retrospective single- and multi-institutional studies were available for each dermoscopic criterion being influenced by intrinsic (age, body site, skin type, genetic alterations, history of melanoma) and extrinsic (UV exposure, partial biopsy) factors, shown in **Table 8**. One randomized controlled trial (122), which shows a quality of evidence A has been identified for the dermoscopic criteria influenced by age.

Table 7: Evidence supporting screening recommendations for the dermoscopic criteria: colour, pattern, pigment distribution and vascular structures.

Dermoscopic criterion	***Quality of evidence: B***	***Quality of evidence: C***
Colour	Prospective single-centre studies (125,126)	Expert reviews (16,104,127–135)
Pattern	Prospective cohort studies (136,137), prospective single-centre (126,138) and multi-institutional studies (139)	Expert reviews (11,16,104,127–134,140–144)
Pigment distribution	Prospective single-centre studies (126)	Expert reviews (128,129)
Vascular structures	Retrospective single-centre study (145)	Expert reviews (128,134)

Table 8: Evidence supporting screening recommendations for the factors influencing dermoscopic nevus morphology.

Factor	***Quality of evidence: A***	***Quality of evidence: B***
Age	Prospective randomised controlled trial (122)	Cohort (146,136,147,148), prospective single centre (80,149–156), prospective multi-institutional (157) and retrospective single centre studies (158)
Site specific		Cohort (146,159–161,137), prospective single centre (149,150,153,155,162–178) and multi-institutional (157), retrospective single centre (158,179–184) and multi-institutional studies (185,186)
Skin type		Cohort (146,147,160,137), prospective single centre (152,176,187) and multi-institutional studies (188)
Genetic alterations		Twin cohort (189), prospective single centre (190–197), and multi-institutional (198), case-control (199,200) and retrospective single centre studies (201,202)
UV radiation		Cohort (203) and prospective single centres studies (149,204–207), systematic review (124)
Partial biopsy		Retrospective multi-institutional study (208)

3.2 Dermoscopic criteria

3.2.1 Colour

The most common colours seen in melanocytic nevi are black, light to dark brown, grey, blue and pink. Each colour under dermoscopy depends on the location of melanin within the layers of the skin (**Figure 7**). A nevus exhibits either one or two of them (16,22,1,104,127,125,126,128–130,209,131–135). In atypical nevi, up to four colours in a single lesion are frequent findings (126).

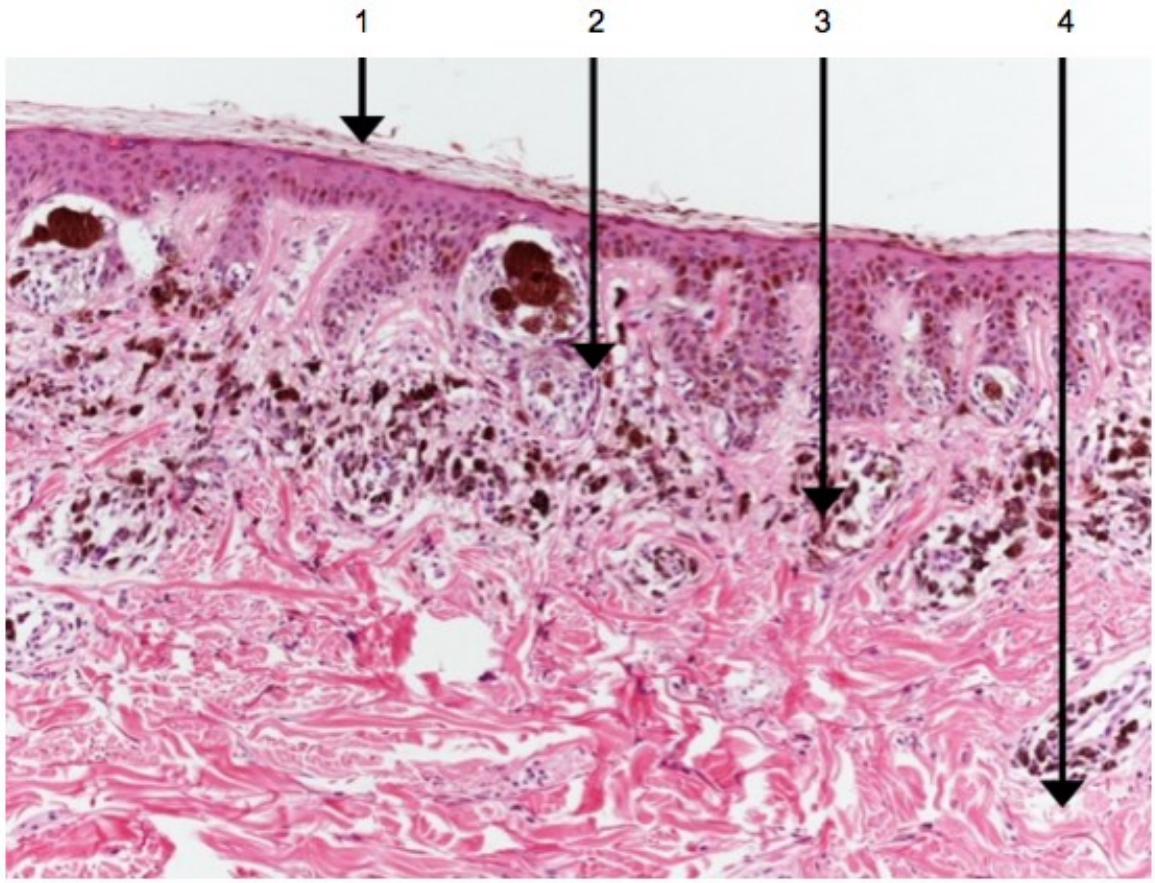

Figure 7: The location of the melanin in different levels of the skin reflects different colours under dermoscopy: black (1), brown (2), grey (3) and blue (4).

3.2.2 Pattern

Melanocytic nevi mostly exhibit the following patterns with a uniform and regular distribution: globular/cobblestone, reticular, starburst and homogeneous/structureless blue (**Figure 8**) (16,1,104,136,137,127,126,128–130,209,131–134,140,138,141,210,142–144). Also homogeneous/structureless brown, pesudonetwork and mixed patterns have been detected among benign

nevi (11,136,127,126,129,209,131–133,139). The latter can further be distinguished into the four most common mixed patterns among melanocytic nevi: central structureless or reticular and peripheral globular (MP), central structureless or globular and peripheral reticular (MC) (**Figure 9**). Each dermoscopic pattern underlies a distinct histopathologic correlate (11).

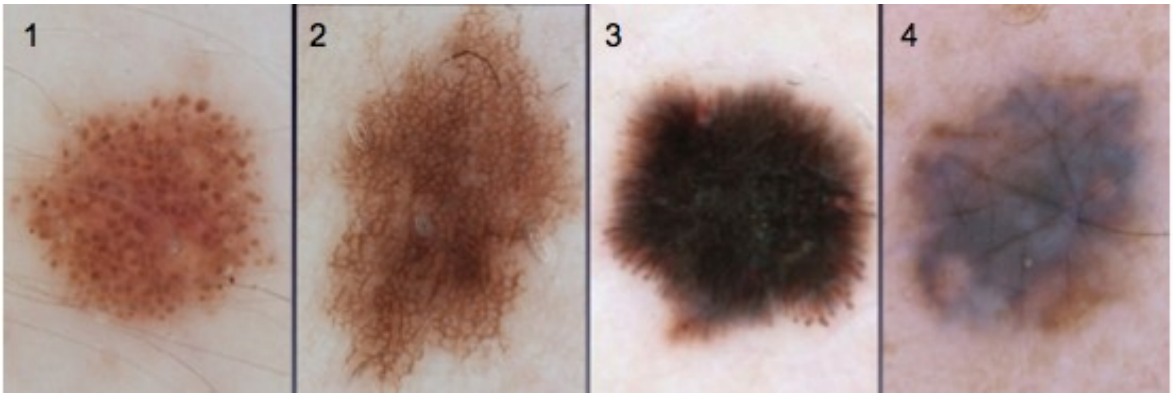

Figure 8: The most common dermoscopic nevus patterns: globular (1), reticular (2), starburst (3) and structureless (4).

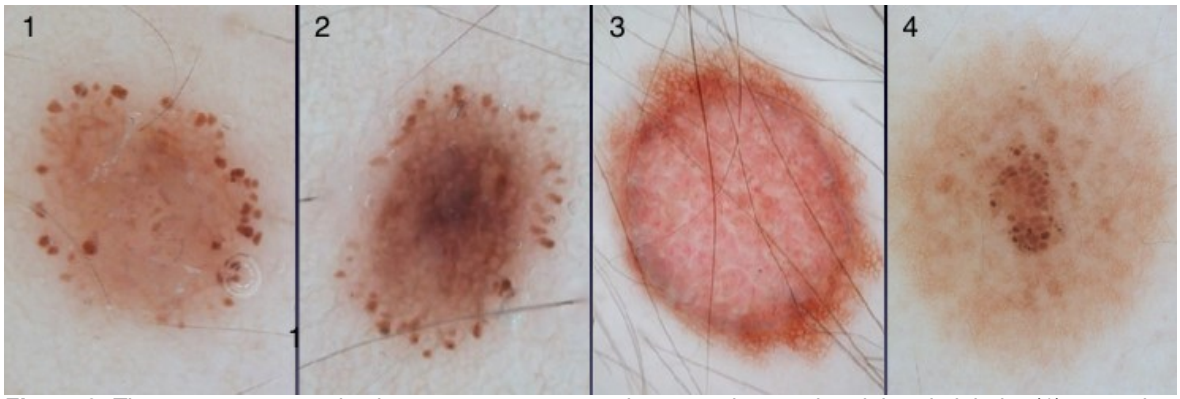

Figure 9: The most common mixed nevus patterns: central structureless and peripheral globular (1), central reticular and peripheral globular (2), central structureless and peripheral reticular (3), central globular and peripheral reticular (4).

3.2.3 Pigment distribution

Pigmentation is either uniformly or non-uniformly distributed within melanocytic nevi. Common non-uniform distribution patterns are namely: central hyper- or hypopigmentation, peripheral hyper- or hypopigmentation as well as multifocal variants of hyper- or hypopigmentation (**Figure 10**) (1,126,128,129)

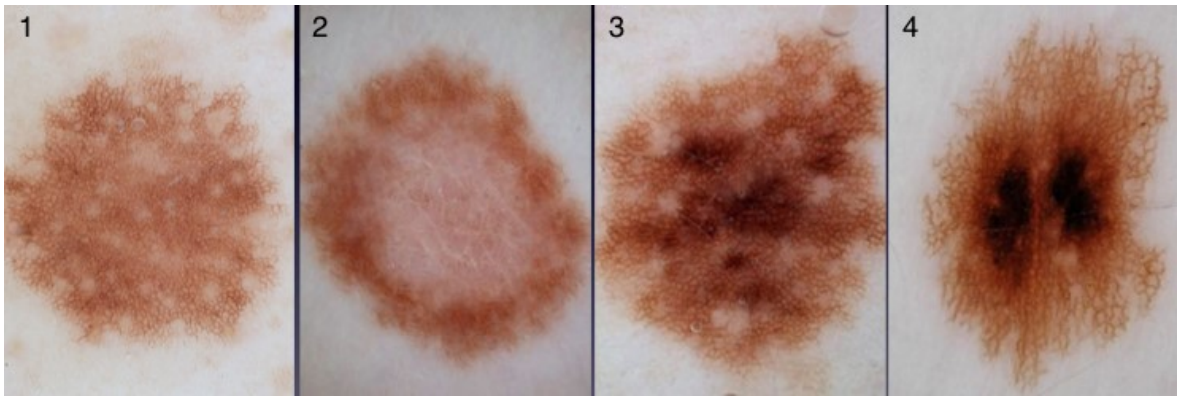

Figure 10: The main types of pigment distribution: uniform pigmentation (1), central hypopigmentation (2), multifocal pigmentation (3) and central hyperpigmentation (4).

