Hypopigmentation

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Hypopigmentation

Edited by

Electra Nicolaidou, MD, PhD
Associate Professor of Dermatology and Venereology
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens

"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Clio Dessinioti, MD, MSc, PhD
Clinical Fellow
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens

"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Andreas D. Katsambas, MD, PhD
Emeritus Professor of Dermatology and Venereology
National and Kapodistrian University of Athens

Head
Dermatology Clinic
Hygeia Hospital
Athens, Greece

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper

International Standard Book Number-13: 978-1-138-50523-0 (Hardback)

Library of Congress Cataloging-in-Publication Data

Names: Nicolaidou, Electra, editor. | Dessinioti, Clio, editor. | Katsambas, A. D. (Andreas D.), 1944- editor.
Title: Hypopigmentation / [edited by] Electra Nicolaidou, Clio Dessinioti, Andreas Katsambas.
Description: New York, NY : CRC Press/Taylor & Francis Group, [2020] |
Includes bibliographical references and index.
Identifiers: LCCN 2019015583| ISBN 9781138505230 (hardback : alk. paper) | ISBN 9781315146454 (ebook)
Subjects: | MESH: Hypopigmentation | Vitiligo | Skin Diseases
Classification: LCC RL790 | NLM WR 265 | DDC 616.5/5--dc23
LC record available at https://lccn.loc.gov/2019015583

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Contents

Preface

The skin is the most visible organ, and dyschromias and disorders of pigmentation may be a common cause of significant psychological burden in affected individuals. Hypopigmentation of the skin is characterized clinically by areas of "off-white" color that is lighter compared to the surrounding normal skin, or by areas of complete loss of pigmentation characterized by absolute white color. Hypopigmentation may reflect cutaneous diseases such as vitiligo or mosaic or post-inflammatory hypopigmentation, or be a marker of underlying systemic disorders and complex genetic syndromes including tuberous sclerosis, albinism, piebaldism, Waardenburg syndrome, and other rare disorders. Moreover, hypopigmentation may be a sign of cutaneous T-cell lymphoma or be induced by drugs, including cancer immunotherapy such as anti-PD-1 agents.

This comprehensive illustrated text from international experts aims to enable clinicians to diagnose and treat the full range of these conditions in children and in adults by discussing detailed clinical clues and presenting signs and explaining the approach to management.

We want to thank all our co-authors for their work and CRC Press/Taylor & Francis and Robert Peden, for their support.

This book is dedicated by all three of us to our families for their patience, support, and thoughtfulness.

Electra Nicolaidou

Clio Dessinioti

Andreas D. Katsambas
Athens, Greece

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Contributors

T. P. Afra
Department of Dermatology
IQRAA International Hospital and Research Centre
Calicut, India

Balachandra Ankad
Rajiv Gandhi University of Health Sciences
Bengaluru, India

Nooshin Bagherani
Dermatologist and Lawyer
Nooshin Bagherani' Office
Arak, Iran

and

Department of Molecular Medicine
Tehran University of Medical Sciences
Tehran, Iran

Giovanni Bagnoni
Unit of Dermatology
Melanoma & Skin Cancer Unit—AVNO
Livorno Hospital
Livorno, Italy

Christina Bergqvist
Department of Dermatology
University Hospital Henri Mondor
Créteil, France

Ivana Binić
University Clinical Centre
Medical School University of Niš
Niš, Serbia

Anastasiya A. Chokoeva
"Pro Art "—Clinic for Dermatology
and Aesthetics
Plovdiv, Bulgaria

Stefana Cretu
Second Clinic of Dermatology
"Colentina" Clinical Hospital
Bucharest, Romania

Katerina Damevska
University Clinic of Dermatology
St. Cyril and Methodius University
Skopje, Republic of North Macedonia

Razvigor Darlenski
Department of Dermatology and Venereology
Trakia University
Stara Zagora, Bulgaria

and

Department of Dermatology and Venereology
Acibadem City Clinic Tokuda Hospital
Sofia, Bulgaria

Angelo Massimiliano D'Erme
Unit of Dermatology
Melanoma & Skin Cancer Unit—AVNO
Livorno Hospital
Livorno, Italy

Clio Dessinioti
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Silvija Duma
University Clinic of Dermatology
St. Cyril and Methodius University
Skopje, Republic of North Macedonia

Viktoria Eleftheriadou
Dermatology
Leicester Royal Infirmary
Leicester, United Kingdom

Khaled Ezzedine
Department of Dermatology
University Hospital Henri Mondor
Créteil, France

Nika Franceschi
Department of Dermatology and Venereology
University Hospital Center Sestre Milosrdnice
Zagreb, Croatia

Serena Gianfaldoni
Department of Dermatology
Guglielmo Marconi University
Rome, Italy

Leon Gilad
Department of Dermatology
Hebrew University of Jerusalem
Jerusalem, Israel

Andy Goren
Department of Dermatology and Venereology
Guglielmo Marconi University
Rome, Italy

Fabrizio Guarneri
Department of Clinical and Experimental Medicine—Dermatology
University of Messina
Messina, Italy

Arieh Ingber
Department of Dermatology
Hadassah University Hospital
Hebrew University of Jerusalem
Jerusalem, Israel

Mira Kadurina
Department of Dermatology
Guglielmo Marconi University
Rome, Italy

Alexander Katoulis
2nd Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Attikon" University General Hospital
Athens, Greece

Andreas D. Katsambas
Dermatology and Venereology
National and Kapodistrian University of Athens
Head
Dermatology Clinic
Hygeia Hospital
Athens, Greece

Maja Kovacevic
Department of Dermatology and Venereology
University Hospital Center Sestre Milosrdnice
Zagreb, Croatia

Daniela Kovacs
Cutaneous Physiopathology and Integrated Center of Metabolomics Research
San Gallicano Dermatological Institute
IRCCS
Rome, Italy

Jovan Lalošević
Clinic of Dermatovenereology
Clinical Center of Serbia
Belgrade, Serbia

Irene Latour-Álvarez
Department of Dermatology
University Children's Hospital Niño Jesús
Madrid, Spain

Torello Lotti
Department of Dermatology and Venereology
and
Department of Education Sciences
Guglielmo Marconi University
Rome, Italy

Styliani Mastraftsi
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Alexandra Miniati
Department of Adult Internal Medicine
Lowell General Hospital
Lowell, Massachusetts

Natasa Teovska Mitrevska
Department of Dermatology and Venereology
ReMedika Hospital
Skopje, Republic of North Macedonia

Electra Nicolaidou
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Miloš Nikolić
Department of Dermatovenereology
University of Belgrade School of Medicine
Belgrade, Serbia

Suzana Nikolovska
University Clinic of Dermatology
St. Cyril and Methodius University
Skopje, Republic of North Macedonia

Davinder Parsad
Department of Dermatology, Venereology, and Leprology
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Athanasios I. Pavlidis
Department of Dermatology
Errikos Dunant Hospital Center
Athens, Greece

Igor Peev
University Clinic of Plastic and Reconstructive Surgery
St. Cyril and Methodius University
Skopje, Republic of North Macedonia

Andrej Petrov
Department of Dermatology and Venereology
Acibadem Sistina Hospital
Skopje, Republic of North Macedonia

and

Faculty of Medicine
Goce Delcev University
Shtip, Republic of North Macedonia

Mauro Picardo
Cutaneous Physiopathology and Integrated Center of Metabolomics Research
San Gallicano Dermatological Institute
IRCCS
Rome, Italy

Vesna Pljakoska
Department of Dermatology and Venereology
Acibadem Sistina Hospital
Skopje, Republic of North Macedonia

Dorothea Polydorou
Department of Dermatology and Venereology
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Ranthilaka R. Ranawaka
Dermatology Clinic
General Hospital Kalutara
Sri Lanka

Muhammed Razmi T.
Department of Dermatology
IQRAA International Hospital and Research Centre
Calicut, India

Dimitris Rigopoulos
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Carmen Maria Salavastru
Paediatric Dermatology Discipline
"Carol Davila" University of Medicine and Pharmacy
Bucharest, Romania

Dimitrios Sgouros
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Polytimi Sidiropoulou
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Viktor Simeonovski
University Clinic of Dermatology
St. Cyril and Methodius University
Skopje, Republic of North Macedonia

Mirna Situm
Department of Dermatology and Venereology
University Hospital Center Sestre Milosrdnice
Zagreb, Croatia

Bruce R. Smoller
Department of Pathology
and
Department of Dermatology
University of Rochester
Rochester, New York

Efthymia Soura
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Andrija Stanimirovic
Department of Clinical Medicine
University of Applied Health Sciences
Zagreb, Croatia

Christina Stefanaki
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Alexander J. Stratigos
1st Department of Dermatology and Venereology
National and Kapodistrian University of Athens
"Andreas Sygros" Hospital for Skin and Venereal Diseases
Athens, Greece

Ljubica Suturkova
Faculty of Pharmacy
St. Cyril and Methodius University
Skopje, Republic of North Macedonia

George Sorin Tiplica
Second Clinic of Dermatology
"Colentina" Clinical Hospital
and
Second Dermatology Discipline
"Carol Davila" University of Medicine
and Pharmacy
Bucharest, Romania

Antonio Torrelo
Department of Dermatology
University Children's Hospital Niño Jesús
Madrid, Spain

Yan Valle
Vitiligo Research Foundation
New York, New York

Aleksandra Vojvodic
Department of Dermatology and Venereology
Military Medical Academy
Belgrade, Serbia

Uwe Wollina
Department of Dermatology and Venereology
Stadtisches Klinicum Dresden
Dresden, Germany

Basic concepts on melanocyte biology

1

MAURO PICARDO and DANIELA KOVACS

CONTENTS

EVOLUTION/ADAPTATION OF HUMAN PIGMENTATION AND ITS HETEROGENEITY

Melanocytes participate as the major performers in the complex scenario of biological components regulating the process of pigmentation. These cells are specialized in the synthesis of melanin pigments inside membrane-bound organelles, the melanosomes. Along with hemoglobin and carotenoids, melanin is the main pigment responsible for the color variations of our skin and hair. Differences in skin and hair color are considered to be adaptive responses and to be highly related to ultraviolet (UV) exposure and latitude. During evolution, human ancestors living in equatorial Africa were probably characterized by light pigmentation of the body, which was, however, covered by dark hair. The gradual loss of body hair paralleled the increase in the epidermal and stratum corneum thickness and in dark-photoprotective eumelanin pigmentation to prevent the damages of ultraviolet radiation (UVR) near the equator. Under intense UVR exposure, dark skin developed as a protective mechanism to limit destruction of cutaneous and systemic folate. Folate regulates important biological processes such as DNA synthesis, repair, methylation, and maintenance of active spermatogenesis, as well as melanin production. Folate deficiency has been linked to pregnancy complications and severe fetal abnormalities in neural tube development. The sensitivity of folate and of its main serum form, 5-methyltetrahydrofolate, to be degraded by UVR and reactive oxygen species (ROS) supports the hypothesis according to which the increased pigmentation occurring in high UVR-exposed terrestrial areas evolved to prevent fertility reduction caused by folate photodegradation. As hominins gradually moved outside of tropical latitudes, toward Eurasia, the Americas, and nonequatorial Africa, the intensity and duration patterns of UV exposure decreased together with a reduced potential for vitamin D production, thus favoring the promotion of depigmentation. Therefore, the wide array of pigmentation characterizing modern humans seems to be guided on the one hand by the need to promote photoprotection near the equator (stimulating the dark constitutive pigmentation) and on the other to promote the ultraviolet B (UVB)-induced photosynthesis of vitamin D at the poles (stimulating light constitutive pigmentation).[1–3] On the other hand, the evolution of epidermal pigmentation has been also proposed as a protective strategy against UV-mediated damages to the skin permeability barrier and as a defense against the high water loss occurring in dessicating external environments such as the sub-Saharan African regions. In support of this hypothesis, in comparison to lightly pigmented individuals, darkly skinned people show a more acidic pH of the stratum corneum, which is further acidified by the slow and delayed degradation/extrusion of melanin. It has been also theorized that the melanocytes of darkly skinned people secrete paracrine mediators able to stimulate epidermal differentiation and the production of lipids positively involved in the constitution of the skin barrier, thus efficiently improving barrier competence in dark skin. Moreover, a pigmented epidermis displays enhanced antimicrobial defense, a property strictly co-regulated and interconnected with permeability barrier homeostasis.[4–6]

Melanocytes originate from neural crest multipotent precursors and after steps of migration, proliferation, and differentiation finally settle into epidermis and hair follicles as well as extracutaneous sites, for example, mucosa, cardiovascular system, adipose tissue, cochlea, and choroid.[7–9] In the skin, they differentiate into dentritic pigment-producing melanocytes (Figure 1.1) and are distributed among keratinocytes of the epidermal basal layer and in hair follicles (Figure 1.2). Synthesized melanin primarily aims at protecting from the harmful effects of UV radiation derived from sunlight as well as, nowadays, from indoor tanning apparatuses, thanks to its ability to absorb UVR and damaging free radicals. The tanning response and the resulting promotion of pigmentation constitute the main protective mechanisms activated following acute and chronic UV exposure by melanocytes and the skin in its entirety.