3.2.4 Vascular structures

The occurrence of vessels is an important dermoscopic criterion for the characterisation of non-pigmented (or slightly pigmented) melanocytic lesions. The most common benign vascular features found among nevi are: comma-shaped vessels (**Figure 11**) (congenital/dermal nevi) and dotted vessels (**Figure 11**) (Spitz nevi, Clark nevi in fair skin types) (128,134,145).

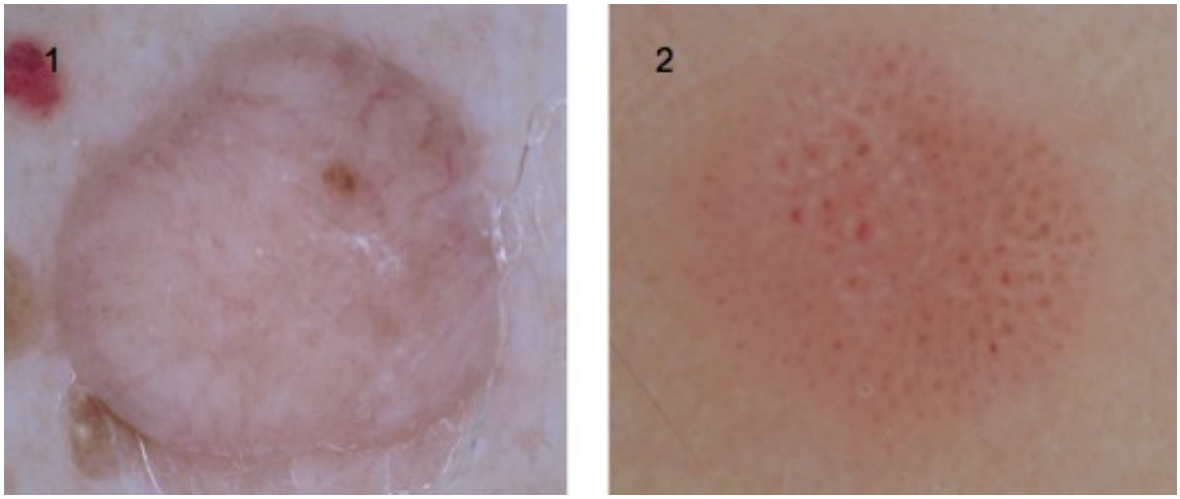

Figure 11: Dermoscopic vascular structures: (1) comma-shaped vessels of a hypopigmented dermal nevus and (2) dotted vessels of a Spitz nevus.

3.3 Patient-related factors influencing nevus morphology

3.3.1 Intrinsic factors

3.3.1.1 Age

The most prevalent nevus pattern among childhood, adolescence, adulthood and the elderly are the globular pattern, a mixed pattern with peripheral globules and central reticular area, the reticular pattern and a structureless or residual globular pattern, respectively (11,16,80,149,150,154,157,201,129,211). As a sign of nevus growth, a mixed pattern with peripheral globules principally occurs among children and adolescents until the third decade of life and rapidly disappears thereafter, finally developing a reticular pattern (157,139,211,212).

3.3.1.2 Body-site

While nevi exhibiting a globular pattern (i.e. large nodular/raised/dermal nevi) are predominantly found on individuals head and neck area as well as the trunk (especially upper parts, shoulders) (11,16,149,150,157,137,175,211), reticular nevi (i.e. small flat/compound/junctional nevi) prevail on the extremities but are also disseminated over the trunk (11,16,137,175,211). Nevi exhibiting a mixed pattern with central globules and peripheral network (MC) or peripheral globules and central network (MP) tend to appear on the trunk (150,157). Unspecific (e.g. homogeneous) pattern is mostly found in nevi occurring on the extremities (150,175).

3.3.1.2.1 Special body-sites

The anatomical structure of the skin on special body-sites such as the acres, mucosal areas, genital area, the scalp and milk line (breast) shows peculiar features. Thus, melanocytic nevi exhibit decisive clinical and dermoscopic features in these areas. Acral nevi often exhibit the parallel furrow, latticelike, fibrillar pattern, homogeneous, globular or reticular (i.e. crista reticulated) (16,153,158,163,164,174,178,184,128,213,214). The parallel furrow pattern can be further distinguished into a single line, a single dotted line, a double line and a double dotted line variant (158,174,213,214). Among younger individuals and mostly in congenital acral nevi, the *peas-in-a-pod* pattern (combination of parallel furrow pattern and cristad dotted pattern) is quite common (158,174,180,181,213).

Nail matrix nevi are characterised by regularly arranged, homogeneously brownish coloured longitudinal bands (≤3 mm width) on a brownish background (128,214–219). Facial nevi tend to exhibit a pseudonetwork pattern (149) and interfollicular reticular lines (177) due to the peculiar anatomical structure of the face. Genital nevi often exhibit a globular or homogeneous dermoscopic pattern (16,166–168,179,182,186,141,220,221). Nevi on the milk line or on flexural areas such as inguinal, popliteal, axillar or antecubal area are weakly described up to now. Only a few case reports have been published (141). Among nevi of the breast, irregular globules and dots as well as an atypical pigment network are common findings under dermoscopy (159). The dermoscopic features mostly seen in nevi of the scalp are structureless, globular/cobblestone as well as comma/dotted vessels and the reticular pattern (169,170,222). Further common features are perifollicular pigment distribution or hypopigmentation and central hypopigmentation (eclipse nevi) (16,169–171,222).

3.3.1.3 Skin-type

Different skin-types are related to different predominant nevus morphologies shown in **Table 9**.

Table 9: Predominant nevus morphology among different skin-types (11,137,146,187,188).

Skin type	*Colour*	*Pattern*	*Pigment distribution*	*Nevus size*	*Quality of evidence: B*
I	Light brown to orange	Globular, homogeneous, mixed	Central hypopigmentation	Large	Expert review (11), cohort (137) and prospective single-centre studis (187)
II	Light brown to orange	Globular homogeneous, mixed	Uniform or multifocal pigmentation	Large	Expert review (11), cohort (137,146) and prospective single-centre studies (187)
III	Dark brown to black	Reticular	Uniform or multifocal pigmentation	Small	Expert review (11) and cohort studies (137,146)
IV	Dark brown to black	Reticular	Central hyperpigmentation	Small	Expert review (11) and cohort studies (137,146)
V	Dark brown	Reticular	Central hyperpigmentation	Small	Cohort (146), prospective single-centre (187) and multi-centre studies (188)
VI	Black, blue, grey	Structureless	Central hyperpigmentation	Small	Prospective single-centre (187) and multi-centre studies (188)

3.3.1.4 Genetic alterations

Oncogenic BRAF is common in Clark (i.e. dysplastic nevi), small congenital and acquired nevi (223), while mutations in NRAS, HRAS and GNAQ genes are mainly found in intermediate to large congenital, Spitz and blue nevi, respectively (11,16,143,144,223–225). In addition to HRAS mutations, Spitz nevi may also carry BAP1 alterations as well as kinase fusions as a result of ROS1, NTRK1, ALK, BRAF and RET polymorphisms (195,198,223,224,226). Melanocytic nevi, which harbour mutated $BRAF^{V600E}$ more frequently show a globular or a mixed dermoscopic pattern than a reticular pattern (191,196,201).

Atypical nevi are associated with red hair colour (RHC) variants in the melanocortin 1 receptor (MC1R) (192,200,223). While nevi from carriers of two RHC polymorphisms commonly show homogeneous structureless areas, carriers without RHC variants exhibit dark-brown coloured nevi mostly showing streaks and a pigment network (192,223). A further association of RHC variant carriers and hypopigmented atypical nevi has been made (227). The appearance of vessels has been correlated to CDKN2A G101W mutation carriers (200).

Further candidate loci have been identified to be linked with nevus count and morphology. IRF4 polymorphism, especially the rs12203952 T allele correlate with an increased count of flat (i.e. reticular) nevi as well as a decreased (i.e. globular) count of raised nevi. PARP1 (rs3219090), CDK6 (rs2079147) and PLA2G6 (rs738322) polymorphisms come along with a decreased nevus count (197). Nevi with SNPs (single nucleotide polymorphisms) in IRF4 and TERT mostly express a globular pattern. In contrast, SNPs in CDKN1B, MTAP and PARP1 show reticular patterned nevi (197).

A rare polymorphism in MITF E318K has been reported to be linked with a high nevus count (193,199) and reticular patterned nevi (193).

3.3.1.5 Melanoma

It has been found, that individuals at high melanoma risk (meaning personal or first degree history of melanoma) exhibit higher nevus counts than individuals at low melanoma risk (150,200). Patients with personal history of melanoma often show a multicomponent/complex predominant nevus pattern (200). Additionally, more atypical features such as atypical network and irregular pigmentation have been

found (200). Patients with a personal history of melanoma tend to have a higher count of changeable melanocytic nevi, which are defined to be nevi changing in size (≥ 20% increase/decrease) or newly appearing nevi measuring ≥ 5mm (161).

3.3.1.6 Pregnancy

Nevi in pregnant women often undergo an increase in size, which is significantly bodysite specific on the abdomen and breasts (228,229). Frequent dermoscopic changes include the reticular pattern becoming clearer and more prominent and the globular pattern showing an increased number of darker brown globules in the periphery (228,230). The occurrence of nevi exhibiting a mixed pattern (central network with a peripheral rim of globules) is a common observation (157). Further observations conclude the presence of vessels under dermoscopy (228–230).

3.3.2 Extrinsic factors

3.3.2.1 UV-irradiation

Furthermore, UV radiation frequently involves clinical and dermoscopic changes in melanocytic nevi. Common clinical changes include an increase in diameter (205,206), gain in pigmentation, the appearance of an erythema and surface crusting, mostly occurring at the periphery of the lesion (207). Frequent dermoscopic changes observed are an increase in diameter and number of globules and dots (203–207), the appearance of a prominent pigment network as well as an overall darkening of the lesion and the development of branched streaks (204–206). Further changes such as the appearance of diffuse erythema, blurring of pigment network, increase in regression structures, presence of diffuse pigmentation, an increase in regression structures and the appearance of dotted vessels within the lesion and the surrounding skin have been discovered under dermoscopy (203,205,207).

3.3.2.2 Partial biopsy

Recurrent nevi commonly exhibit radial lines, symmetric and heterogeneous pigmentation pattern and a centrifugal growth pattern under dermoscopy (208,209,231,232). The most evident clinical and dermoscopic criterion is that the growth pattern does not exceed the scar’s edges (208,209,231,232). The scar is visible as a hypopigmented structureless area under dermoscopy (208).

4 Discussion

The incidence of melanoma is steadily rising over the last decades. As prognosis is influenced by tumour thickness, early diagnosis and prompt surgical removal of melanoma represents the main stay in treatment (123). A high nevus count and the presence of clinically atypical nevi are strong risk factors for melanoma. Thus, regular dermatologic consultations and proper differentiation between benign and malignant lesions should be made. Dermoscopy is a reliable non invasive diagnostic tool providing a deep look into submacroscopic structures of melanocytic lesions *in vivo* (104). Dermoscopic imaging offers features for the classification of melanocytic nevi. This systematic review provides and summarizes the results from 2009 up to now concerning common dermoscopic features of melanocytic nevi as well as the intrinsic and extrinsic factors influencing nevus morphology.

Firstly, the rule of colours under dermoscopy is crucial for differentiating benign melanocytic lesions from malignant (104). Each dermoscopic colour reflects pigmented, melanin-loaded melanocytes in different layers of the skin (**Figure 7**) (1,104). Black colour results from pigmentation in the corneal layer and upper epidermis. Brown is due to pigmentation in the epidermis while grey reflects pigmented melanocytes in the papillary (upper) dermis. Because of the spectrum of visibility of light, pigmentation located in deeper layers of the dermis (i.e. reticular dermis) is presented in a blue colour. Red colour represents an increased vascularisation. Regression or scarring areas often reflect white colours under dermoscopy. The latter two features (i.e. red and white colour) are frequently found in melanomas and are seldom exhibited in benign melanocytic nevi (1,104). Because of the fact that regression may occur in melanomas and nevi, the appearance of blue, grey and white combinations should be treated with caution (125). In particular when >10 % of the lesions' surface show any regression feature. Still, the analysis of colour alone is still not sufficient to rule out melanoma but the principle "the more colours, the more suspect" may be useful for diagnosing atypical lesions (1,104).

Despite colours, the dermoscopic nevus classification includes the identification of an overall nevus pattern. The most common identified benign patterns are namely the globular, reticular, starburst and homogeneous/structureless pattern (**Figure 8**), whereas each underlies a distinct histopathologic correlate (1,104,127,142).

The globular pattern illustrates dermal nests of melanocytes while the reticular pattern exhibits melanocytic nests at the peaks of the rete ridges and an increased number of melanocytes in the basal layer (11).
Regarding these results, the globular pattern summarises small congenital, compound and dermal nevi (104). Lentiginous and junctional as well as congenital nevi on the lower extremities predominantly exhibit a reticular pattern (104). Like reticular patterned nevi, homogenous brown nevi show similar histopathologic correlates. The starburst pattern is commonly exhibited in Spitz and Reed nevi, while a homogeneous blue pattern without any other dermoscopic feature characterises the dermoscopic appearance of blue nevi (104,127). In addition, the pseudonetwork pattern is especially found in facial intradermal nevi of the Miescher type (127). To differentiate common nevi from atypical lesions, the phrase “the more colours, the more structures, the more suspect” can be used (1,104).
Among nonpigmented or hypopigmented melanocytic nevi, the appearance of vascular structures may be the only visible dermoscopic criterion. Thus, certain nevi tend to exhibit certain vessels, as for example dermal and Spitz nevi particularly show comma-shaped and dotted vessels under dermoscopy, respectively (128). The study by Argenziano et al. (145) revealed, that dotted vessels (**Figure 11**) are generally predictive for melanocytic lesions (90%, $p<0.001$) and predominantly found in Spitz nevi with a prevalence of 77,8% of the lesions but also in Clark nevi (25,7%) and melanoma (22,7%). Comma-shaped vessels (**Figure 11**) are significantly associated with congenital/dermal nevi with a prevalence of 66,3% (145). In fair skinned individuals, common acquired nevi may appear in red colouration, which is due to a low amount of melanin. Thus the vascular structures get visible to the naked eye and may exhibit loosely arranged dotted vessels, associated with comma vessels, dermoscopically (128).
Dermoscopy also revealed the predominant dermoscopic patterns of Spitz nevi, namely: the starburst, the globular, the homogeneous, the reticular (114) and an atypical multicomponent pattern (115). Spitz nevi still represent controversial clinical, dermoscopic and histopathologic features. Although they are considered to illustrate benign melanocytic lesions, they are the most common mimickers of melanoma and thus need to undergo proper diagnostic procedures (128,140). While observers are still not concordant in their histopathological findings because

of the enormous morphological variety including atypical features, an agreement on dermoscopic results has been found. Hence, the most prevailing patterns of Spitz nevi are the starburst and an atypical multicomponent pattern (melanoma-like) (34,0% and 23,4%) (140). Similar results have been found in a study by De Giorgi (138) with 20% and 27%, respectively. An age dependent predominant pattern has been found in addition. While children under 12 years of age represent a reticular dermoscopic pattern, older patients commonly show a homogeneous pattern in these lesions (140). This matches the previous findings of De Giorgi et al. (138), who examined Reed nevi in an early evolutional stage and revealed a predominant reticular pattern in these lesions (40%). These results deviate from the age-dependent nevus patterns of common congenital and acquired nevi, which let us presume a distinct natural evolution of Spitz nevi (156,128,130,140,138). In addition, these results deviate from former investigators, who revealed the development of Spitz nevi firstly showing a globular pattern, evolving into a starburst and eventually ending up in a homogeneous or reticular pattern (130,143). However, the fact that the risk of a spitzoid looking lesion increases with age and particularly after puberty explains the management rule to excise all spitzoid looking lesions, especially after puberty (128,140).

In contrary to the dynamic life cycle of Spitz/Reed nevi, blue nevi are commonly accepted to show stable features throughout a lifetime. Dermoscopic examination almost always reveals a homogeneous pattern showing one ore two colours (blue, blue-grey, blue-brown, blue-black), which tend to be a reliable feature of blue nevi (16,135,141,142). In general, they do not need any further monitoring, in exception of rapidly growing cellular blue nevi. These lesions may show signs of atypia and thus an excision has to be performed to rule out melanoma (16). Blue nevi may also occur in combination with other nevus subtypes, most commonly with congenital nevi. Therefore, dermoscopic examination often shows a homogeneous blue pattern mixed with either globular or reticular features (16). Any change in structure or size in combination with dermoscopic patterns, which is highly suggestive for nodular melanoma, melanoma metastasis or pigmented basal cell carcinoma, should be regarded as suspicious and thus undergo surgical excision (104). Especially multichromatic pigmented blue lesions combined with other local dermoscopic criteria suspicious for melanoma (i.e. peripheral streaks, vessels, blue-white veil) should be excised (142).

In case of uncertainty of grading a melanocytic lesion whether to be of benign or malignant behaviour, digital-dermoscopic follow-up is widely useful to monitor potential changes in these lesions. A meta-analysis conducted on digital follow-up studies provides evidence, that dermoscopic monitoring of melanocytic lesions results in early melanoma detection with low excisional rates. The main out-come suggests, that short term monitoring is useful for focussing on a single lesion, while long term follow-up particularly raises surveillance in patients of high melanoma risk (i.e. high nevus counts, atypical mole syndrome) (123).

Table 10 Common dermoscopic features of melanocytic nevi (16,127–131,134,135,142,143,145,233)

Nevus type	***Dermal***	***Compound***	***Junctional***	***Blue***	***Spitz/ Reed***	***Congenital***	***Atypical***
Dermoscopic features							
Colour	Skin-coloured or brown	Light to dark brown	Light to dark brown	Steel-blue; combined type: blue-brown, blue-grey, blue-black, blue-white	Pink to brown, blue, black	Light to dark brown, black	Any colour of common nevi
Pattern	Globular, Cobblestone; None or homogeneous brown Miescher: pseudonetwork	Globular, cobblestone, reticulo-globular, uniformly distributed	Reticular, uniformly distributed	Homogeneous without pigment pattern	Starburst, globular, homogeneous	Globular, cobblestone (head, neck), Reticular (extremities), homogeneous brown	Reticular, reticuloglobular
Pigment distribution	Uniform	Uniform	Central hyperpigmentation	Uniform	Uniform	Uniform, irregular	Variable: Peripheral hypo-/hyperpigmentation Central hypo-/hyperpigmentation Patchy hypo-/hyperpigmentation
Vascular features	Comma shaped vessels, dotted vessels	none	none	none	Dotted vessels	Comma-shaped vessels	none

4.1 Age

Results are concordant concerning age-dependent nevus count, which increases from puberty until midlife and decreases thereafter (11,16,80,146,136,147,152,154,157,211). In contrary to the predominance of globular nevi in children, most of the nevi developing in adulthood show a reticular pattern (16,136,211).

Stinco et al. (154) investigated the dermoscopic patterns of congenital and early acquired (within the first 2 years of life) melanocytic nevi. They found the globular pattern to be predominant in both types of nevi (51,3% and 57,9%) which further supports the idea that both types, truly congenital and tardive or early acquired melanocytic nevi may be regarded as one category of nevi (154), which can be summarised using the dermoscopic criterion as “globular” nevi.

Another finding is that nevi exhibiting a reticular dermoscopic pattern tend to involute due to regression or apoptosis (211,234,235), while nevi showing a globular or structureless pattern remain until an advanced age, eventually displaying intradermal nevi of the Miescher or Unna type in adults (80,211). A recent study examining the age-dependent appearance of facial nevi suggests furthermore, that also facial nevi undergo time-related changes (155). According to this study findings, facial nevi in younger individuals appear flat and pigmented, while in older individuals they appear raised with a globular or hypopigmented aspect (155).

This age-dependent predominance of globular and reticular nevus pattern has led to the hypothesis of two distinct pathways of nevogenesis (157,211). The early onset of globular nevi is said to be congenitally caused, while the later occurrence of reticular nevi leads to the hypothesis of being determined by exogenous influences like UV radiation (157,211). The former are further hypothesized to derive from dermally located melanoblasts (i.e. immature melanocytes) and remain throughout life persisting as intradermal nevi of the elderly (80,211). The latter are said to come from epidermal melanocytes (i.e. mature melanocytes) that grow in response to external influences such as UV irradiation (211).

Nevi exhibiting a peripheral rim of brown globules (i.e. MP pattern) can be frequently seen in younger individuals. It is a sign of benign nevus growth and provides symmetrical enlargement (**Figure 12**) (139,212). On the contrary, this

feature should be treated with caution in patients older than 50 (150,157,211). While other melanoma-specific criteria can be absent, the occurrence of peripheral globules can lead to the diagnosis of an otherwise delusive melanoma. Therefore, Zalaudek et al. (157) recommended dermoscopic monitoring of the symmetry of enlargement of nevi exhibiting MP pattern found in individuals less than 50, while excision in older individuals (150,157). It is hypothesized, that MP nevi develop into reticular or MC patterns later on, as they exhibit a similar anatomical distribution (157).

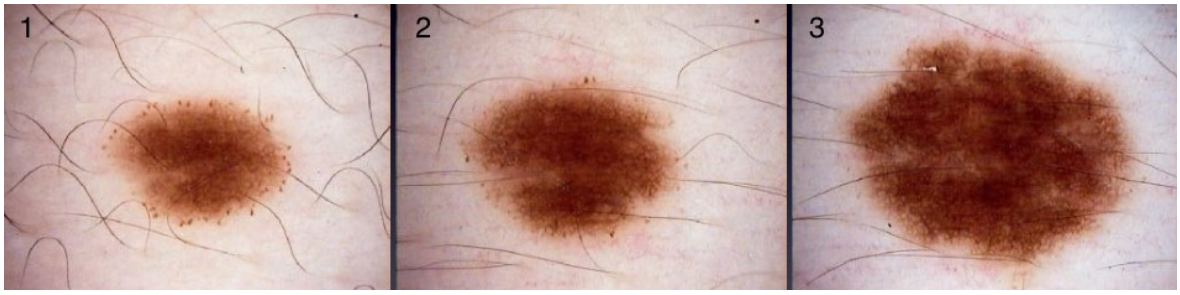

Figure 12: Symmetrically enlarging melanocytic nevus. 1. Central network with a peripheral rim of globules. 2. Symmetrical enlargement of the network with peripheral globules. 3. Entirely enlarged melanocytic nevus showing a reticular pattern.