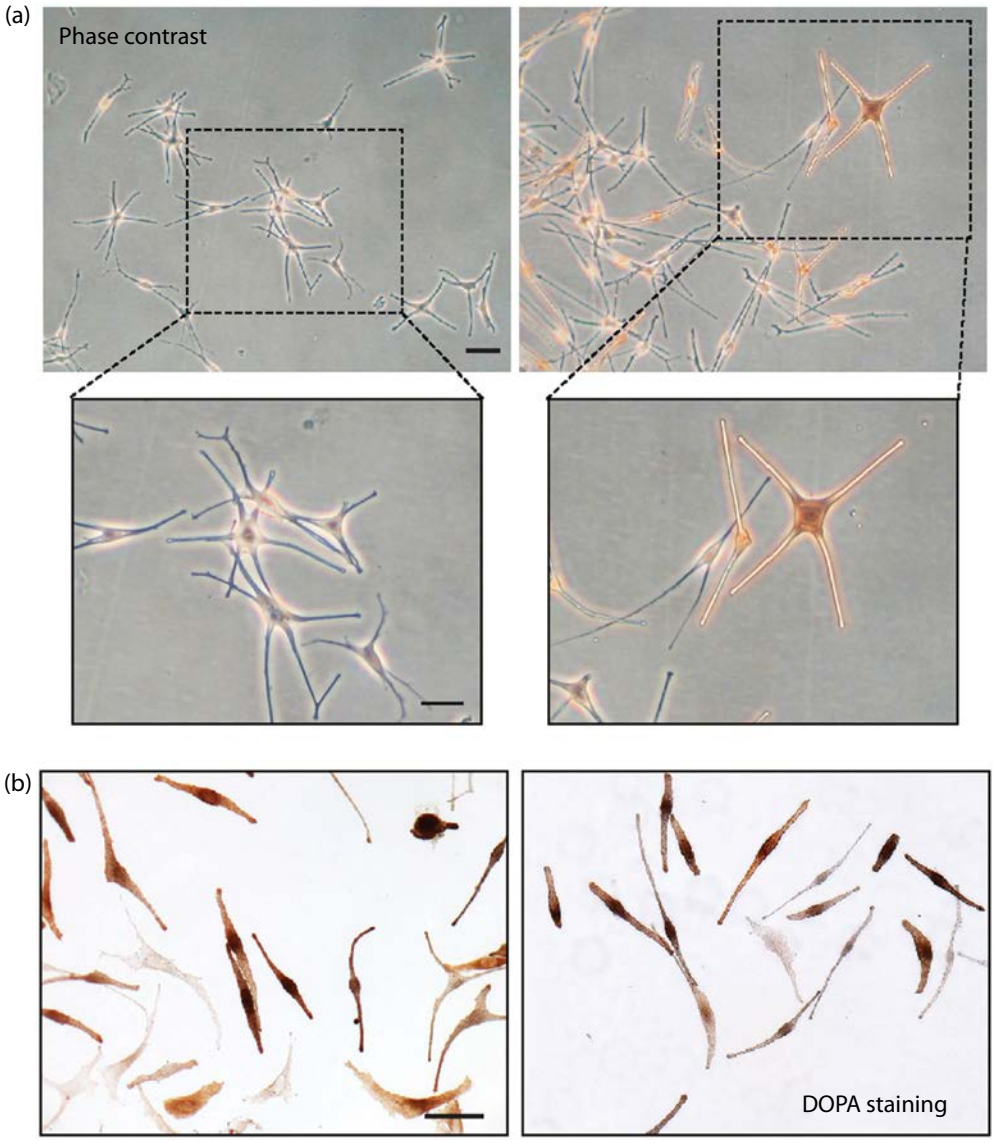

Figure 1.1 (a) Phase contrast microscopic analysis of primary cultures of normal human melanocytes showing the typical dendritic shape. (b) DOPA staining of human primary melanocytes displaying the cellular brown/black appearance due to the activity of tyrosinase on DOPA substrate. Scale bar: a, b: 50 μm.

Melanocytes actively interact with both epidermal and dermal compartments. Each melanocyte, through its dendrites, is in mutual connection with about 30–40 keratinocytes, constituting the epidermal melanin unit (Figure 1.3), and with dermal fibroblasts, thus establishing a finely balanced network of cell–cell crosstalk, ultimately influencing the color of the skin. Differentiated melanocytes display a low growth rate and elevated resistance to apoptosis as a result of their high intrinsic expression of the anti-apoptotic protein Bcl-2.[10] Despite variations in the density of melanocytic cells in diverse body areas, their overall number appears constant among human populations. Differences in ethnic color are rather related to the type and quantity of produced melanin and to its transfer, distribution pattern, and degradation into neighboring keratinocytes. There are two main types of melanin synthesized through the multistep process of melanogenesis: red/yellow pheomelanin and brown/black or dark eumelanin, which are both produced in different ratios. In light-skinned people, the predominant melanin type is usually pheomelanin, the melanosomes are smaller and less condensed, and they are transferred to keratinocytes grouped in membrane-bound clusters containing four to eight melanosomes.[11,12] As light keratinocytes terminally differentiate, melanosome structures are fully degraded in the upper epidermal layers.[11] Differently, in dark-skinned people, eumelanin is the main produced melanin type, and melanosomes are larger and more copious but singularly packaged and transferred into the surrounding keratinocytes, where their degradation and disappearance are slower[13] (Figure 1.4).

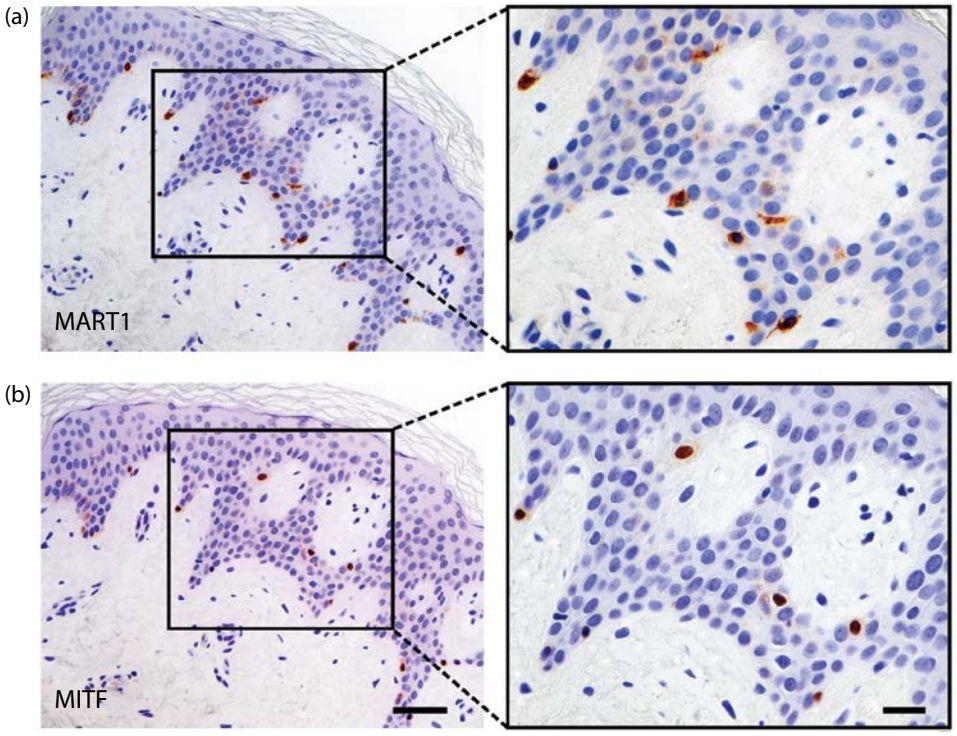

Figure 1.2 Serial sections of a skin specimen showing the presence of melanocytes identified using the melanocyte markers MART1 (melanoma antigen recognized by T cells 1) (melanosome structural protein) (a), and MITF (microphtalmia-associated transcription factor) (b). Nuclei are counterstained with hematoxylin. Right panels represent higher-magnification images of the black boxed areas. Scale bar: Left panels: 50 µm; higher-magnification images on the right panels: 20 µm.

MELANOCYTES AND MELANIN SYNTHESIS

A decisive aspect in determining skin color is the type of melanin synthesized by melanocytes. Melanin synthesis occurs within specialized membrane-bound organelles, the melanosomes, through four stages of maturation. Melanin arrangement inside melanosomes guarantees the protection of other cell compartments from oxidative stress produced during pigment synthesis and, at the same time, condensates melanin for its transfer to kertinocytes.[14] While maturing, melanosomes progressively acquire structural and enzymatic proteins, allowing them to produce pigment. At stage I, melanosomes appear as round vesicles without structural constituents. Progressing to stage II, they assemble into elongated fibrillar organelles containing structural (e.g., Pmel17—melanosomal matrix protein 17, also known as PMEL, SILV, gp100) and enzymatic proteins (tyrosinase), but they still lack pigment. Then, melanin synthesis begins and the produced pigment is placed on internal fibrils (stage III). At stage IV, melanosomes are mature and fully melanized. They are deprived of tyrosinase activity and are transferred along dendrites and then to the surrounding keratinocytes.[12] Within melanosomes, melanin synthesis occurs through a sequence of reactions guided by the coordinate actions of crucial enzymes, namely tyrosinase, tyrosinase-related protein 1 (TYRP-1),

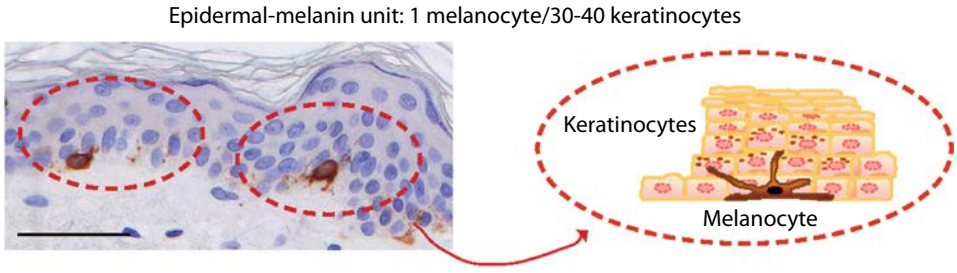

Figure 1.3 The epidermal-melanin unit showing the interactions between melanocytes and the surrounding keratinocytes. Left panel: Detection of melanocytes on a section of a skin specimen by immunohistochemical analysis of the expression of MART1. Scale bar: 50 µm.