A study about dermoscopic nevus features in children identified changes in the dermoscopic patterns at 1-year-follow-up. The changes where observed in 45 of the 836 persistent nevi in 19,4% of the children, basically exhibiting a reticular or mixed pattern located on the upper limbs, neck or trunk (149). In concordance with this finding, a further study following up dermoscopic nevus patterns for 7 years found changes in the morphology of 18% of the monitored nevi, especially during early childhood (3-6 years) (151). The changes observed were mainly from a globular to a mixed pattern (globular-reticular), from a mixed pattern to a reticular pattern and from a globular to a reticular pattern, with decreasing incidence respectively (35, 24 and 14 of overall 128 changing nevi) (151). Scope et al. (236) suggested a possible explanation of this finding shown in **Figure 13**. This scheme may explain the predominance of globular nevi during childhood.

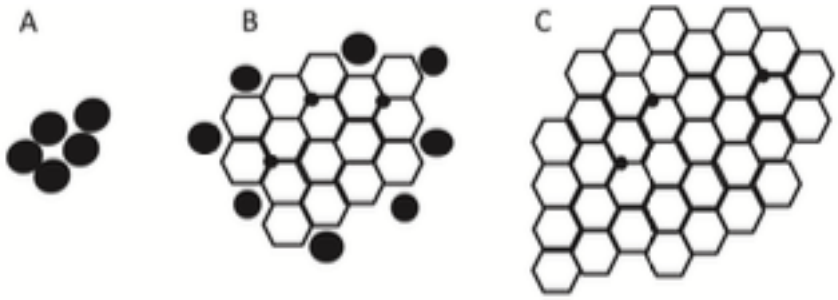

Figure 13: Schematic illustration of changing nevi from a globular to a reticular pattern (236). A. In the initial phase, peripheral globules are densely packed together. B. Within gaining in size, a reticulated centre appears exhibiting the signs of a growing nevus with a peripheral rim of globules. C. The nevus shows a uniform reticular pattern by loosing the globules in the periphery, which marks the final phase of senescence.

Another prospective follow-up study found a small amount of nevi changing of morphology, which is commonly shifting from a patterned feature to a homogeneous (28%), and reverse (18%) (147). Pizzichetta et al. (156) reported similar results (11% and 21%). However, it should be noted that such change of patterns is only seldom observable and that the majority of reticular and globular nevi remain stable through childhood and adolescence, supporting the distinct pathways of both entities (147,156). Although it appears that the decrease of nevus count after midlife is mainly due to the disappearance of reticular nevi, Scope et al. (147) found “nevus volatility” (i.e. the development as well as the disappearance of nevi) being a common event also during early adolescence. Especially children with a high back nevus count (> 10) are commonly affected. This observation was also made by Wollina et al. (122). Thus, the authors conclude that digital dermoscopic monitoring is a valuable tool to observe changes and volatility of nevi in children to better understand their natural evolution as well as involution.

In contrast, nevus change and the development of new nevi in adults are sensitive for the detection of melanoma. Some changes associated with melanoma are the appearance of new colours, changes of pigmentation, the loss of symmetry and change of overall shape as well as the occurrence of new dermoscopic structures and regression structures. However, some changes, like the appearance of blue-white or blue-grey colours or regressing structures (e.g. in Halo nevi and blue nevi) can also be present in melanocytic nevi (125,126,210,142). Interestingly, there is evidence that nevus changes are not only seen in young individuals, but that nevi may still change in the elderly (>65 years). Changes in this latter group include

loss of pigmentation, involution but also increase in size, mostly histopathologically diagnosed as “dysplastic” nevi (148,211). Based on this data, some suggest to proper monitor these lesions rather than to surgically excise them at baseline (136). A digital follow-up study conducted on high melanoma risk patients revealed, that most of melanomas can be diagnosed within one year of follow-up (125). Hence, it is recommended to monitor suspicious lesions at least for a year, especially in patients at high risk for melanoma.

4.2 Body-site

Reticular, globular, mixed and homogeneous nevus pattern tend to exhibit a distinct anatomical distribution. Among younger participants (children and adolescents) an increased distribution of globular nevi on the upper back has been observed (16,146,157). Gamo (175) and Fonseca (137) also found the globular pattern to be predominant in upper body regions while reticular (and homogeneously) patterned nevi tend to prevail on the extremities. The constitutional pathway of nevogenesis of globular nevi further explains their anatomical distribution. It is hypothesized, that globular nevi derive from melanoblasts, which migrate from the neural crest to the skin in the following directions: cephalad-caudal, dorso-ventral and proximal-distal (137). Disconcordant with other authors, Sosa-Seda et al. (146) found the predominant pattern on individuals upper back to be reticular (90%). This can be explained by the big sample size of dark skinned individuals (ST II 3,3%, ST III 28,9%, ST IV 46,7%, ST V 21,1%), which are prone to exhibit a predominant reticular pattern (146). Fonseca et al. (137) also found this association in their cohort of dark individuals.

4.2.1 Acral

4.2.1.1 Palms and soles

Background skin anatomy seems to be the most important influencer in nevus morphology. It is known that the epidermal rete ridges reflect the melanin distribution within the lines of melanocytes and keratinocytes, exhibiting a pigment network (137). Hence, nevi on special body sites like the acres, genitals, scalp or milk line represent distinct features under dermoscopy. Up to now, acral nevi are among the most described entity (153,158,163,164,174,178,180,181,184,213).

Because of the peculiar anatomical condition in glabrous skin, nevi and melanomas tend to follow the furrows (**Figure 14**) and ridges (**Figure 16**), respectively (16,213). Many observers agree in their findings that the parallel furrow (**Figure 14**), the lattice-like (**Figure 15**) and the fibrillar patterns (**Figure 15**) are the most common among acral melanocytic nevi (153,158,160,163,174,184,213,214). Other studies have found the homogeneous (160,163,165), the reticular (162,164) as well as the globular pattern (164) to be one of the three major patterns of acral nevi. A cross-sectional study examining acral nevi only in skin type V and VI patients revealed, that the fibrillar followed by an homogeneous pattern were the most prevalent among this population (173). The different results of the three major patterns are listed in **Table 11**.

Figure 14: Acral nevi showing the parallel furrow pattern dermoscopically.

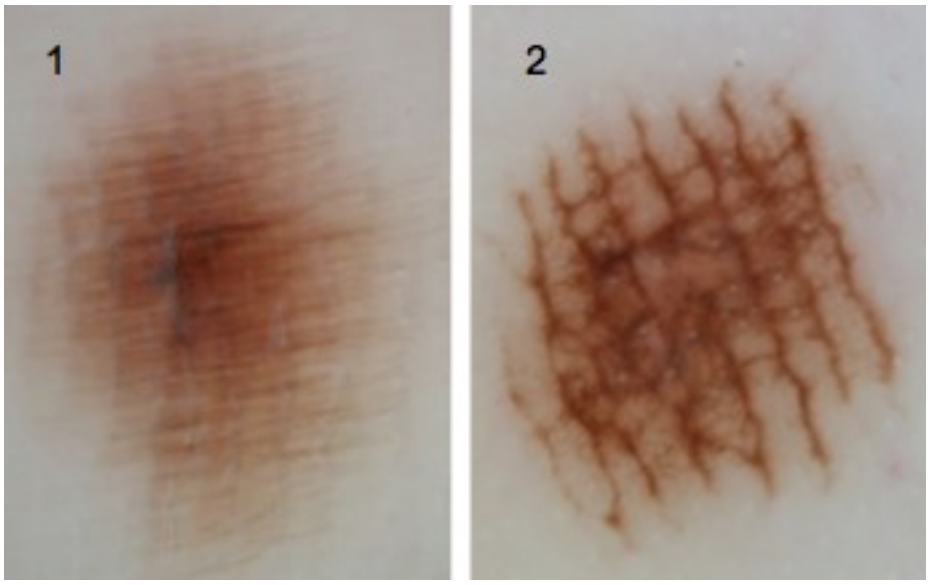

Figure 15: Dermoscopy of acral nevi showing the (1) fibrillar and (2) lattice-like pattern.

Table 11 Prevalence of the major dermoscopic patterns of acral nevi in different studies.

Criterion	***Nevi, No. (%)***										
	Chuah et al. (153) (France)	Fargnoli et al. (158) (Italy)	Madankumar et al. (160) (USA)		Ahmadabad et al. (162) (Iran)	Barquet et al. (163) (Uruguay)	Kokgil et al. (164) (Turkey)	Elwan et al. (165) (Egypt)	Gill et al. (173) (USA)	Suzaki et al. (174) (Japan)	Wawrzynkiewicz et al. (184) (Poland)
Parallel furrow	**44 (77)**	**53 (71)**	**107 (48)**	**170 (43)**	**24 (51)**	**81 (51)**	**262 (63)**	**148 (66)**	**6 (14)**	**188 (45)**	**80 (22)**
Fibrillar	**6 (10)**	**11 (15)**	**18 (8)**	29 (7)	4 (9)	11 (7)	21 (5)	14 (6)	**15 (35)**	**79 (19)**	**109 (30)**
Latticelike	**5 (9)**	6 (8)	**35 (16)**	**53 (13)**	**11 (23)**	**21 (13)**	18 (4)	**20 (9)**	4 (9)	16 (4)	**120 (33)**
Homogeneous	NE	0	16 (7)	**41 (10)**	5 (11)	**20 (13)**	16 (4)	**17 (8)**	**6 (14)**	1 (<1)	NE
Globular	NE	6 (8)	NE	NE	1 (2)	15 (10)	**32 (8)**	4 (2)	3 (7)	7 (2)	NE
Reticular	NE	0	NE	NE	**10 (21)**	0	**51 (12)**	4 (2)	0	9 (2)	NE
*Crista dotted**	NE	**16 (21)**	NE	NE	NE	NE	NE	NE	NE	**47 (11)**	NE
Parallel ridge	2 (4)	0	1 (<1)	1 (<1)	2 (4)	NE	1 (<1)	5 (2)	NE	4 (1)	NE
Total	57 (100)	75 (100)	225 (100)	396 (100)	47 (100)	158 (100)	419 (100)	224 (100)	43 (100)	420 (100)	360 (100)
Skin type	NE	NE	Non-hispanic white	Skin-of-colour	III - IV	II - VI	NE	NE	V - VI	NE	NE

Bold = 3 major patterns; abbreviation: NE, not evaluated; *“peas-in-a-pod” pattern

These different results concerning the three *major* patterns in acral nevi are possibly caused by the different ethnicities observed. Alongside with this, the work of Palicka (176) agreed with the idea of ethnical differences by showing an association of relatively large and dark pigmented acral nevi with skin of colour in comparison to white individuals. Nevertheless, studies concordantly find the parallel furrow pattern to be the most prevalent pattern of acral melanocytic nevi in light-skinned children (77% and 71%) (153,158) and adults (51%, 63% and 66%) (**Table 11**) (163–165,213). Clinically and dermoscopically, the parallel furrow pattern exhibits brownish coloured, linear pigmentation along the sulci of the skin (**Figure 14**) (213,214). In addition, four different variants of the parallel furrow pattern have been identified: the single line, the single dotted line, the double line and the double dotted line variant (158,213,214). The lattice-like pattern shows parallel pigmented lines along the sulci combined with lines crossing the sulci (**Figure 15**) (213,214). This pattern follows the peculiar anatomical structure of the arch area on the sole, where it mostly can be found (178,180,184). Densely arranged fibrillar pigmentation, crossing the skin margins is the dermoscopic feature of nevi exhibiting the fibrillar pattern (**Figure 15**) (213,214). It is hypothesized, that the fibrillar as well as the lattice-like pattern derive from the parallel furrow pattern, expressing different dermoscopic characteristics caused by anatomical varieties (174,178,213). Therefore, it has been shown, that the fibrillar pattern tends to occur on the soles rather than on the palms, being a sign of nevi on weight bearing areas (163,164,178,184,213,214). Elwan et al. (165) also found the fibrillar pattern on the palms of farm workers, which showed thickened cornified layers, may resulting from labour. Furthermore, changes from a parallel furrow into a fibrillar pattern have been observed during follow-up by Chuah et al. (153), which verifies this hypothesis. The work of Nagashima (178) and Wawrzynkiewicz (184) also revealed site-specific differences of dermoscopic pattern in acral nevi of the soles. Their results are concordant with other authors concerning the distribution of the fibrillar and lattice-like pattern. Thus, one nevus can exhibit more than one of the three major patterns, simulating the arrangement of the local transverse ridges (178,213).

In addition, age-related differences of nevus morphology on acral skin have been identified. The *peas-in-a-pod* pattern (combination of parallel furrow pattern with

crista dotted pattern) is widely seen among younger individuals (21% and 11%; (158,174)) (**Table 11**). It may derive from congenital or early acquired acral nevi (153,158,174,180,181,213). This pattern is considered to be the predominant acral nevus pattern of the youth, similar to the globular pattern seen on non-acral skin (174,180). Suzaki et al. (174) added further results concerning an age-dependent occurrence of the different types of parallel furrow pattern. The double line variant predominantly occurs in younger individuals, which may conform to a globular pattern in common nevi. In contrast, the single line variant prevails in older patients and thus may be equivalent to reticular patterned nevi.
Although the parallel ridge pattern has been observed in a few benign nevi (**Table 11**) (160,162,165,180,181), also rarely in congenital acral nevi (153,237), this feature still reveals the major criterion (coming along with pigmentation irregularity) for acral early melanoma (**Figure 16**) (213). It is said, that the positive predictive value of the parallel ridge pattern for melanoma is about 99%, while the specificity of the parallel furrow pattern an its variants is about 98% for benign acquired nevi (213). Saida et al. revised a 3 step algorithm for the management of acquired acral pigmented lesions (213). The algorithm is shown in **Figure 17**. Sometimes, a discrimination if the pigmentation whether follows the furrows or the ridges can be challenging. Thus, the furrow ink test is recommended for pattern identification. Therefore, the periphery of the lesion gets coloured green or blue to identify the furrows and observe whether the pigmentation follows the coloured furrows or the ridges (213,214).

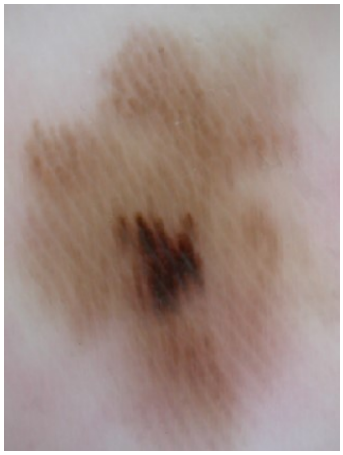

Figure 16: Dermoscopy of an acral melanoma: parallel ridge pattern.

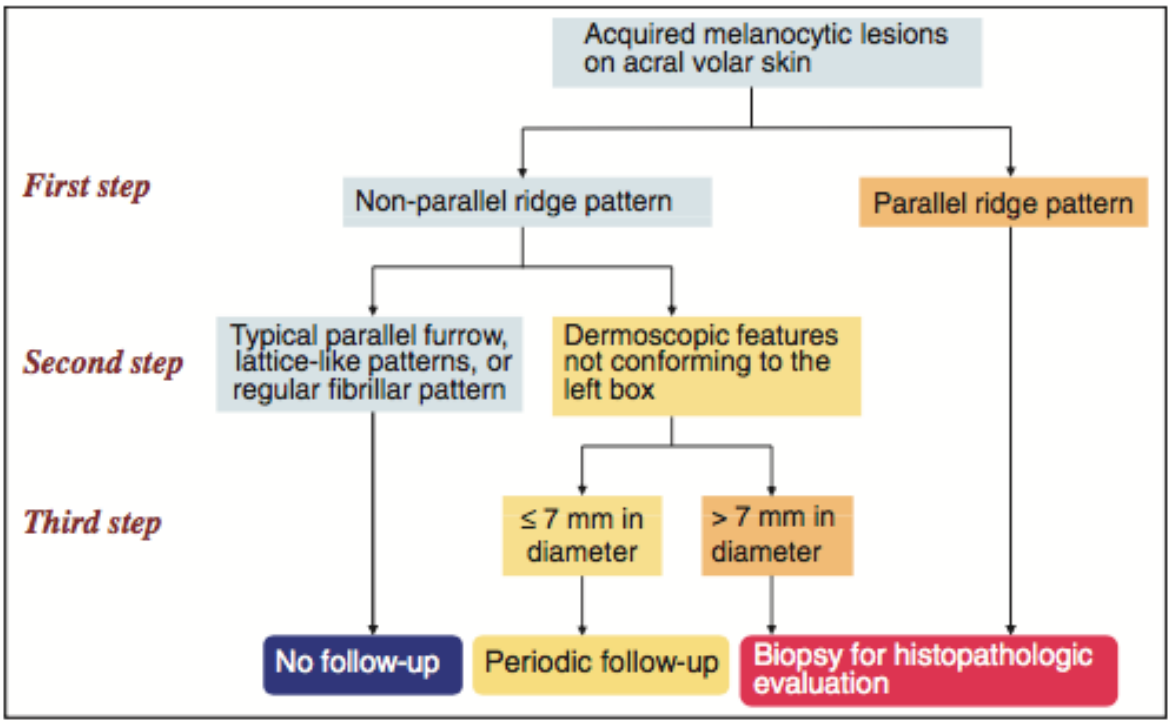

Figure 17: 3-step algorithm for the management of acquired acral lesions. Lesions showing a parallel ridge pattern are recommended to be excised. Typical parallel furrow pattern, lattice-like patterns, regular fibrillar patterns, that is to say regularly and symmetrically arranged fibrils, can be diagnosed as benign and do not need to be monitored. Other patterns like reticular, globular, homogeneous, globulostreak-like and transition patterns are recommended to biopsy when the diameter of the lesion exceeds 7mm (213).

A study comparing different skin-types regarding the appearance of acral melanocytic nevi revealed, that patients with darker skin-types (Fitzpatrick ST IV to VI) are more likely to feature at least one acral nevus (160 of 362 patients; 44%) than patients with skintypes I or II (118 of 426 patients; 28%) (160). Tuma et al. (187) is concordant concerning this observation (ST V-VI: 57% vs. ST I-II: 23%). This may be explained by the hypothesis, that skin-of-colour individuals are more susceptible to develop acral nevi on their palms and soles, which are not as protected from UV radiation as the rest of their skin. A genetic/hereditary background may contribute to this hypothesis (160). It has further been found that white individuals, which exhibit at least one acral nevus, show increased total body nevus counts (160). Considering the fact that an increased number of melanocytic nevi is said to be an important risk factor for developing melanoma, the occurrence of an acral nevus may increase the risk in white individuals as well. Hence, individuals showing at least one acral nevus may benefit from total body examination.

4.2.1.2 Nail matrix

Having a look at nail pigmentation, benign longitudinal melanonychia rarely occurs in the Caucasian population (1,4%) (217). It is mainly seen in young individuals, mainly affecting the thumb, followed by the great toe and the index (183,216,217,219). The dermoscopic diagnosis of nevi of the nail-matrix illustrates regularly arranged longitudinal lines that are homogeneously brown to black coloured on a brownish background (**Figure 18**) (214–216,219). The bands usually exhibit a regular thickness (≤3 mm) (155–157). The colour varies from light to dark brown and black (217) and depends on the individuals skin-type (e.g. darker ST reveal darker nevi and melanomas of the nail) (214). It is to say that darker pigmentation often comes along with a Pseudo-Hutchinson sign because of dark pigment shining through the transparent nail fold (219).

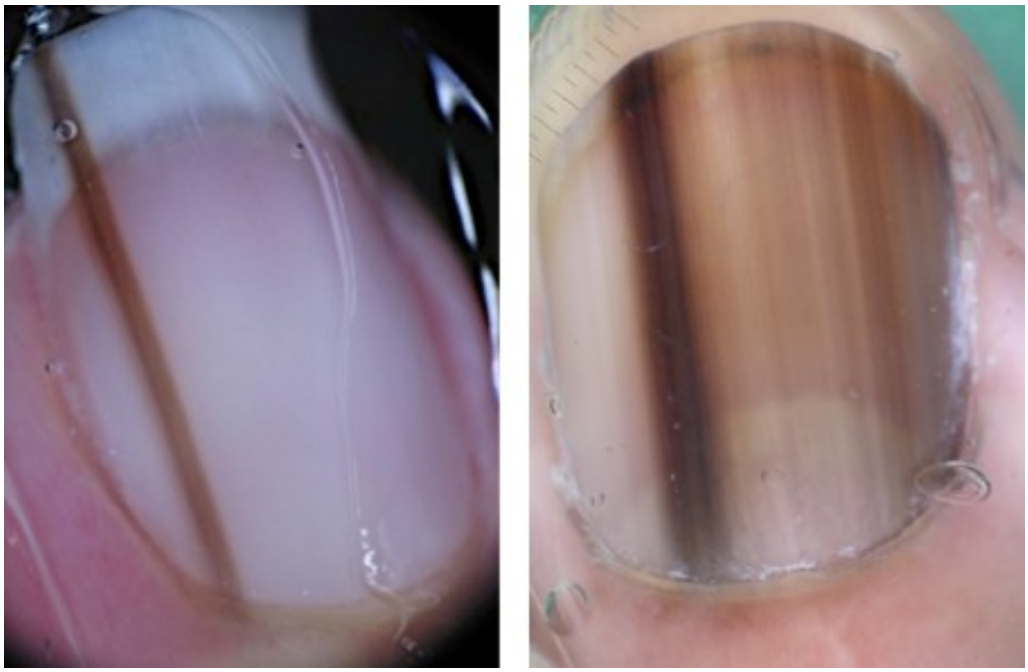

Figure 18: Longitudinal melanonychia: Subungual nevus (left) vs. melanoma (right).