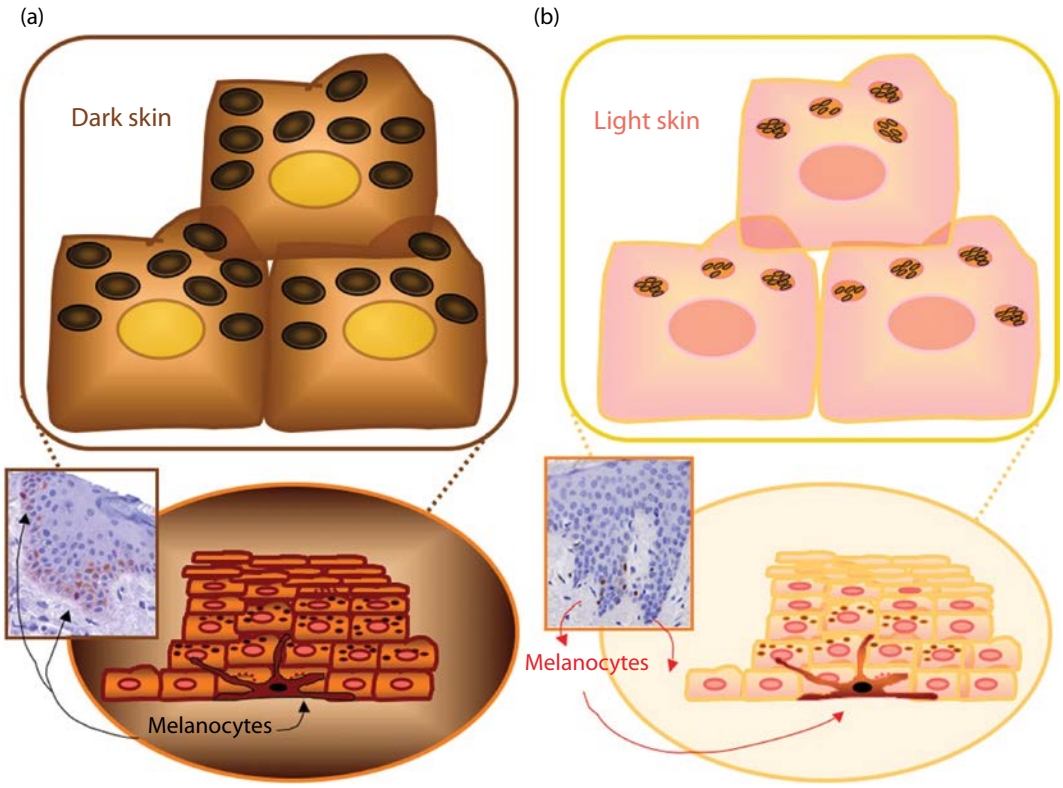

Figure 1.4 Pigmentation in dark and light skin. In dark-skinned people (left panel, a), melanosomes are large, abundant, and transferred to keratinocytes as singly packaged organelles. In light-skinned individuals (right panel, b), melanosomes are small, less matured, and transferred to keratinocytes as clusters in membrane-bound organelles, encompassing more melanosomes. Insert in a: immunohistochemical analysis of the expression of the melanocyte marker MITF in a darkly pigmented skin specimen. Arrows indicate stained melanocytes. Melanin pigment is observable inside basal and suprabasal keratinocytes. Insert in b: immunohistochemical analysis of the expression of the melanocyte marker MITF in a lightly pigmented skin specimen. Arrows indicate stained melanocytes.

and tyrosinase-related protein 2/dopachrome tautomerase (TYRP-2, DCT). The cooperation of these three enzymes leads to the production of two main melanin-type biopolymers: red-yellow pheomelanin and brown-black eumelanin. Melanogenic enzyme functionality and substrate obtainability drive the type of melanins produced. Tyrosinase governs the initial synthesis steps, hydroxylating L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) (the earliest melanogenesis rate restricting step) and subsequently oxidizing DOPA to DOPAquinone. At this point, when sulfhydryl groups such as L-cysteine are available, dopaquinone reacts with them, forming cysteinylDOPA isomers, including 5-S-cysteinylDOPA and 2-S-cysteinylDOPA. They are hence oxidized and polymerize, producing pheomelanins via benzothiazine intermediates. As sulfhydryl groups are not available, dopaquinone is spontaneously subjected to cyclization and rearrangement to DOPAchrome. DOPAchrome spontaneously decarboxylates into 5, 6 dihydroxyindole (DHI), forming, by rapid oxidation and polymerization, dark brown-black insoluble DHI-melanin. In the presence of the enzymatic protein dopachrome tautomerase (TYRP2, DCT), dopachrome will generate DHI-2-carboxylic-acid (DHICA). TYRP1 catalyzes further DHICA oxidation and polymerization, leading to light-brown, fairly soluble DHICA eumelanin[15] (Figures 1.5 and 1.6). Eumelanin is prevalent in dark-skinned/black-haired individuals and protects from UV damage. Pheomelanin, which is higher in people with fair skin and red hair, generates an increased amount of free radicals, thus inducing more harmful effects. Several genes involved in melanin synthesis and melanosome formation, as well as in pigment trafficking inside melanocytes and melanin transfer to keratinocytes, decisively influence the variations in pigmentation observed among human populations. Multiple genes are known to directly or indirectly impact pigmentation, and mutations of many of these genes may lead to pigmentary disorders, either as hyper- or hypopigmentation.[16,17]

MELANOSOME TRANSPORT INSIDE MELANOCYTES AND MELANOSOME TRANSFER TO KERATINOCYTES

As melanosomes differentiate, they progressively move from the melanocyte perinuclear area to the dendrite tips. Melanosome intracellular movement occurs both antero- and retrogradely, toward microtubule proteins belonging to the kinesin and dynein/dynein-associated protein superfamilies, respectively. In the dendrites,

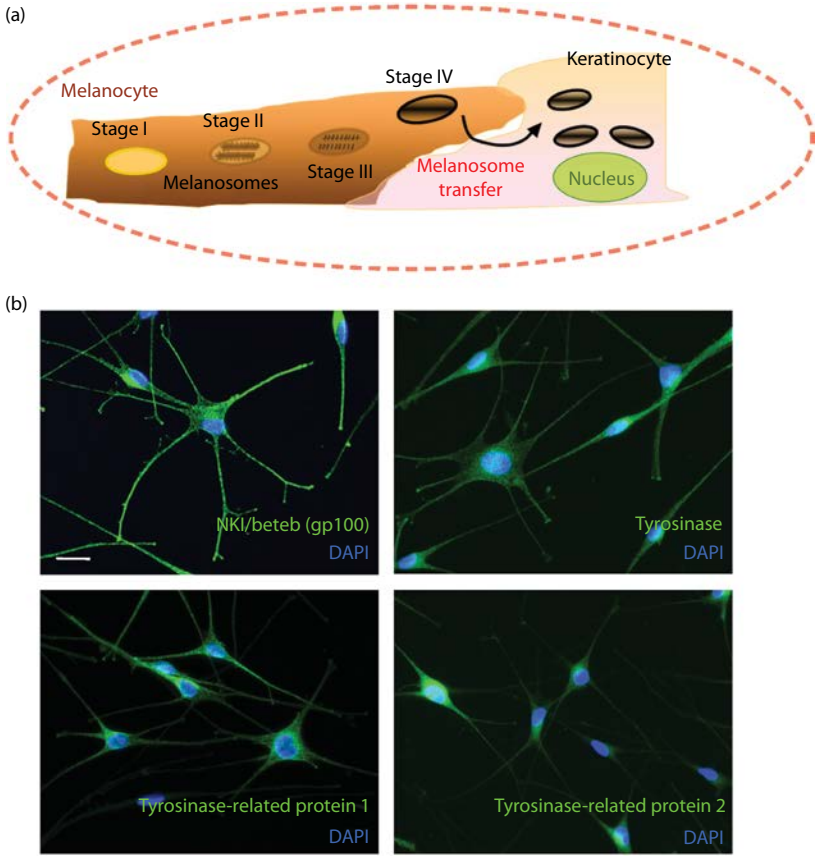

Figure 1.5 (a) Cartoon depicting the four stages of melanosome maturation within melanocytes. While maturing, melanosomes acquire the structural and enzymatic components necessary to produce melanin. (b) Immunofluorescence analysis of the expression of the structural melanosome-associated protein NKIbeteb/gp100 and of the enzymatic proteins tyrosinase, tyrosinase-related protein 1, and tyrosinase-related protein 2 in human primary melanocytes. Nuclei are counterstained with 4′,6′-diamidino-2 phenylindole (DAPI). Scale bar: 20 μm.

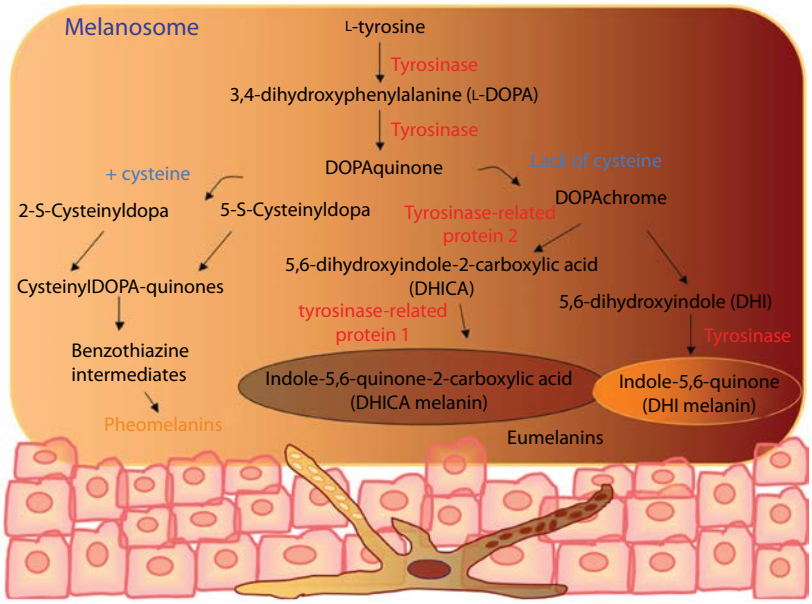

Figure 1.6 Melanin biosynthetic pathway. Two major melanin forms are synthesized within melanosomes: red-yellow pheomelanin and brown-black eumelanin.

melanosomes are then connected with peripheral actin filaments by a tripartite complex composed of the small GTPase Rab27a, its effector protein melanophillin, and the actin motor myosin Va, allowing their detachment from the microtubules and their settling close to the plasma membrane.[18,19] From the tips of the dendrites, fully melanized melanosomes are transferred to the neighboring keratinocytes, where they distribute as a supra-nuclear cap, aiming at protecting cell nuclei from the damaging effects of UV. Based on *in vitro* and ultrastructural studies, different models of melanosome intercellular transfer, which are not incompatible with each other, have been hypothesized: (i) Exocytosis of naked melanin (also referred to as melanocore) into the extracellular areas through the fusion of the melanocyte plasma- and melanosome membranes. The pigment particles are then taken up by the surrounding keratinocytes via phagocytosis. (ii) Cytophagocytosis: keratinocytes internalize melanocyte dendrite tips via phagocytosis. Subsequent fusion of lysosomes and dissolution of the melanosome membrane lead to the formation of phagolysosomes. The latter are then gradually degraded in vesicles containing melanin granules spread in the cytoplasm of keratinocytes. Filopodial phagocytosis, in which melanocyte filopodia containing melanosomes are phagocitosed by keratinocytes, has been also reported. (iii) Membrane fusion: melanosomes proceed via a thin, transient channel derived from the fusion of melanocyte-keratinocyte plasma membranes. Melanosome transfer by the fusion model has been also suggested to occur via melanocyte filopodia united with keratinocyte plasma membrane to form a tubular structure of actin filaments. (iv) Transfer through membrane-bound vesicles: melanocytes release membrane vesicles containing melanosomes, which are then phagocytosed by keratinocytes.[20–22]

Keratinocytes, for their part, actively participate in regulating the process of melanosome uptake. The expression of specific receptors on keratinocytes, but not on melanocytes, positively controls melanosome internalization. Among them, the G-protein-coupled protease-activated receptor 2 (PAR-2) is decisive in melanosome uptake by stimulating the process of phagocytosis. PAR-2 receptors are activated by proteolytic cleavage of their extracellular *N*-terminal domain via serine proteases. The cleavage discloses tethered ligands that bind the receptor, thus inducing its activation. Once activated, PAR-2 increases melanosome internalization by a Rho-dependent mechanism.[23,24] PAR-2 expression and activity are upregulated following UV[25] and are also correlated with skin color, showing more elevated levels with respect to lightly pigmented skin.[26] Melanosome transfer is also stimulated by the expression and activation of the keratinocyte growth factor receptor (KGFR) in early differentiated keratinocytes, where the levels of the receptor are increased. KGFR directly promotes the phagocytic process[27,28] (Figure 1.7).