Different diagnoses of longitudinal melanonychia need to be distinguished dermoscopically. Hypermelanoses like subungual hematoma, chronic-trauma-induced, drug-induced and ethnical pigmentation should be differed from melanocytic hyperplasia like nevi and melanomas (214,217). Thus, a diagnostic algorithm for melanonychia has been illustrated (215,217,218). The first step is to identify whether the lesion derives from a melanocytic or a non-melanocytic origin (i.e. nail staining, fungal melanonychia, subungual hematoma). The former needs

to further be distinguished into melanocytic activation (i.e. single: trauma-induced, periungual tumour, nail apparatus lentigo; multiple: drug-induced pigmentation, postinflammatory melanonychia, systemic disease induced, onychomycosis, ethnical pigmentation, Laugier-Hunziker syndrome) or melanocytic proliferation (i.e. benign nail-matrix nevus, subungual melanoma) (215–219). Melanocytic activation appears in a grey colour and is not required to undergo histopathological examination. Brown colouration is highly suggestive for melanocytic proliferation (216,218). In case of the latter, the regularity of the pigmented bands and colours are crucial for further management. Biopsy is recommended when the longitudinal bands are irregularly arranged and express multiple colours, which is suggestive for a malignant lesion (**Figure 18**). When dermoscopy reveals a regular and parallel, single coloured pattern, observation and follow-up tends to be sufficient (215,216). Nevi of the nail-matrix (either congenital or acquired) in children can be more problematic (216–219). These nevi are darker in colour and often exhibit melanoma-like features (i.e. irregularity of the longitudinal lines, variation in colour, triangular shape, deformation of the plate, periungual pigmentation, Hutchinson's and pseudo-Hutchinson's sign, appearance of dots/globules, dermoscopic change over time) (183,214,216,218,219). Ohn et al. (183) conducted a study comparing longitudinal melanonychia in adults and children. They found, that nail matrix nevi in children often exhibit a brown-black colouration (56,9%), while in adults, light brown colouration is significantly more common (60,0%; $p < 0.001$). They also observed more irregular pigmented bands in nail matrix nevi of children (34,5%) than adults (17,1%). This may lead to reassessing the diagnostic algorithm, especially when used in children. Also because melanomas of the nail apparatus rarely occur in the paediatric population, excision needs to be well considered in the paediatric population. On the one hand, it is important not to miss a melanoma. On the other hand, clinicians should avoid unnecessary excisions, which may lead to long-life scars and nail plate deformations. Still, excisional biopsy is recommended in uncertain cases. Up to now, no consensus on modalities for follow-up management of melanonychia has been found. Nevertheless, periodic medical examinations, as well as dermoscopic and photographic documentation, are recommended (219).

4.2.2 Face

The characteristics of facial skin illustrate a thin epidermal layer, a flat dermo-epidermal junction and large pilosebaceous units (214). These anatomical features are in charge of the peculiar clinical and dermoscopic features of facial nevi. While melanocytic nevi of the face tend to be flat in youth (probably compound nevi), they typically present as raised hypopigmented nodular nevi (mostly intradermal nevi) in the adulthood and elderly (**Figure 19**) (155,211). This fact is of practical value for differentiating these lesions from solar lentigo maligna, which mostly presents as a flat pigmented macule (mainly junctional/intraepidermal lesion) (155,211). Still, other non-melanocytic tumours such as basal cell carcinoma, squamous cell carcinoma or sebaceous hyperplasia need to be ruled out because of their similar clinical presentation to raised nevi (155). Regarding flat nevi, a prospective study revealed, that they tend to exhibit interfollicular reticular lines, which were present in 39,4% of all nevi (177). They additionally revealed grey colouration to represent a clue for malignancy (95,8% of melanomas). Nevertheless, grey colours have been found to be commonly present in flat nevi as well (66,7%), which make us regard this feature with caution (177). Additionally, a significant correlation between facial nevi and a higher nevus count has been found (155). The fact given that a high nevus count is associated with an increased melanoma risk, especially individuals presenting a facial melanocytic lesion may benefit from total body examination (155).

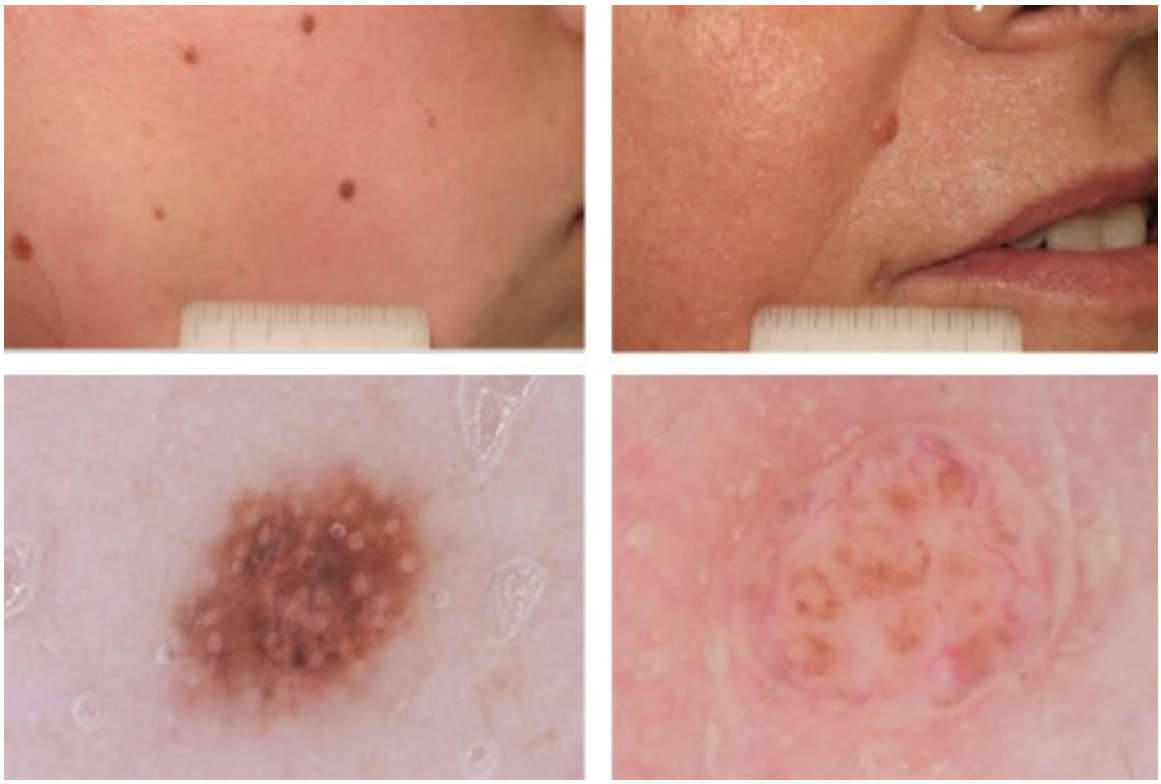

Figure 19: Facial nevi: (left) clinically flat nevus showing a structureless brown dermoscopic pattern with hypopigmented hair follicles; (right) clinically nodular, hypopigmented intradermal nevus showing comma-shaped vessels under dermoscopy.

4.2.3 Mucosa

Mucosal nevi in general conclude nevi of the genitals (i.e. vulva, penis), anal nevi, oral nevi (e.g. lips, enoral area) and nevi of the conjunctiva (167,186). These kinds of nevi are among the least described because of difficulties to examine the mucosal regions. Also, to minimise the risk of any nosocomial infection, special polyvinyl chloride food wraps need to be used to cover the dermatoscope (141).

4.2.3.1 Genital

A retrospective study found that the prevalence of genital nevi in children and adolescents is around 3,5% (179,220). It has also been observed, that most of these nevi occur within the first two years of age (179,220). Vulvar nevi are among the most examined and described regarding nevi of the genitalia and mucosal areas (166,185,220,221,238). They mostly occur single in 2,3% of females (mainly at a young age (182,141)) and are commonly detected during routine gynaecological examination (141,221,238). Melanocytic nevi of the vulva appear as regularly bordered, pink to brown or black macules (flat) or papules (palpable) with a diameter of ≤ 1cm (141), mostly located on the labia maiora, followed by the

labia minora and the clitoral hood (182,220). They often exhibit a globular (**Figure 20**) (16,179,182,220,221) or homogeneous pattern under dermoscopy (166,182,220,221).

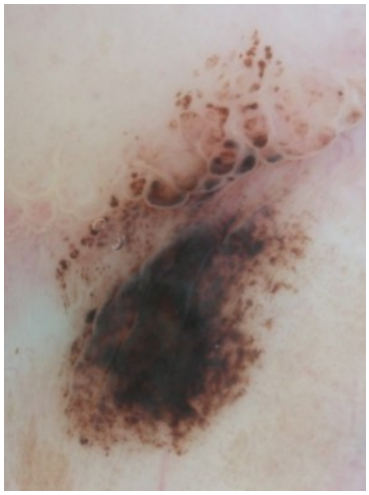

Figure 20: Globular pattern of a vulvar nevus.

Also, these nevi tend to grow proportionally to body growth and thus may exhibit symmetrical change in size and colour as well as overall texture (179).
In addition, Ronger-Salve et al. (166) described a new dermoscopic pattern seen in nevi located at the edge of the labia minora, called the polycircular pattern. This fact may be respected when examining vulvar lesions both dermoscopically and histopathologically.
The prevalence of a globular pattern as well as the early occurrence of genital nevi may lead to the assumption that these nevi are congenitally determined.
A rare subtype (5% of vulvar nevi), namely atypical melanocytic nevi of the genital type (AMNGT) (220), share similar dermoscopic (e.g. blue white veil, irregular dots) and histopathological features with vulvar melanoma and tend to occur in younger individuals as well (16,182,185,221). Dermoscopically, these nevi often exhibit a globular or a mixed pattern, which shows parallel lines combined with globules or homogeneous pigmentation (16,182,185,141,220). Although vulvar melanoma is a rare finding (3-7% of melanomas in women) (166,185), some authors recommend precise follow-up and excision if any melanocytic lesion of the vulva exhibits any signs of atypia (166,185). Common genital nevi (as well as AMNGT) mainly occur in younger individuals, while melanoma tends to develop in an advanced age (182). Ferrari et al. (182) significantly associated nevi and

melanomas by the age of <24 and >35 years, respectively. Hence, the individuals' age is the most important predictive value for differentiating benign melanocytic nevi from melanomas in the genital area (16,182).

4.2.3.2 Oral

Oral pigmented lesions are quite rare. De Giorgi et al. (168) found at least one lesion in 5,7% of their study sample (265 patients), whereby 26,7% of the lesions detected were proven to be benign melanocytic nevi. They were mostly found on the tongue and vermillion border (168). A multicentre observational study revealed that blue, white and grey colours are highly sensitive and specific for malignant mucosal lesions, especially when the lesions exhibit more than one colour (186). However, it is recommended to excise any mucosal lesion larger than 1 cm in diameter, showing grey colour and structureless areas under dermoscopy (141).

4.2.4 Milk line

The dermoscopic features of nevi on the milk line and flexural sites have only been described in a few case reports yet (141). Nevertheless, the knowledge of these nevi still remains important, as they often exhibit similar features like genital nevi or sometimes show very atypical patterns; histopathologically mimicking melanoma, they are sometimes diagnosed as SAMPUS or MELTUMP (141). Their clinical appearance includes a size larger than 6 mm and irregular boarders (141). Dermoscopy often reveals a prominent pigment network, bizarre lines and large globules, which are mainly associated with the texture of the skin in each region (141).

Nevi of the breast often show atypical pigment network and irregular globules and dots under dermoscopy. The stretching of the melanocytic lesions across the convex surface of the female breast may lead to the irregularity of the pattern (159). Looking at nevi of the nipple, a cobblestone pattern can be visible, which mostly presents the normal structure of the skin of the areola (141). Still, the dermoscopic criteria of this special location have not been well established. A case report of a changing nevus of the nipple during pregnancy has been published. The nevus showed numerous irregular features such as irregular brown to blue-grey colours arranged in an irregular cobblestone pattern (239). Thus, distinguishing these nevi from melanoma is still a matter of concern and RCM might be a crucial non-invasive diagnostic tool especially for nevi on these body

sites. However, Merkel et al. (159) suggest to monitor these lesions dermoscopically in case they are small in diameter and occur in young individuals.