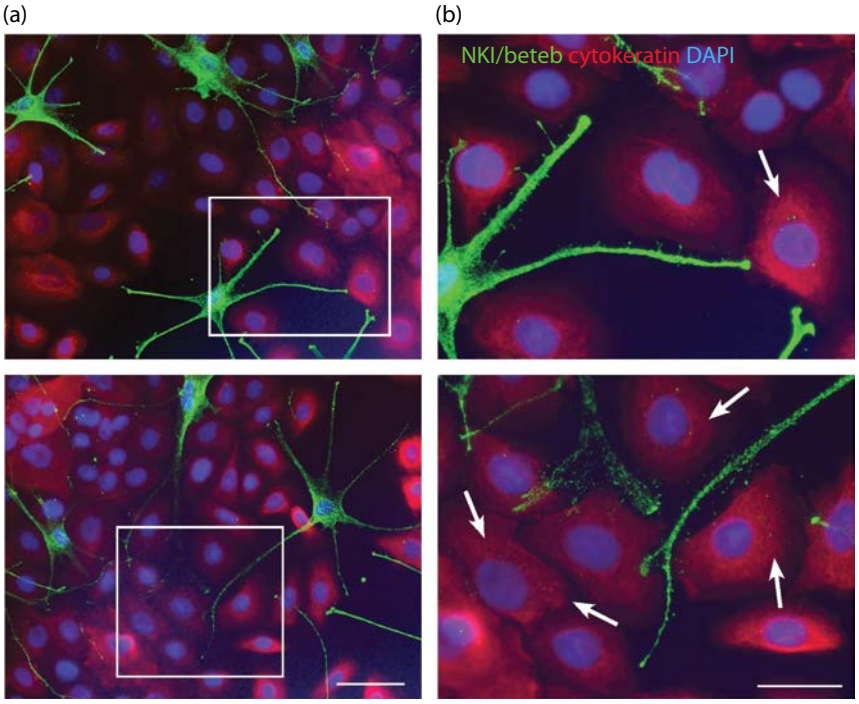

Figure 1.7 Double immunofluorescence staining of human primary melanocyte-keratinocyte co-cultures with anti-NKI-beteb antibody (green signal) to stain melanosomes and with anti-cytokeratin antibody (red signal) to detect keratinocytes. Intracytoplasmic dots positively stained for NKI-beteb are detectable in keratinocytes (white arrows), evidencing melanosome transfer. The images in (b) represent higher magnification of the boxed areas in (a). Scale bar: 50 µm.

CELL–CELL CROSSTALK IN THE CONTROL OF MELANOCYTE FUNCTIONALITY

Melanocyte homeostasis is guided by the active signaling crosstalk established with the surrounding epidermal and dermal microenvironment via secreted factors and intercellular connections.

Melanocyte-keratinocyte interactions

Keratinocytes impact melanocyte functions through adhesion molecules and an inter/intracellular network of paracrine/autocrine bioactive messengers, whose physiological release is upregulated in response to external triggers, first UV exposure and/or also inflammatory stimuli. Binding to their specific receptors, keratinocyte-derived mediators activate intracellular signaling pathways controlling the growth, survival, differentiation, and pigment synthesis of melanocytic cells.

Among these growth factor/receptor axes, the pro-opiomelanocortin (POMC) cleavage peptides alpha-melanocyte stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH), via signaling through the G protein-coupled receptor melanocortin 1 receptor (MC1R), are key players in the induction of melanocyte differentiation and melanin synthesis. Activation of MC1R through cAMP-dependent signaling promotes the upregulation of the transcription factor microphtalmia-associated transcription factor (MITF). MITF is considered a crucial transcription factor for melanocyte functions (Figure 1.8), regulating the transcription of pigmentation-related genes (e.g., tyrosinase, TYRP-1, TYRP-2, PMEL, MART1), thus promoting melanocyte differentiation, as well as genes linked to survival (e.g., Bcl-2), cell cycle, and metabolism (e.g., CDK2).[29] Through the induction of MITF and, consequently, the pigmentation-related genes, MC1R regulates the production of eu- versus pheomelanin. Activating the receptor by agonists such as α-MSH or ACTH, the production of eumelanin is stimulated. Differently, the action of an antagonist, for example, Agouti signaling protein, may lead to the synthesis of pheomelanin. MC1R variants with a weak functionality are observed in fair-skinned/red-haired people, who are characterized by a prevalence of pheomelanin, a feeble potential for tanning, and increased risk for melanoma and nonmelanoma skin cancers.[30] Upon UV exposure, direct transcriptional activation of POMC/alpha-MSH occurs in keratinocytes by the tumor-suppressor protein p53,[31] thus promoting melanocyte functions. Besides its central role in regulating pigmentation, MC1R influences several other processes, not only in melanocytes but also in the skin microenvironment in its entirety, maintaining genomic integrity, controlling oxidative stress, and promoting the antioxidant defense system.[32] Recently, a connection between MC1R and nuclear receptor activation has been described, further underlying the multitude of functions guided by MC1R in cells and tissues. α-MSH has been shown to activate the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ) through the induction of the phosphatidylinositol [PI(4,5)P2/PLCβ] signal pathway, demonstrating how MC1R has a role in controlling extrapigmentary functions such as proliferation via lipid mediators.[32,33]

Many other melanocyte mitogen and melanogen factors are produced by keratinocytes, for example, stem cell factor (SCF), endothelin-1 (ET-1), basic fibroblast growth factor (bFGF/FGF2), granulocyte-macrophage colony-stimulating factor (GM-CSF), and hepatocyte growth factor (HGF). As for α-MSH, the synthesis of most of them is significantly increased following UV irradiation. ET-1 acts, binding to endothelin receptor type B (EDNRB), promoting melanocyte growth and melanogenesis.[34] The SCF/c-kit tyrosine kinase receptor axis favors melanocyte survival and melanin production.[35] Comparable to POMC, the transcription and synthesis of both ET-1 and SCF are stimulated by p53.[36] Along with growth factors, other mediators released by keratinocytes in the course of biological processes such as inflammation or wound healing may function as activators of melanocytes. Among them, the arachidonic acid–derived lipid molecules prostaglandins E2 and F2a stimulate melanocyte dendricity and melanogenesis.[37] Keratinocytes secrete also nerve growth factor (NGF), which is implicated in melanocyte dendrite formation and melanin synthesis, survival, and migration.[38] In

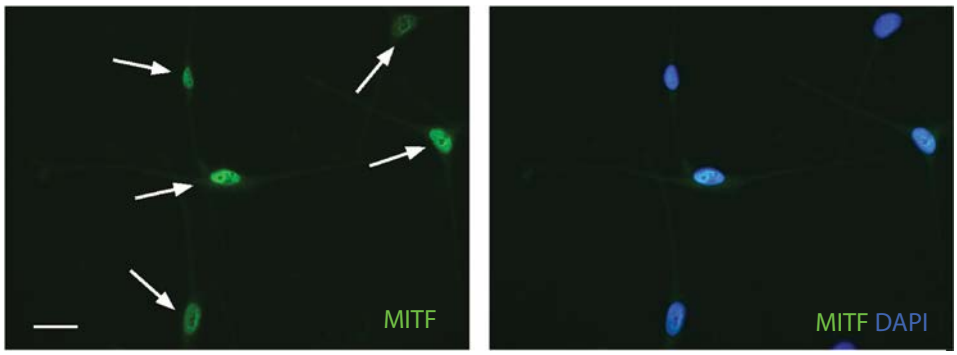

Figure 1.8 Immunofluorescence analysis of MITF expression (white arrows) in primary cultures of human melanocytes. Nuclei are counterstained with DAPI. Scale bar: 20 μm.

the finely balanced crosstalk between keratinocytes and melanocytes, alongside messengers acting as positive inducers of the functionality of the latter, keratinocytes also release some inhibiting factors. TGF-β inhibits melanocyte proliferation, differentiation, and melanin synthesis. The production of TGF-β in keratinocytes is suppressed upon UV exposure, and such an event allows the upregulation of the transcription factor SOX3 in melanocytes, thus stimulating the pigmentation process.[39] Keratinocytes, as well as melanocytes themselves, express bone morphogenic proteins (BMPs), signaling molecules belonging to the TGFβ1 superfamily. Among them, BMP-4 is able to inhibit melanogenesis, decreasing tyrosinase expression. On the contrary, BMP-6 acts in the opposite way, stimulating melanin synthesis through the induction of tyrosinase expression and activity, together with melanin transfer from melanocytes to keratinocytes.[40,41] Following UV exposure, keratinocytes are also stimulated to synthesize the cytokine interferon gamma (IFN-γ), which exerts an inhibitory effect on pigmentation, decreasing the expression of enzymes deputed to melanin biosynthesis, thus impeding melanosome maturation.[42] Additional keratinocyte-derived cytokines with downregulating effects on melanization and melanocyte proliferation are interleukin 6 (IL-6), interleukin 1 alpha (IL-1α), and tumor necrosis factor alpha (TNF-α)[43] (Figure 1.9a).

Melanocyte-fibroblast interactions

Dermal fibroblasts play an active role in modulating melanocyte homeostasis through the secretion of growth factors and cytokines, which act both in a synergistic and sometimes overlapping fashion with respect to the keratinocyte-mediated signaling network. Additionally, some paracrine messengers released by fibroblasts can indirectly target melanocyte functions, inducing the production of biofactors able to either block or stimulate melanocyte activities in keratinocytes. Similar to growth factors and cytokines synthesized by keratinocytes, in this intricate epithelial-mesenchymal interaction, some fibroblastic bioactive messengers act as melanocyte activators, others as inhibitors. The physiological hypopigmented phenotype of the palms and soles has been attributed to increased expression of the Wnt pathway antagonist dickkopf1 (DKK1) in these body areas. This site-specific fibroblast-derived factor exerts a dual action: on the one hand, it suppresses melanocyte growth and melanin synthesis, and on the other, it acts on keratinocytes, decreasing the expression of the proteinase-activated receptor 2 actively involved in the process of melanosome transfer.[44] Furthermore, fibroblasts share with keratinocytes the production of TGF-β, with repressive properties on melanocytes.[39] However, the largest number of fibroblast-derived messengers exert a positive action on melanocyte activities, acting on their growth, survival, migration, and pigment production. Some of these pro-pigmenting mediators are also produced by epidermal cells, for example, SCF, HGF, and bFGF;

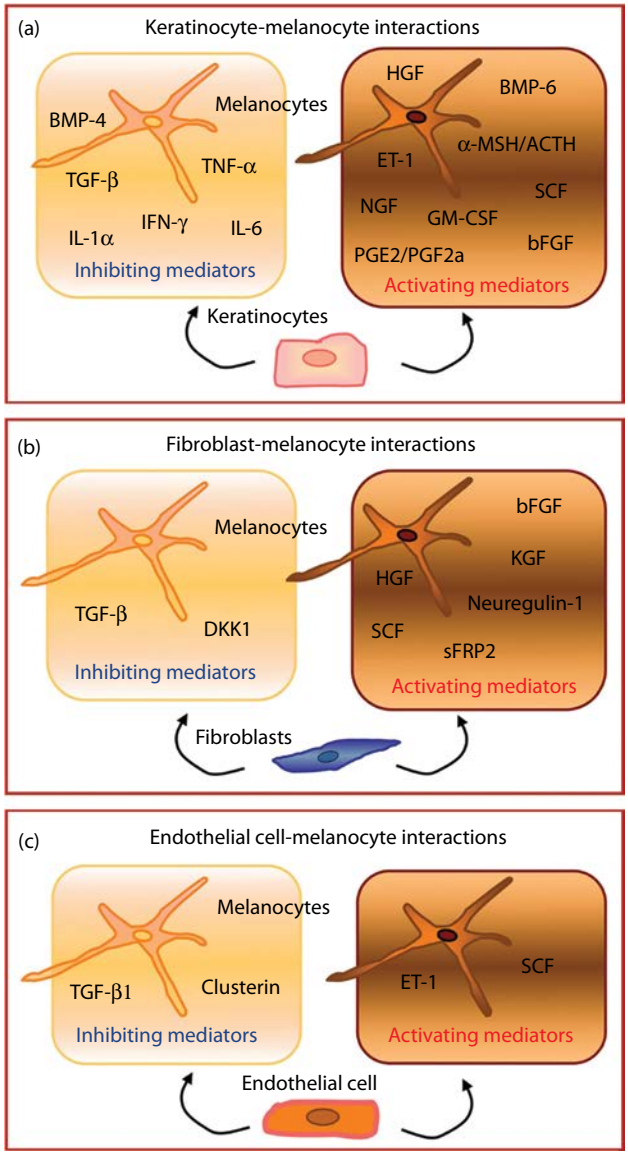

Figure 1.9 Summary of the stimulating and inhibiting bioactive mediators involved in the regulation of melanocyte functionalities. (a) Keratinocyte-derived messengers. (b) Fibroblast-derived messengers. (c) Endothelial cell-derived messengers.

others are exclusively of fibroblastic origin. Among the latter, neuregulin-1 has been demonstrated to be highly expressed in fibroblasts of type VI skin, where it positively participates in the regulation of constitutive pigmentation of darker skin.[45] Keratinocyte growth factor (KGF) belongs to the family of fibroblast growth factors and represents a further mesenchymal-specific pro-pigmenting paracrine mediator. KGF directly promotes melanosome transfer via activation of its receptor KGFR in keratinocytes. Additionally, it upregulates the synthesis and release of SCF from keratinocytes, thus indirectly promoting melanocyte pro-pigmenting and pro-growing activities. It has been also demonstrated that the treatment with KGF alone or in combination with IL-1α increases melanin production and

deposition in pigmented epidermal equivalents and human skin explants.[27,46,47] The Wnt modulator secreted frizzled-related protein 2 (sFRP2) has been recently discovered as a further fibroblast-secreted stimulating factor, thanks to its ability to increase the expression levels of MITF and tyrosinase through beta catenin signaling[48] (Figure 1.9b).

Melanocyte-endothelial cell interactions

In the complex scenario of the epidermal-dermal interactions emerging as crucially involved in mediating melanocyte homeostasis under both physiological and pathological conditions, several reports have now been focused on the epithelial/endothelial cell–cell interplay. However, contradictory effects are reported in the literature, showing both positive and negative regulatory abilities of vascular endothelial cells on the process of pigmentation. A stimulatory effect of endothelial cell-derived ET-1 on melanogenesis, via the signaling pathway of the EDNRB on melanocytes, has been reported.[49] On the other hand, subsequent studies demonstrated the ability of endothelial cells to inhibit pigmentation via the secretion of high amounts of TGF-β1 and/or clusterin, which downregulate MITF and tyrosinase, thus keeping the level of produced pigment low.[50,51] Interestingly, upon UV irradiation, endothelial cells are activated to secrete increased levels of SCF, responsible for the paracrine stimulation of melanocytes and consequently increasing skin pigmentation[52] (Figure 1.9c).

EXTRACELLULAR MATRIX MICROENVIRONMENT AND MELANOCYTE HOMEOSTASIS

The epidermal and dermal extracellular matrix (ECM) microenvironment influences a large number of skin functions, for example, cell–cell crosstalk, adhesion, support, and migration. Dynamic interplays among extracellular matrix proteins, cells, and bioactive mediators are also critical regulators of melanocyte activities and cutaneous pigmentation. Early studies demonstrated the ability of several ECM proteins derived from dermal fibroblasts and endothelial cells (e.g., collagen I, collagen IV, fibronectin) to increase proliferation and tyrosinase activity in melanocytes cultured in media lacking mitogens.[53] More recently, the keratinocyte-derived ECM factor laminin-332 has been shown to promote the adhesion and migration of melanocytes,[54] as well as the synthesis of melanin by stimulating the extracellular uptake of the pigment precursor tyrosine.[55] ECM components also constitute a reservoir for cytokines and growth factors, thus regulating their local amount and activity. For instance, an uncontrolled degradation of heparan sulfate at the dermal-epidermal junction, as happens for the activation of heparanase following UV exposure, may result in excessive diffusion through the basement membrane of heparin-binding growth factors, such as the pro-pigmenting factors HGF and FGFs. Consequently, the uncontrolled propagation of growth factors and cytokines among the epidermis and dermis may inappropriately activate melanocytes.[56]

CONCLUDING REMARKS

Despite the relatively low number of melanocytes distributed throughout the epidermis in comparison to their neighboring keratinocytes, these cells represent intriguing and master players in the control of a multitude of cutaneous biological functions. Melanocyte homeostasis has been guided, over time, by both intrinsic and extrinsic factors (above all, UV exposure) that have contributed and are still contributing to the development and evolution of the pigmentary system. All these influences create an intricate and finely balanced signaling crosstalk, in which melanocytes exert a central and dynamic role in controlling the equilibrium and protection of the skin in its entirety. On the other hand, the network of bioactive messengers acts bidirectionally to and from the melanocytes toward the other dermal and epidermal cells. As a result, this mutual interaction confers on the whole cutaneous microenvironment the ability to strongly influence melanocytes themselves and therefore to contribute to both constitutive pigmentation and, whenever altered, to the onset and persistence of pigmentary disorders.

REFERENCES

1. Jablonski NG, Chaplin G. Colloquium paper: Human skin pigmentation as an adaptation to UV radiation. *Proc Natl Acad Sci USA*. 2010;107(Suppl 2):8962–8968.
2. Jablonski NG, Chaplin G. The colours of humanity: The evolution of pigmentation in the human lineage. *Philos Trans R Soc Lond B Biol Sci*. 2017;372(1724).
3. Jones P, Lucock M, Veysey M, Beckett E. The vitamin D–folate hypothesis as an evolutionary model for skin pigmentation: An update and integration of current ideas. *Nutrients*. 2018;10:554.
4. Gunathilake R, Schurer NY, Shoo BA et al. pH-regulated mechanisms account for pigment-type differences in epidermal barrier function. *J Invest Dermatol*. 2009;129:1719–1729.
5. Elias PM, Williams ML. Re-appraisal of current theories for the development and loss of epidermal pigmentation in hominins and modern humans. *J Hum Evol*. 2013;64:687–692.
6. Elias PM, Williams ML. Basis for the gain and subsequent dilution of epidermal pigmentation during human evolution: The barrier and metabolic conservation hypotheses revisited. *Am J Phys Anthropol*. 2016;161:189–207.
7. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. *Nature*. 2007;445:843–850.
8. Kawakami A, Fisher DE. Key discoveries in melanocyte development. *J Invest Dermatol*. 2011;131(E1):E2–E4.
9. Plonka PM, Passeron T, Brenner M et al. What are melanocytes really doing all day long…? *Exp Dermatol*. 2009;18:799–819.
10. McGill GG, Horstmann M, Widlund HR et al. Bcl2 regulation by the melanocyte master regulator MITF modulates lineage survival and melanoma cell viability. *Cell*. 2002;109:707–718.

11. Thong HY, Jee SH, Sun CC, Boissy RE. The patterns of melanosome distribution in keratinocytes of human skin as one determining factor of skin colour. *Br J Dermatol*. 2003;149:498–505.
12. Costin GE, Hearing VJ. Human skin pigmentation: Melanocytes modulate skin color in response to stress. *FASEB J*. 2007;21:976–994.
13. Ebanks JP, Koshoffer A, Wickett RR et al. Epidermal keratinocytes from light vs. dark skin exhibit differential degradation of melanosomes. *J Invest Dermatol* 2011;131:1226–1233.
14. Denat L, Kadekaro AL, Marrot L et al. Melanocytes as instigators and victims of oxidative stress. *J Invest Dermatol* 2014;134:1512–1518.
15. Nguyen NT, Fisher DE. MITF and UV responses in skin: From pigmentation to addiction. *Pigment Cell Melanoma Res*. 2019;32:224–236.
16. Sturm RA. Molecular genetics of human pigmentation diversity. *Hum Mol Genet*. 2009;18:R9–17.
17. Yamaguchi Y, Hearing VJ. Melanocytes and their diseases. *Cold Spring Harb Perspect Med*. 2014;4:pii: a017046.
18. Barral DC, Seabra MC. The melanosome as a model to study organelle motility in mammals. *Pigment Cell Res*. 2004;17:111–118.
19. Wasmeier C, Hume AN, Bolasco G, Seabra MC. Melanosomes at a glance. *J Cell Sci*. 2008; 121:3995–3999.
20. Van Den Bossche K, Naeyaert JM, Lambert J. The quest for the mechanism of melanin transfer. *Traffic*. 2006;7:769–778.
21. Singh SK, Kurfurst R, Nizard C et al. Melanin transfer in human skin cells is mediated by filopodia—A model for homotypic and heterotypic lysosome-related organelle transfer. *FASEB J*. 2010;24:3756–3769.
22. Tadokoro R, Takahashi Y. Intercellular transfer of organelles during body pigmentation. *Curr Opin Genet Dev*. 2017;45:132–138.
23. Seiberg M. Keratinocyte-melanocyte interactions during melanosome transfer. *Pigment Cell Res*. 2001;14:236–242.
24. Scott G, Leopardi S, Parker L et al. The proteinase-activated receptor-2 mediates phagocytosis in a Rho-dependent manner in human keratinocytes. *J Invest Dermatol*. 2003;121:529–541.
25. Scott G, Deng A, Rodriguez-Burford C et al. Protease-activated receptor 2, a receptor involved in melanosome transfer, is upregulated in human skin by ultraviolet irradiation. *J Invest Dermatol*. 2001;117:1412–1420.
26. Babiarz-Magee L, Chen N, Seiberg M, Lin CB. The expression and activation of protease-activated receptor-2 correlate with skin color. *Pigment Cell Res*. 2004;17:241–251.
27. Cardinali G, Ceccarelli S, Kovacs D et al. Keratinocyte growth factor promotes melanosome transfer to keratinocytes. *J Invest Dermatol*. 2005;125:1190–1199.
28. Belleudi F, Purpura V, Scrofani C et al. Expression and signaling of the tyrosine kinase FGFR2b/KGFR regulates phagocytosis and melanosome uptake in human keratinocytes. *FASEB J*. 2011;25:170–181.
29. Kawakami A, Fisher DE. The master role of microphthalmia-associated transcription factor in melanocyte and melanoma biology. *Lab Invest*. 2017;97:649–656.
30. Yamaguchi Y, Brenner M, Hearing VJ. The regulation of skin pigmentation. *J Biol Chem*. 2007;282:27557–27561.
31. Cui R, Widlund HR, Feige E et al. Central role of p53 in the suntan response and pathologic hyperpigmentation. *Cell*. 2007;128:853–864.
32. Maresca V, Flori E, Picardo M. Skin phototype: A new perspective. *Pigment Cell Melanoma Res*. 2015;28:378–389.
33. Flori E, Rosati E, Cardinali G et al. The α-melanocyte stimulating hormone/peroxisome proliferator activated receptor-γ pathway down-regulates proliferation in melanoma cell lines. *J Exp Clin Cancer Res*. 2017;36:142.
34. Imokawa G, Yada Y, Miyagishi M. Endothelins secreted from human keratinocytes are intrinsic mitogens for human melanocytes. *J Biol Chem*. 1992;267:24675–24680.
35. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev*. 2004; 84:1155–1228.
36. Murase D, Hachiya A, Amano Y et al. The essential role of p53 in hyperpigmentation of the skin via regulation of paracrine melanogenic cytokine receptor signaling. *J Biol Chem*. 2009;284:4343–4353.
37. Scott G, Leopardi S, Printup S et al. Proteinase-activated receptor-2 stimulates prostaglandin production in keratinocytes: Analysis of prostaglandin receptors on human melanocytes and effects of PGE2 and PGF2alpha on melanocyte dendricity. *J Invest Dermatol*. 2004;122:1214–1224.
38. Truzzi F, Marconi A, Pincelli C. Neurotrophins in healthy and diseased skin. *Dermatoendocrinol*. 2011;3:32–36.
39. Yang G, Li Y, Nishimura EK et al. Inhibition of PAX3 by TGF-beta modulates melanocyte viability. *Mol Cell*. 2008;32:554–563.
40. Yaar M, Wu C, Park HY et al. Bone morphogenetic protein-4, a novel modulator of melanogenesis. *J Biol Chem*. 2006;281:25307–25314.
41. Singh SK, Abbas WA, Tobin DJ. Bone morphogenetic proteins differentially regulate pigmentation in human skin cells. *J Cell Sci*. 2012;125:4306–4319.
42. Natarajan VT, Ganju P, Singh A et al. IFN g signaling maintains skin pigmentation homeostasis through regulation of melanosome maturation. *Proc Natl Acad Sci USA*. 2014;111:2301–2306.