4.2.5 Scalp

Several studies examining scalp nevi have been conducted. Melanocytic nevi of the scalp clinically appear as flat or slightly elevated, symmetrical lesions (169). Observers agree, that they are more frequent in male individuals (63% male vs. 37% female; 60 nevi in 18 boys vs. 28 nevi in 21 girls; 46,3% male vs. 22,1% female) (169–172). Zalaudek et al. (169) proposed to categorise these nevi into six groups, namely common, papillomatous, eclipse, congenital, atypical and blue, with decreasing incidence. Their clinical appearance and undergoing dermoscopic patterns are described in **Table 12**. An interesting finding is, that papillomatous nevi tend to occur in older individuals (169,141). This incidence supports the model of the age-dependent incidence of nodular intradermal nevi in the elderly. In addition, observers agree in their findings, that the scalp nevus count increases with age and goes down until the elderly (170–172). This is similar to the frequent finding of an age-dependent total nevus count, which increases until midlife and goes down thereafter. Eclipse nevi which generally exhibit a pigmented rim can be considered to be typical in the paediatric population (**Figure 21**) (16,169,170,222).

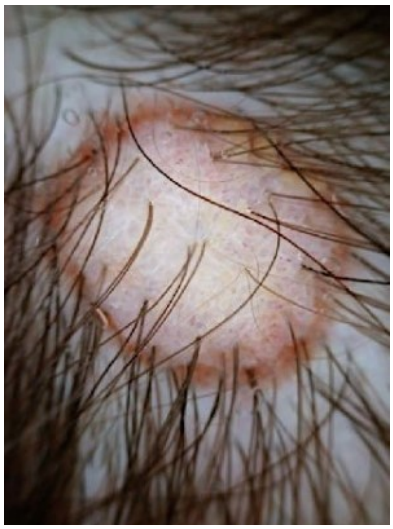

Figure 21: Eclipse nevus.

Tcheung (170) and Gupta (171) additionally observed a small extent of cockade nevi (central darker globular/network pattern, lighter homogeneous inner ring combined with a darker peripheral network) among children (209). Further, a

significant association of scalp nevi with congenital nevi on the torso has been found, which supports the hypothesis that scalp nevi may be constitutional determined (16,169). In general, scalp nevi tend to exhibit numerous features and variegations in pigmentation. Follow-up revealed several (77% of nevi) benign changes of nevus morphology, mostly becoming more atypical, which may be caused by an increase in diameter or different colour variegations (171). Nevertheless, scalp nevi, which deviate from the described features (mainly atypical nevi), need to be treated with caution in order not to miss any malignancy (169). Both the different morphological faces and the “hidden” location of scalp nevi complicate an early diagnosis of melanoma, which is crucial for the patients’ survival and prognosis. Thus, especially individuals of high melanoma risk are recommended to undergo careful whole body examination including the scalp.

Table 12 Clinical and dermoscopic features of scalp nevi (169,142,222).

Subgroup	***Clinical appearance***	***Dermoscopic features***
Common	Flat, structureless light brown	Globular, rarely reticular pattern, uniform, multifocal or perifollicular pigmentation
Papillomatous	Nodular, papillamtous surface	Structureless, red to light-brown pigmentation, comma vessels
Eclipse	Flat, central hypopigmentation	Peripheral network, central and Perifollicular hypopigmentation, dotted vessels
Congenital	Flat, Central hyperpigmentation, multifocal pigmentation	Globular and structureless pattern, muticoloured
Blue	Papular, nodular, blue, blue-grey, blue-brown colouration	Structureless blue pigmentation, often multichromatic (blue-grey, blue-brown, blue-black), whitish scarlike areas
Atypical	Variable	Network pattern, perifollicular hypopigmentation

4.3 Skin-type

Studies are concordant in their observations, that lighter individuals significantly show a higher total nevus count than darker ones (152,175,188). Additionally, some studies show, that the different skin-types come along with distinct predominant nevus morphology. Melanocytic nevi in individuals with ST I and II

particularly exhibit uniformly distributed light brown to orange colour, potentially showing central (ST I) or multifocal (ST II) hypopigmentation and are generally large in size (**Figure 22**) (11,187). ST III and IV individuals prevail to exhibit dark brown to black nevi with multifocal (ST III) or central (ST IV) hyperpigmentation, which are small in size (**Figure 22**) (11). Patients with skin-of-colour most often present dark brown reticular patterned (ST V) or structureless (ST VI) nevi that show central hyperpigmentation (187,188). ST VI also often comes along with black, blue or grey coloured nevi, whereas a structureless feature correlates with the latter two colours (188).

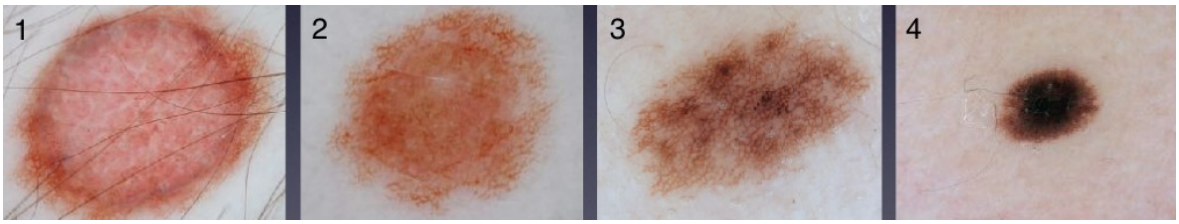

Figure 22: Skin-type-related predominant dermoscopic nevus patterns. (1) orange, light brown colouration, centrally hypopigmented; (2) light brown colouration with foci of hypopigmentation; (3) dark brown colour with foci of hyperpigmentation; (4) dark brown colouration with central hyperpigmentation.

Lallas (188) and Tuma (187) found, that nevi in black individuals (ST V and VI) share the same features as nevi previously exposed to UV-rays. These features are black dots and pigment blotches, decreased hypopigmented areas and the appearance of a prominent network (187). Hence, it is hypothesized that this features illustrate a natural protection against sun exposure in black people (187). Because the development of melanoma in skin-of-colour individuals is exceedingly rare and so is the awareness about melanoma risk. Additionally, pigmented tumours on dark skin are less evident and therefore lead to a late diagnosis. Thus, melanoma in dark skinned individuals has a worse prognosis than in white skinned patients (188).

4.4 Genetic alterations

The most prevalent and discussed genetic alteration occurring in both melanocytic nevi and melanomas is located in the $BRAF^{V600E}$ gene. This mutation interferes in the RAS-RAF-MEK-ERK- pathway, which is highly responsible for the regulation of cell proliferation. Research revealed, that small congenital and acquired melanocytic nevi often harbour mutations in $BRAF^{V600E}$, particularly exhibiting a

globular or homogeneous pattern under dermoscopy (194,196,223). The fact that the latter entities (both small congenital and acquired nevi) share overlapping dermoscopic and histopathologic features as well as the same mutations, a dermoscopic classification may be more useful than the former (congenital and acquired), as Zalaudek already proposed (1). Globular nevi (that is to say dermal or compound nevi) are three times more likely to express $BRAF^{V600E}$ mutations than reticular patterned nevi (junctional nevi) (86,7% vs. 20%; P = 0,002) (11,201). Several observers agree with this finding (191,201). Further studies additionally found a high frequency of $BRAF^{V600E}$ mutations in nevi exhibiting a mixed pattern (growing nevi) under dermoscopy (191,201). These findings let suggest that $BRAF^{V600E}$ mutation is acquired early in childhood and adolescence (11,191). Hence, the former idea of a UV-induced somatic mutation in the BRAF gene is challenged (11). Considering the facts that oncogenic BRAF predominantly occurs in globular (dermal) and mixed patterned (peripheral rim of globules; that is to say: growing) nevi as well as its association with cell senescence, Zalaudek et al. (11) proposed an idea which explains the role of BRAF in the evolution of melanocytic nevi. It says, that because of polyclonality for BRAF (223), mutated cells initially induce nevus growth. While wild-type cells remain proliferative, mutant cells enter growth arrest after a limited amount of cell cycles. After senescence and the loss of proliferative capacity, the melanocytic cells tend to involute and lead to the disappearance of nevi (11).

Hence, the traditional idea of stepwise malignant tumour progression from benign to dysplastic nevus and eventually to melanoma with $BRAF^{V600E}$ mutations as initial drivers is not supported by some authors (223,224).

It has been revealed, that melanocytic nevi often harbour mutations in $BRAF^{V600E}$ (196) and $NRAS^{Q61}$ genes but are not in an increased risk of developing melanoma (190). Tan et al. (240) recently found a case of melanoma exhibiting BRAF wild-type, which arose within a $BRAF^{V600E}$ mutated dysplastic nevus. While $BRAF^{V600E}$ mutation leads to a faster growth in melanomas, this effect could not be found in melanocytic nevi (196). It is thought, that $BRAF^{V600E}$ mutations in nevi do not act oncogenic but lead to cell senescence and thus growth arrest (196) which is ascribed to an activation of $p16^{INK4a}$ and acidic β-galactosidase (11).

In contrast, intermediate to large congenital nevi often harbour mutation in the NRAS genes, which are said to occur already *in utero* (194,224). Charbel et al.

(194) identified the NRAS mutation in 18 of 19 giant CMN (94,7%), which represents the only recurrent somatic mutation in whole exome sequencing. HRAS and GNAQ mutations have been associated with Spitz and blue nevi, respectively (16,223,225). The work of Bender et al. (202) demonstrated that 86,7% (26/30) of cellular and common blue nevi harbour GNAQ mutations, which highly verifies former findings (224). It has further been shown, that oncogenic GNAQ is not sufficient for the genesis of melanoma. This finding supports the generally stable and benign nature of blue nevi (224). HRAS is said to have a high affinity for the PI3K/ATK-pathway, whose activation leads to the symmetrical overgrowth of epitheloid cells. This idea may partly explain the development of Spitz nevi, as HRAS cannot be found in every single lesion. However, a positive HRAS mutation tends to correlate with a favourable prognosis, as this genetic alteration has not been found in spitzoid melanomas so far (224). Wiesner et al. (195,226) found another subset of spitzoid proliferations, namely “atypical Spitz tumours” (AST), to be associated with BRAF mutations in combination with BAP1 bi-allelic loss. These lesions appear multiple, skin-coloured and raised, showing overlapping histopathological features with both Spitz nevi and melanoma. They are said to form a distinct subset of melanocytic neoplasms (224). In addition, genetic alterations in ROS1, NTRK1, ALK, BRAF and RET are found to result in kinase fusions among the entire spectrum of spitzoid neoplasms, including Spitz nevi, AST and spitzoid melanomas (198). It is said, that these fusions occur early in the development of spitzoid tumours and thus may be necessary, but insufficient for malignant transformation (198).

An association between MC1R mutations in RHC carriers and dysplastic nevi has been found (192,200,223). In an analysis of 876 atypical nevi, Quint et al. (192) revealed that nevi in carriers of two RHC variants mostly show structureless areas and nevi in individuals without RHC polymorphisms significantly show a dark-brown colour, pigment network and streaks (192,223). A further study of 62 nevi in multiple melanoma patients showed an association between CDKN2A G101W mutation carriers and the appearance of vessels under dermoscopy. In addition, any MC1R variant is associated with signs of atypia (200,223). Zalaudek et al. (227) also found an association with “white” (hypopigmented) atypical nevi in carriers of RHC variants, which is in accordance with these findings.