43. Swope VB, Abdel-Malek Z, Kassem LM, Nordlund JJ. Interleukins 1 alpha and 6 and tumor necrosis factor-alpha are paracrine inhibitors of human melanocyte proliferation and melanogenesis. *J Invest Dermatol*. 1991;96:180–185.
44. Yamaguchi Y, Morita A, Maeda A, Hearing VJ. Regulation of skin pigmentation and thickness by Dickkopf 1 (DKK1). *J Investig Dermatol Symp Proc*. 2009;14:73–75.
45. Choi W, Wolber R, Gerwat W et al. The fibroblast-derived paracrine factor neuregulin-1 has a novel role in regulating the constitutive color and melanocyte function in human skin. *J Cell Sci*. 2010;123(Pt 18):3102–3111.
46. Kovacs D, Cardinali G, Aspite N et al. Role of fibroblast-derived growth factors in regulating hyperpigmentation of solar lentigo. *Br J Dermatol*. 2010;163:1020–1027.
47. Chen N, Hu Y, Li WH et al. The role of keratinocyte growth factor in melanogenesis: A possible mechanism for the initiation of solar lentigines. *Exp Dermatol*. 2010;19:865–872.
48. Kim M, Han JH, Kim JH et al. Secreted frizzled-related protein 2 (sFRP2) functions as a melanogenic stimulator; the role of sFRP2 in UV-induced hyperpigmentary disorders. *J Invest Dermatol*. 2016; 136:236–244.
49. Regazzetti C, De Donatis GM et al. Endothelial cells promote pigmentation through endothelin receptor B activation. *J Invest Dermatol*. 2015;135:3096–3104.
50. Park JY, Kim M, Park TJ, Kang HY. TGFb1 derived from endothelial cells inhibits melanogenesis. *Pigment Cell Melanoma Res*. 2016;29:477–480.
51. Kim M, Lee J, Park TJ, Kang HY. Paracrine crosstalk between endothelial cells and melanocytes through clusterin to inhibit pigmentation. *Exp Dermatol*. 2018;27:98–100.
52. Kim M, Shibata T, Kwon S et al. Ultraviolet-irradiated endothelial cells secrete stem cell factor and induce epidermal pigmentation. *Sci Rep*. 2018;8:4235.
53. Hedley S, Gawkrodger DJ, Weetman AP, MacNeil S. Investigation of the influence of extracellular matrix proteins on normal human melanocyte morphology and melanogenic activity. *Br J Dermatol*. 1996;135:888–897.
54. Chung H, Suh EK, Han IO, Oh ES. Keratinocyte-derived laminin-332 promotes adhesion and migration in melanocytes and melanoma. *J Biol Chem*. 2011;286:13438–13447.
55. Chung H, Jung H, Lee JH et al. Keratinocyte-derived laminin-332 protein promotes melanin synthesis via regulation of tyrosine uptake. *J Biol Chem*. 2014; 289:21751–21759.
56. Iriyama S, Ono T, Aoki H, Amano S. Hyperpigmentation in human solar lentigo is promoted by heparanase-induced loss of heparan sulfate chains at the dermal-epidermal junction. *J Dermatol Sci*. 2011;64:223–228.

1. Dessinioti C, Stratigos AJ, Rigopoulos D, Katsambas AD. A review of genetic disorders of hypopigmentation: Lessons learned from the biology of melanocytes. *Exp Dermatol*. 2009;18(9):741–749.
2. Mollet I, Ongenae K, Naeyaert JM. Origin, clinical presentation, and diagnosis of hypomelanotic skin disorders. *Dermatol Clin*. 2007;25(3):363–371, ix.
3. Ortonne JP, Bahadoran P, Fitzaptrick TB et al. Hypomelanoses and hypermelanoses. In: Freedberg IM, Eisen AZ, Woff K. et al., eds. *Fitzpatrick's Dermatology in General Medicine*. New York: McGraw-Hill; 2003:836–881.
4. Saleem MD, Oussedik E, Schoch JJ, Berger AC, Picardo M. Acquired disorders with depigmentation: A systematic approach to vitiliginoid conditions. *J Am Acad Dermatol*. 2018.
5. Saleem MD, Oussedik E, Picardo M, Schoch JJ. Acquired disorders with hypopigmentation: A clinical approach to diagnosis and treatment. *J Am Acad Dermatol*. 2018.
6. Narayanan V. Tuberous sclerosis complex: Genetics to pathogenesis. *Pediatr Neurol*. 2003;29(5):404–409.
7. Tomita Y, Suzuki T. Genetics of pigmentary disorders. *Am J Med Genet C Semin Med Genet*. 2004;131C(1):75–81.
8. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. *Nature*. 2007;445(7130):843–850.
9. Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism. *Proc Natl Acad Sci USA*. 1991;88(19):8696–8699.
10. Dessinioti C, Stratigos AJ. Piebaldism. https://www.dermatologyadvisor.com/dermatology/piebaldism/article/691421/. Accessed January 2, 2019.
11. Zazo Seco C, Serrao de Castro L, van Nierop JW et al. Allelic mutations of KITLG, encoding KIT ligand, cause asymmetric and unilateral hearing loss and Waardenburg syndrome type 2. *Am J Hum Genet*. 2015;97(5):647–660.
12. Liu XZ, Newton VE, Read AP. Waardenburg syndrome type II: Phenotypic findings and diagnostic criteria. *Am J Med Genet*. 1995;55(1):95–100.
13. Smith SD, Kelley PM, Kenyon JB, Hoover D. Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF. *J Med Genet*. 2000;37(6):446–448.
14. Wei ML. Hermansky-Pudlak syndrome: A disease of protein trafficking and organelle function. *Pigm Cell Res*. 2006;19(1):19–42.
15. Minic S, Trpinac D, Obradovic M. Incontinentia pigmenti diagnostic criteria update. *Clin Genet*. 2014;85(6):536–542.
16. Ezzedine K, Lim HW, Suzuki T et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012;25(3):E1–E13.

17. Gogas H, Ioannovich J, Dafni U et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med*. 2006;354(7):709–718.
18. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49(4):243–254.
19. Fitzpatrick TB, Szabo G, Hori Y, Simone AA, Reed WB, Greenberg MH. White leaf-shaped macules. Earliest visible sign of tuberous sclerosis. *Arch Dermatol*. 1968;98(1):1–6.
20. Teng JM, Cowen EW, Wataya-Kaneda M et al. Dermatologic and dental aspects of the 2012 International Tuberous Sclerosis Complex Consensus statements. *JAMA Dermatol*. 2014;150(10):1095–1101.
21. Arbiser JL. Efficacy of rapamycin in tuberous sclerosis-associated hypopigmented macules: Back to the future. *JAMA Dermatol*. 2015;151(7):703–704.
22. Wataya-Kaneda M, Tanaka M, Yang L et al. Clinical and histologic analysis of the efficacy of topical rapamycin therapy against hypomelanotic macules in tuberous sclerosis complex. *JAMA Dermatol*. 2015;151(7):722–730.
23. Jozwiak S, Sadowski K, Kotulska K, Schwartz RA. Topical use of mammalian target of rapamycin (mTOR) inhibitors in tuberous sclerosis complex-A comprehensive review of the literature. *Pediatr Neurol*. 2016;61:21–27.
24. Malissen N, Vergely L, Simon M, Roubertie A, Malinge MC, Bessis D. Long-term treatment of cutaneous manifestations of tuberous sclerosis complex with topical 1% sirolimus cream: A prospective study of 25 patients. *J Am Acad Dermatol*. 2017;77(3):464–472. e463.

1. Nordlund JJ. The medical treatment of vitiligo: An historical review. *Dermatol Clin*. 2017;35(2):107–116.
2. Koranne RV, Sachdeva KG. Vitiligo. *Int J Dermatol*. December 1988;27(10):676–681.
3. Adams, F. (Trans.-Ed.). *The Genuine Works of Hippocrates*. London: The Sydenham Society, 1848.
4. Najamabadi M. *Tarikh-e-Tibbe-Iran*, Volume I. Teheran, Iran: Shamsi, 1934.
5. Ebbel B. *The Papyrus Ebers*. Copenhagen: Levin and Munskgaard, 1937.
6. Gauthier Y, Benzekri L. Historical aspects. In: Picardo M, Taieb A, eds. *Vitiligo*. Berlin, Heidelberg: Springer-Verlag; 2010:3–9.
7. Kopera D. History and cultural aspects of vitiligo. In: Hann S-K, Nordlund J, eds. *Vitiligo: A Monograph on the Basic and Clinical Science*. Oxford, UK: Blackwell Scientific Publishers; 2000:13–17.
8. Panda AK. The medicohistorical perspective of vitiligo. *Bull Ind Hist Med* 2005;25:41–46.
9. Hann SK, Chung HS. Historic view of vitiligo in Korea. *Int J Dermatol* 1997;36:313–315.
10. Lee S. Vitiligo auf einem historischen Portrait. *Hautarzt* 1982;33:335–336.
11. Brocq L, ed. *Traitment des Maladies de la Peau*. Paris: Doin, 1892:853–855.
12. Kaposi M, ed. *Pathologie and Therapie der Hautkrankheiten*. 5th ed. Berlin/Wien: Urban and Schwarzenberg, 1st ed, 1879:703–707.
13. Prasad PV, Bhatnagar VK. Medico-historical study of "Kilasa" (vitiligo/leucoderma) a common skin disorder. *Bull Ind Inst Hist Med* 2003;33:113–127.
14. Goldman L, Richard S, Moraites R. White spots in biblical times. *Arch Derm* 1966;93:744–753.
15. Brito PS. On leucoderma, vitiligo, ven kuttam (Tamil) or cabbare (Singhalese), and several new methods of treatment. *Br Med J* 1885;1(1269):834–835.
16. Singh G, Ansari Z, Dwivedi RN. Letter: Vitiligo in ancient Indian medicine. *Arch Dermatol*. 1974; 109(6):913.
17. Nair BK. Vitiligo—A retrospect. *Int J Dermatol*. 1978;17(9):755–917.
18. Shree Gulabkunverba Ayurvedic Society, ed. *Charaka Samhita*. Jamnagar, India: Shree Gulabkunverba Ayurvedic Society, 1949.
19. Khushboo PS, Jadhav VM, Kadam VJ, Sathe NS. *Psoralea corylifolia* Linn.—"*Kushtanashini*." *Pharmacogn Rev*. 2010;4(7):69–76.
20. Hann SK, Nordlund JJ, editors. *Vitiligo: A Monograph on the Basic and Clinical Science*. New York: John Wiley & Sons, 2008.
21. Menon AN. Ultra-violet therapy in cases of leucoderma. *Ind Med Gaz* 1945;80:612–614.
22. Fahmy IR, Abu-Shady H, Schönberg AA. Crystalline principle from *Ammi majus* L., *Nature* 1947;160(4066):468.
23. Fahmy IR, Abu-Shady H. *Ammi majus* Linn: The isolation and properties of ammoidin, ammidin and majudin, and their effect in the treatment of leukoderma. *QJ Pharm Pharmacol*. 1948;21(4): 499–503.
24. El-Mofty AM. A preliminary clinical report on the treatment of leukoderma with *Ammi majus* Linn, *J Egypt Med Assoc*. 1948;31:651–665.
25. Lerner AB, Denton CR, Fitzpatrick TB. Clinical and experimental studies with 8-methoxypsoralen in vitiligo. *J Invest Dermatol*. 1953;20(4):299–314.
26. Pathak MA, Mosher DB, Fitzpatrick TB. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5′,8-trimethylpsoralen, and psoralen in vitiligo. *Natl Cancer Inst Monogr*. 1984;66:165–173.
27. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *N Engl J Med*. 1974;291(23):1207–1211.
28. Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *J Photochem Photobiol B*. 1992;30(14):3–22.

29. Parsad D, Kanwar AJ, Kumar B. Psoralen-ultraviolet A vs. narrow-band ultraviolet B phototherapy for the treatment of vitiligo. *J Eur Acad Dermatol Venereol*. 2006;20(2):175–177.
30. Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Arch Dermatol*. 1997;133(12):1525–1528.
31. Scherschun L, Kim JJ, Lim HW. Narrow-band ultraviolet B is a useful and well-tolerated treatment for vitiligo. *J Am Acad Dermatol*. 2001;44(6):999–1003.
32. Whitton ME, Pinart M, Batchelor J, Leonardi-Bee J, González U, Jiyad Z, Eleftheriadou V, Ezzedine K. Interventions for vitiligo. *Cochrane Database Syst Rev*. 2015;(2):CD003263.
33. Kandil E. Vitiligo: Response to 0.2% betamethasone 17-valerate in flexible collodion. *Dermatologica*. 1970;141:277–81.
34. Kandil E. Treatment of vitiligo with 0.1% betamethasone 17-valerate in isopropyl alcohol: A double blind trial. *Br J Dermatol*. 1974;91:457–460.
35. Koopmans-van DB, Goedhart-van DB, Neering H, van Dijk E. The treatment of vitiligo by local application of betamethasone 17-valerate in a dimethyl sulfoxide cream base. *Dermatologica*. 1973;146:310–314.
36. Bleehen SS. The treatment of vitiligo with topical corticosteroids. Light and electronmicroscopic studies. *Br J Dermatol*. March 1976;94(Suppl 12):43–50.
37. Clayton R. A double-blind trial of 0%–05% clobetasol proprionate in the treatment of vitiligo. *Br J Dermatol*. 1977;96(1):71–73.
38. Kumari J. Vitiligo treated with topical clobetasol propionate. *Arch Dermatol*. 1984;120(5):631–635.
39. Liu XQ, Shao CG, Jin PY, Wang HQ, Ye GY, Yawalkar S. Treatment of localized vitiligo with ulobetasol cream. *Int J Dermatol*. May 1990;29(4):295–297.
40. Westerhof W, Nieuweboer-Krobotova L, Mulder PG, Glazenburg EJ. Left-right comparison study of the combination of fluticasone propionate and UV-A vs. either fluticasone propionate or UV-A alone for the long-term treatment of vitiligo. *Arch Dermatol*. 1999;135(9):1061–1066.
41. Grimes PE, Soriano T, Dytoc MT. Topical tacrolimus for repigmentation of vitiligo. *J Am Acad Dermatol*. 2002;47(5):789–791.
42. Smith DA, Tofte SJ, Hanifin JM. Repigmentation of vitiligo with topical tacrolimus. *Dermatology*. 2002;205(3):301–303.
43. Grimes PE, Morris R, Avaniss-Aghajani E, Soriano T, Meraz M, Metzger A. Topical tacrolimus therapy for vitiligo: Therapeutic responses and skin messenger RNA expression of proinflammatory cytokines. *J Am Acad Dermatol*. 2004;51(1):52–61.
44. Mayoral FA, Gonzalez C, Shah NS, Arciniegas C. Repigmentation of vitiligo with pimecrolimus cream: A case report. *Dermatology*. 2003;207(3):322–323.
45. Dash B, Kashyap L, eds. *Diagnosis and Treatment of Diseases in Ayurveda*, Volume 5. New Delhi, India: Concept Publishing Company, 1991.
1. Lotti T, Hautmann G, Hercogovà J. Vitiligo: Disease or symptom? From the confusion of the past to current doubts. In: Lotti T, Hercogovà J, eds. *Vitiligo. Problems and Solutions*. New York: Marcel Dekker; 2004:1–14.
2. Lee BW, Schwartz RA, Hercogová J, Valle Y, Lotti TM. Vitiligo road map. *Dermatol Ther*. 2012;25(Suppl C):S44–S56.
3. Taïeb A, Picardo M; VETF Members. The definition and assessment of vitiligo: A consensus report of the Vitiligo European Task Force. *Pigment Cell Res*. 2007;20:27–35.
4. Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. *Int J Dermatol* 2012;51:1206–1212.
5. Alzolibani AA, Robaee AA, Zedan K. Genetic epidemiology and heritability of vitiligo. In: Dr. Hwa Park KK. ed. *Vitiligo—Management and Therapy*. 2011.
6. Sehgal VN, Srivastava G. Vitiligo: Compendium of clinico-epidemiological features. *Indian J Dermatol Venereol Leprol*. 2007;73:149–156.
7. Howitz J, Brodthagen H, Schwartz M et al. Prevalence of vitiligo. Epidemiological survey on the Isle of Bornholm, Denmark. *Arch Dermatol*. 1977;113:47–52.
8. Lotti T, Hanna D, Buggiani G, Urple M. The color of the skin: Psycho-anthropologic implications. *JCosmet Dermatol*. 2005;4(3):219–220.
9. Ahmed I, Ahmed S, Nasreen S. Frequency and pattern of psychiatric disorders in patients with vitiligo. *J Ayub Med Coll Abbottabad*. 2007;19(3):19–21.
10. Handa S, Kaur I. Vitiligo: Clinical findings in 1436 patients. *J Dermatol*. 1999;26:653–657.
11. Lotti TM, Berti SF, Hercogova J et al. Vitiligo: Recent insights and new therapeutic approaches. *G Ital Dermatol Venereol*. 2012;147(6):637–647.
12. Wang X, Du J, Tinglin Wang T et al. Prevalence and clinical profile of vitiligo in China: A community based study in six cities. *Acta Derm Venereol*. 2013;93:62–65.
13. McBurney E. Vitiligo: Clinical picture and pathogenesis. *Arch Intern Med*. 1979;139:1295–1297.
14. Alikhan A, Felsten LM, Daly M et al. Vitiligo: A comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *J Am Acad Dermatol*. 2011;65:473–491.
15. Behl PN, Kotia A, Sawal P. Vitiligo: Age group related trigger factor and morphological variants. *Indian J Dermatol Venereol Lepr*. 1994;60:275–279.
16. Nicolaidou E, Antoniou C, Miniati A et al. Childhood- and later-onset vitiligo have diverse epidemiologic and clinical characteristics. *J Am Acad Dermatol*. 2012;66:954–958.

17. Ezzedine K, Diallo A, Léauté-Labrèze C et al. Pre- vs. post-pubertal onset of vitiligo: Multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo. *Br J Dermatol*. 2012;167:490–495.
18. Al-Refu K. Vitiligo in children: A clinical-epidemiologic study in Jordan. *Pediatr Dermatol*. 2012;29:114–115.
19. van Geel N, Mollet I, Brochez L et al. New insights in segmental vitiligo: Case report and review of theories. *Br J Dermatol*. 2012;166:240–246.
20. Sun XK, Xu AE, Meng W et al. Study on genetic epidemiology on 815 patients with vitiligo in the Zhejiang area. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2005;26:911–914.
21. Spritz RA. Modern vitiligo genetics sheds new light on an ancient disease. *J Dermatol*. 2013;40(5): doi:10.1111/1346-8138.12147.
22. Laberge G, Mailloux CM, Gowan K et al. Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. *Pigment Cell Res*. 2005;18:300–305.
23. Alkhateeb A, Fain PR, Thody A et al. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. *Pigment Cell Res*. 2003;16:208–214.
24. Jin Y, Ferrara T, Gowan K et al. Next-generation DNA re-sequencing identifies common variants of TYR and HLA-A that modulate the risk of generalized vitiligo via antigen presentation. *J Invest Dermatol*. 2012;132(6):1730–1733.
25. Zhang XJ, Chen JJ, Liu JB. The genetic concept of vitiligo. *J Dermatol Sci*. 2005;39(3):137–146.
26. Lotti T, D'Erme AM. Vitiligo as a systemic disease. *Clin Dermatol*. 2014;32(3):430–434.
27. Nejad SB, Qadim HH, Nazeman L et al. Frequency of autoimmune diseases in those suffering from vitiligo in comparison with normal population. *Pak J Biol Sci*. 2013;16(12):570–574.
28. Gill L, Zarbo A, Isedeh P et al. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. *J Am Acad Dermatol*. 2016;74(2):295–302.
29. Chen YT, Chen YJ, Hwang CY et al. Comorbidity profiles in association with vitiligo: A nationwide population-based study in Taiwan. *J Eur Acad Dermatol Venereol*. 2015;29(7):1362–1369.
30. Pietrzak A, Bartosińska J, Hercogová J et al. Metabolic syndrome in vitiligo. *Dermatol Ther*. 2012;(25 Suppl 1):S41–S43.
31. Spritz RA. The genetics of generalized vitiligo: Autoimmune pathways and an inverse relationship with malignant melanoma. *Genome Med*. 2010;2:78.
32. Silverberg JI, Reja M, Silverberg NB. Regional variation of and association of US birthplace with vitiligo extent. *JAMA Dermatol*. 2014;150(12):1298–305.
33. Lee DY, Kim CR, Lee JH. Trichrome vitiligo in segmental type. *Photodermatol Photoimmunol Photomed*. 2011;27(2):111–112.
34. Chandrashekar L. Dermatoscopy of blue vitiligo. *Clin Exp Dermatol*. 2009;34(5):e125–e126.
35. Huggins RH, Janusz CA, Schwartz RA. Vitiligo: A sign of systemic disease. *Indian J DermatolVenereolLeprol*. 2006;72:68–71.
36. Akay BN, Bozkir M, Anadolu Y et al. Epidemiology of vitiligo, associated autoimmune diseases and audiological abnormalities: Ankara study of 80 patients in Turkey. *J Eur Acad Dermatol Venereol*. 2010;24(10):1144–1150.
37. Anbar T, Hay RA, Abdel-Rahman AT et al. Clinical study of nail changes in vitiligo. *J Cosmet Dermatol*. 2013;12:67–72.
38. Ezzedine K, Lim HW, Suzuki T et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012;25(3):E1–13.
39. Ezzedine K, Gauthier Y, Léauté-Labrèze C et al. Segmental vitiligo associated with generalized vitiligo (mixed vitiligo): A retrospective case series of 19 patients. *J Am Acad Dermatol*. 2011;65:965–971.
40. Kovacevic M, Stanimirovic A, Vucic M et al. Mixed vitiligo of Blaschko lines: A newly discovered presentation of vitiligo responsive to combination treatment. *Dermatol Ther*. 2016;29(4): 240–243.
41. Hann SK, Lee HJ. Segmental vitiligo: Clinical findings in 208 patients. *J Am Acad Dermatol*. 1996;35:671–674.
42. Hercogová J, Schwartz RA, Lotti TM. Classification of vitiligo: A challenging endeavor. *Dermatol Ther*. 2012;25(Suppl 1):S10–S16.
1. Tobin DJ, Swanson NN, Pittelkow MR et al. Melanocytes are not absent in lesional skin of long duration vitiligo. *J Pathol*. 2000;191(4):407–416.
2. Schallreuter KU, Bahadoran P, Picardo M et al. Vitiligo pathogenesis: Autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? *Exp Dermatol*. 2008;17(2):139–140.
3. Boniface K, Seneschal J, Picardo M et al. Vitiligo: Focus on clinical aspects, immunopathogenesis and therapy. *Clin Rev Allergy Immunol*. 2018;54(1):52–67.
4. Cavalli G, Hayashi M, Jin Y et al. MHC class II super-enhancer increases surface expression of HLA-DR and HLA-DQ and affects cytokine production in autoimmune vitiligo. *Proc Natl Acad Sci USA*. 2016;113(5):1363–1368.
5. Jin Y, Andersen G, Yorgov D et al. Genome-wide association studies of autoimmune vitiligo identify 23 new risk loci and highlight key pathways and regulatory variants. *Nat Genet*. 2016;48(11):1418–1424.
6. Cheong KA, Chae SC, Kim YS et al. Association of thymic stromal lymphopoietin gene −847C>T polymorphism in generalized vitiligo. *Exp Dermatol*. 2009;18(12):1073–1075.