In a recent study on 353 genotyped children, Orlow et al. (197) associated MC1R variants and 85 other candidate loci with dermoscopic features and nevus count. They found, that IRF4 (interferon regulatory factor 4) gene polymorphism (rs12203952) is highly linked with nevus count. The rs12203952 T allele correlates with an increased count of flat nevi (i.e. compound or junctional nevi) as well as a decreased count of raised nevi. Further polymorphisms of PARP1 (rs3219090), CDK6 (rs2079147) and PLA2G6 (rs738322) come along with a decreased nevus count (197). Globular-patterned nevi are associated with SNPs (single nucleotide polymorphisms) in IRF4 (especially the T allele) and TERT, while a reticular pattern is linked with SNPs in CDKN1B, MTAP and PARP1, compared to homogeneous nevi (197). In contrast, no association between MC1R variant carriers and nevus count has been found.

Furthermore, a rare germline mutation in the MITF (microphthalmia transcription factor) E318K protein has been linked with both a high nevus count and a reticular dermoscopic pattern. In a recent study, Sturm et al. (193) detected this correlation in 5 of 6 carriers of MITF E318K mutation. Potrony et al. (199) described similar findings, since these carriers were associated with nevus counts >200.

The fact that nevi with certain dermoscopic patterns correlate with different genetic alterations suggests a molecular link with nevus morphology. Further studies may be helpful for better understanding both nevus and melanoma development.

Looking beside genetic alterations, heritability of nevus counts and morphology has been investigated in general. An adult cohort study examining 76 monozygotic and 144 dizygotic twins revealed a constitutional component in total nevus count as well as the changes of the overall number of nevi. Further heritable correlations have been found for the counts of medium-sized nevi, of light-brown-coloured nevi and for the counts of nevi exhibiting a nonspecific dermoscopic patter, while these associations are more common on sun-exposed body sites (189). These findings strongly suggest the possibility of candidate genes being involved in nevogenesis. Further studies need to be conducted for a better understanding of heritable nevus patterns in order to stratify melanoma risk.

4.5 Melanoma

Individuals having a family or personal history of melanoma are prone to have more nevi than patients without (150,200). In addition, the dermoscopic nevus pattern of patients with a personal history of melanoma more often shows atypical features such as irregular pigmentation and atypical network as well as a multicomponent predominant pattern (200). While Bassoli (200) did find an association with a complex/multicomponent pattern and personal history of melanoma, Douglas et al. (150) did not. This may be due to the inclusion of individuals with both a personal and family history of melanoma of the latter study. Abbott et al. (161) conducted a study investigating nevus change in size in patients at high risk for melanoma. They revealed, that individuals with a family history of melanoma are threefold more likely to exhibit changeable nevi (that is to say nevi decreasing/increasing ≥ 20 % in size or newly appearing nevi measuring ≥ 5 mm in diameter) than individuals without. Nevertheless, regarding globular and reticular patterned nevi, patients with melanoma history exhibit both patterns in the same way as non-melanoma patients (200). This fact further confirms the classification of these two distinct subtypes of melanocytic nevi, disregarding of occurring in melanoma prone patients or not. However, further studies on patients with personal history of melanoma need to be conducted to better understand the manner of benign nevi in these patients.

4.6 Pregnancy

It has previously been reported that some melanocytic nevi (6%) undergo some changes during pregnancy (230). Current reviews investigated several studies which examined nevi in pregnant women (228–230). Various changes such as an increase in size, changes in colouration, and changes under dermoscopy and in histopathology have been observed. A consensus has been found, that an increase in size of nevi is body-site specific and commonly derives from an expansion of the skin in the abdominal area and breasts, while back nevi and lesions on the extremities frequently mostly remain stable (228). Regarding colour changes, the results persist to show insufficient evidence. Whereas a few observers report lightening of melanocytic lesions, some monitored overall darkening and an increase in pigmentation (228,229). A prominence of pigment

network (reticular pattern) may be related to the thinning of the skin in expanding areas (228). An increased blood volume and vessel proliferation may explain the frequent occurrence of vessels in nevi under dermoscopy (228).
The occurrence of mixed patterned nevi (central network with a peripheral rim of globules) is very common in pregnant women (157,228). As this type of dermoscopic pattern is a sign of growing nevi, which is as well very frequent in adolescents, it is assumed to be related to an environment rich in growth hormones (157,229). It is said, that nevus growth may be caused by α-melanocyte-stimulating hormone, which also occurs during pregnancy (157,230). All in all, these changes have been observed to mainly reflect a stretching of the skin and completely regress within the first six months after delivery (228–230). Hence, the changes of dermoscopic features not necessarily indicate melanoma in pregnant women as they usually increase symmetrically without variegation of pigmentation. The incidence of melanoma is not higher in pregnant patients. However, any feature suggestive for melanoma in pregnant patients should be treated like in non-pregnant women in order not to delay diagnosis and treatment (228–230).

4.7 UV exposure

Regarding the morphologic changes of nevi after UV exposure, several studies have been conducted up to now. Common clinical and dermoscopic changes such as an increase in diameter, overall darkening and an increase of dots and globules (203–207) as well as inflammatory signs such as erythema have been observed (205,207). Lin et al. (203) found different UV-induced alterations in distinct nevus subtypes according to their dermoscopic pattern. While reticular nevi mostly displayed blurring of the pigment network, globular nevi showed an increase of pigment intensity as well as an increased number of globules and dots. According to Ghani-Nejad et al. (204), the formation of pigmented dots and globules, which represents the most common UV-induced alteration (62,1%), results from melanocytic proliferation and/or an increase in melanin synthesis. It is said, that UV-radiation provokes the secretion of melanocyte-stimulating hormone and an up-regulation of the expression of the corresponding receptors, which would explain the former. A digital follow-up study revealed, that these effects and changes fully dissolve within one year after a single intense exposure (205). It is

also said, that increased nevi fully return to their former diameter already within three months after irradiation (203).

Up to now, no consensus has been made if sunscreen use positively affects nevus development (124,205). Whereas the application of sunscreen is higher in individuals exhibiting lighter skintypes, it is known that they are more prone to develop melanocytic nevi in general. Thus, an evident comparison of the habits of sunscreen use between the different skintypes has to be performed (124). Carrera et al. (207) demonstrated a slight difference of changes in melanocytic nevi between sunscreen and physically protected lesions. They observed less clinical and dermoscopic changes in nevi protected by either sunscreen or physical barriers like textiles. Still, a physical protection tends to provoke less visible changes, but neither of both protection variants could completely prevent the effects of UV irradiation (207). When performing a study to evaluate the effects of narrowband ultraviolet B (NB-UVB) and psoralen-ultraviolet A (PUVA) radiation on dermoscopic features of nevi, Ghani-Nedja (204) also found dermoscopic changes in physically protected nevi (43,2% of protected nevi vs. 91,8% of unprotected nevi). Even if no *in vivo* changes were visible, histopathologic and immunopathologic examination revealed inflammatory signs and melanocytic activation (207). This indicates that UV exposure may lead to melanocytic damage, whether protected or not (207).

4.8 Partial biopsy

When melanocytic lesions undergo incomplete removals, melanocytic tumours cells (either benign or malignant) may remain within the excoriation and lead to recurrence of the pigment (3,4% recurrence rate) (232). These recurrent melanocytic lesions are hard to distinguish between being a benign nevus (**Figure 23**) or melanoma, mainly because of the distortion within the surgical scar or local inflammation (208). Therefore, the most important diagnostic criterion is the knowledge of the histologic outcome of the primary surgery, as recurrent lesions commonly emerge from the former lesions and rarely undergo malignant transformation (208,231). However, if histopathologic results are missing, the International Dermoscopy Society investigated different diagnostic features of benign and malignant recurrent melanocytic lesions (**Table 13**) (208). An additional important dermoscopic feature is the appearance of the scar as a

hypopigmented structureless area (208). For recurrent lesions, which exhibit benign signs, dermoscopic monitoring within 2 to 3 months is said to be sufficient. Still, if any doubtful lesion occurs, excisional biopsy is still the gold standard treatment up to now (208).

Table 13 Anamnestic, clinical and dermoscopic features of recurrent nevi and melanoma (208,231).

Recurrent melanocytic nevus	***Recurrent melanoma***
< 30 years of age	> 30 years of age
Appearance of the pigmented lesion within 6 months after primary removal	Appearance of the pigmented lesion > 1 year after primary removal
	Location on the head/neck area
Dermoscopic features	
Globules	
Radial lines	Circles (facial)
Symmetric pattern	Asymmetric pattern
Heterogeneous pigmentation	Eccentric hyperpigmentation
Centrifugal growth	Chaotic, noncontinuous growth pattern, pigmentation traversing the scar's edge

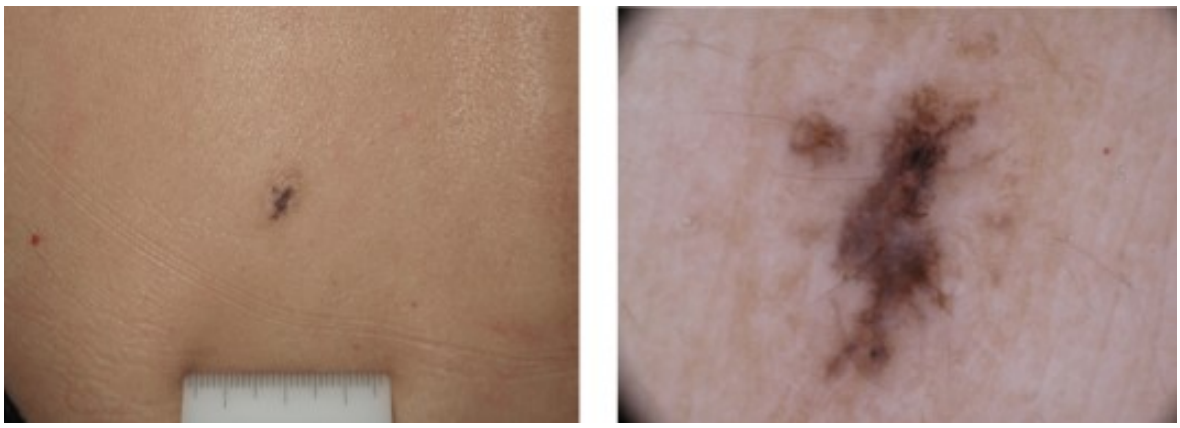

Figure 23: Recurrent nevus.

5 Conclusion

Dermoscopy is a non-invasive tool, which facilitates having a deep look into nevus morphology and identifying malignant lesions at an early stage. Still, surgical removal of worrisome lesions, which often results in numerous interventions and lasting scars, are often performed without necessity. This review provides a basic dermoscopic classification of melanocytic nevi and further recent information about different conditions changing dermoscopic features. Hence, it is advisable not only to look through the dermatoscope but also to involve the patients' habits and clinical appearance in general for better distinction of melanocytic nevi. Digital dermoscopic follow-up in combination with the provided information of this review may help clinicians and dermatologists to optimise decision-making aimed at early melanoma detection and avoidance of unnecessary excisions.

However, although numerous literature was published since 2009, the majority of publications achieve only weak evidence (level B or C). According to this, larger prospective studies are needed to be conducted in the future.

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