7. Birlea SA, Jin Y, Bennett DC et al. Comprehensive association analysis of candidate genes for generalized vitiligo supports *XBP1*, *FOXP3* and *TSLP*. *J Invest Dermatol*. 2011;131:371–381.
8. Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol*. 2010;11(4):289–293.
9. Guerra L, Dellambra E, Brescia S et al. Vitiligo: Pathogenetic hypotheses and targets of current therapies. *Curr Drug Metab*. 2010;11(5):451–467.
10. Salem MM, Shalbaf M, Gibbons NC et al. Enhanced DNA binding capacity on up-regulated epidermal wild-type p53 in vitiligo by H_2O_2-mediated oxidation: A possible repair mechanism for DNA damage. *FASEB*. 2009;23(11):3790–3807.
11. Moretti S, Fabbri P, Baroni G et al. Keratinocyte dysfunction in vitiligo epidermis: Cytokine microenvironment and correlation to keratinocyte apoptosis. *Histol Histopathol*. 2009;24(7):849–857.
12. McGill GG, Horstmann M, Widlund HR et al. Bcl-2 regulation by the melanocyte master regulator MITF modulates lineage survival and melanoma cell viability. *Cell*. 2002;109:707–718.
13. Wańkowicz-Kalińska A, van de Wijngaard RM, Tigges BJ et al. Immunopolarization of CD4+ and CD8+ T cells to type-1-like is associated with melanocyte loss in human vitiligo. *Lab Invest*. 2003;83(5):683–695.
14. Aroni K, Voudouris S, Ioannidis E et al. Increased angiogenesis and mast cells in the center compared to the periphery of vitiligo lesions. *Arch Dermatol Res*. 2010;302:601–607.
15. Mandelcorn-Monson RL, Shear NH, Yay E et al. Cytotoxic T lymphocyte reactivity to gp100, MelanA/MART1 and tyrosinase in HLA-A2-positive vitiligo patients. *J Invest Dermatol*. 2003;121:550–556.
16. Van Geel N, Speeckaert R, Taieb A et al. on behalf of the other VETF members. Koebner's phenomenon in vitiligo: European position paper. *Pigment Cell Melanoma Res*. 2011;24(3):564–573.
17. Van den Boorn JG, Konijnenberg D, Dellemijn TA et al. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. *J Invest Dermatol*. 2009;129(9):2220–2232.
18. Rashighi M, Agarwal P, Richmond JM et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med*. 2014;6(223):223ra23.
19. Sandoval-Cruz M, Garcia-Carrasco M, Sánchez-Porras R et al. Immunopathogenesis of vitiligo. *Autoimmune Rev*. 2011;10(21):762–765.
20. Waterman EA, Gawkrodger DJ, Watson PF et al. Autoantigens in vitiligo identified by the serological selection of a phage-displayed melanocyte cDNA expression library. *J Invest Dermatol*. 2010;130(1):230–240.
21. Kemp EH, Emhemad S, Akhtar S et al. Autoantibodies against tyrosinase hydroxylase in patients with non-segmental (generalized) vitiligo. *Exp Dermatol*. 2011;20(1):35–40.
22. Mohler T, Scheibenbogen C, Hafele J et al. Regulation of interleukin-8 mRNA expression and protein secretion in a melanoma cell line by tumour necrosis factor-alpha and interferon-gamma. *Melanoma Res*. 1996;6:307–311.
23. Norgauer J, Dichmann S, Peters F et al. Tumor necrosis factor alpha induces upregulation of CXC-chemokine receptor type II expression and magnifies the proliferative activity of CXC-chemokines in human melanocytes. *Eur J Dermatol*. 2003;13:124–129.
24. Luger TA, Schwarz T. Evidence of an epidermal cytokine network. *J Invest Dermatol*. 1990;95:100–14S.
25. Miniati A, Weng Z, Zhang B et al. Stimulated human melanocytes express and release interleukin-8, which is inhibited by luteolin: Relevance to early vitiligo. *Clin and Experimental Dermatol*. 2014;39:54–57.
26. Toosi S, Orlow SJ, Manga P. Vitiligo-inducing phenols activate the unfolded protein response in melanocytes resulting in upregulation of IL-6 and IL-8. *J Invest Dermatol*. 2012;132:2601–2609.
27. Arck PC, Slominski AT, Theoharides TC et al. Neuroimmunology of stress: Skin takes center stage. *J Invest Dermatol*. 2006;126(8):1697–1704.
28. Slominski AT, Wortsman J. Neuroendocrinology of the skin. *Endocr Rev*. 2000;21:457–487.
29. Donelan J, Boucher W, Papadopoulou N et al. Corticotropin-releasing hormone induces skin vascular permeability through a neurotensin-dependent process. *Proc Natl Acad Sci USA*. 2006;103(20):7759–7764.
30. Slominski AT, Tobin DJ, Shibahara S et al. Melanin pigmentation in mammalian skin and its hormone regulation. *Physiol Rev*. 2004;84:1155–1228.
31. Dessinioti C, Antoniou C, Katsambas A et al. Melanocortin 1 receptor variants: Functional role and pigmentary associations. *Photochem Photobiol*. 2011;87(5):978–987.
32. Kingo K, Aunin E, Karelson M et al. Gene expression analysis of melanocortin system in vitiligo. *J Dermatol Sci*. 2007;48(2):113–122.
33. Traks T, Keermann M, Karelson M et al. Polymorphism in melanocortin system and MYG1 genes are associated with vitiligo. *J Eur Acad Dermatol Venereol*. 2019;33(2):e65–e67.
34. Agretti P, De Marco G, Sansone D et al. Patients affected by vitiligo and autoimmune diseases do not show antibodies interfering with the activity of the melanocortin 1 receptor. *J Endocrinol Invest*. 2010;33(11):784–788.
1. Koga M. Vitiligo: A new classification and therapy. *Br J Dermatol*. 1977;97:255–261.

2. Ezzedine K, Lim HW, Suzuki T et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012; 25:E1–E13.
3. van Geel NA, Mollet IG, De Schepper S et al. First histopathological and immunophenotypic analysis of early dynamic events in a patient with segmental vitiligo associated with halo nevi. *Pigment Cell Melanoma Res*. 2010;23:375–384.
4. Taieb A, Morice-Picard F, Jouary T et al. Segmental vitiligo as the possible expression of cutaneous somatic mosaicism: Implications for common non-segmental vitiligo. *Pigment Cell Melanoma Res*. 2008;21:646–652.
5. Koga M, Tango T. Clinical features and course of type A and type B vitiligo. *Br J Dermatol*. 1988; 118:223–228.
6. el-Mofty AM, el-Mofty M. Vitiligo. A symptom complex. *Int J Dermatol*. 1980;19:237–244.
7. Hann SK, Lee HJ. Segmental vitiligo: Clinical findings in 208 patients. *J Am Acad Dermatol*. 1996;35:671–674.
8. Barona MI, Arrunategui A, Falabella R et al. An epidemiologic case-control study in a population with vitiligo. *J Am Acad Dermatol*. 1995;33:621–625.
9. Hann SK, Park YK, Chun WH. Clinical features of vitiligo. *Clin Dermatol*. 1997;15:891–897.
10. Ezzedine K, Diallo A, Leaute-Labreze C et al. Halo naevi and leukotrichia are strong predictors of the passage to mixed vitiligo in a subgroup of segmental vitiligo. *Br J Dermatol*. 2012; 166:539–544.
11. Ezzedine K, Gauthier Y, Leaute-Labreze C et al. Segmental vitiligo associated with generalized vitiligo (mixed vitiligo): A retrospective case series of 19 patients. *J Am Acad Dermatol*. 2011;65: 965–971.
12. van Geel N, De Lille S, Vandenhaute S et al. Different phenotypes of segmental vitiligo based on a clinical observational study. *J Eur Acad Dermatol Venereol*. 2011;25:673–678.
13. Mulekar SV, Al Issa A, Asaad M et al. Mixed vitiligo. *J Cutan Med Surg*. 2006;10:104–107.
14. Schallreuter KU, Kruger C, Rokos H et al. Basic research confirms coexistence of acquired Blaschkolinear vitiligo and acrofacial vitiligo. *Arch Dermatol Res*. 2007;299:225–230.
15. Schallreuter KU, Kruger C, Wurfel BA et al. From basic research to the bedside: Efficacy of topical treatment with pseudocatalase PC-KUS in 71 children with vitiligo. *Int J Dermatol*. 2008;47:743–753.
16. Wu CS, Yu HS, Chang HR et al. Cutaneous blood flow and adrenoceptor response increase in segmental-type vitiligo lesions. *J Dermatol Sci*. 2000;23:53–62.
17. Silverberg NB. Update on childhood vitiligo. *Curr Opin Pediatr*. 2010;22:445–452.
18. Wang X, Du J, Wang T et al. Prevalence and clinical profile of vitiligo in China: A community-based study in six cities. *Acta Derm Venereol*. 2013;93:62–65.
19. Nicolaidou E, Antoniou C, Miniati A et al. Childhood- and later-onset vitiligo have diverse epidemiologic and clinical characteristics. *J Am Acad Dermatol*. 2012;66:954–958.
20. Lerner AB. Vitiligo. *J Invest Dermatol*. 1959;32:285–310.
21. Hann SK, Chang JH, Lee HS et al. The classification of segmental vitiligo on the face. *Yonsei Med J*. 2000;41:209–212.
22. Park JH, Jung MY, Lee JH et al. Clinical course of segmental vitiligo: A retrospective study of eighty-seven patients. *Ann Dermatol*. 2014;26:61–65.
23. Gauthier Y, Cario Andre M, Taieb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? *Pigment Cell Res*. 2003;16:322–332.
24. Happle R. [Segmental type 2 manifestation of autosome dominant skin diseases. Development of a new formal genetic concept]. *Hautarzt*. 2001;52:283–287.
25. Happle R. Superimposed segmental manifestation of polygenic skin disorders. *J Am Acad Dermatol*. 2007;57:690–699.
26. Gauthier Y, Taïb A. Proposal for a new classification of segmental vitiligo of the face. *Pigment Cell Melanoma Res*. 2006;19:515.
27. Bae JM, Yoo HJ, Kim H, Lee JH, Kim GM. Combination therapy with 308-nm excimer laser, topical tacrolimus, and short-term systemic corticosteroids for segmental vitiligo: A retrospective study of 159 patients. *J Am Acad Dermatol*. 2015;73:76–82.
28. Ezzedine K, Eleftheriadou V, Whitton M et al. Vitiligo. *Lancet*. 2015;386:74–84.
1. Kruger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. *Int J Dermatol*. 2012;51:1206–1212.
2. Malhotra N, Dytoc M. The pathogenesis of vitiligo. *J Cutan Med Surg*. 2013;17:153–172.
3. Ezzedine K, Lim HW, Suzuki T et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012;25:E1–13.
4. Nicolaidou E, Antoniou C, Miniati A, Lagogianni E, Matekovits A, Stratigos A, Katsambas A. Childhood- and later-onset vitiligo have diverse epidemiologic and clinical characteristics. *J Am Acad Dermatol*. 2012;66:954–958.
5. Ezzedine K, Diallo A, Léauté-Labrèze C et al. Pre- vs. post-pubertal onset of vitiligo: Multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo. *Br J Dermatol* 2012;167:490–495.
6. Agarwal S, Gupta S, Ojha A, Sinha R. Childhood vitiligo: Clinicoepidemiologic profile of 268 children from Kumaun region of Uttarakhand, India. *Pediatr Dermatol* 2013;30:348–353.

7. Halder RM, Grimes PE, Cowan CA, Enterline JA, Chakrabarti SG, Kenney JA. Childhood vitiligo. *J Am Acad Dermatol*. 1987;16:948–954.
8. Cho S, Kang H-C, Hahm J-H. Characteristics of vitiligo in Korean children. *Pediatr Dermatol*. 2000;17:189–193.
9. Howitz J, Brodthagen H, Schwartz M, Thomsen K. Prevalence of vitiligo. Epidemiological survey of the Isle of Bornholm, Denmark. *Arch Dermatol*. 1977;113:47–52.
10. Wang X, Du J, Wang T et al. Prevalence and clinical profile of vitiligo in China: A community-based study in six cities. *Acta Derm Venereol*. 2013;93:62–65.
11. Handa S, Dogra S. Epidemiology of childhood vitiligo: A study of 625 patients from North India. *Pediatr Dermatol*. 2003;20:207–210.
12. Hu Z, Liu J-B, Ma S-S, Yang S, Zhan XJ. Profile of childhood vitiligo in China: An analysis of 541 patients. *Pediatr Dermatol*. 2006;23:114–116.
13. Marinho Fde S, Cirino PV, Fernandes NC. Clinical epidemiological profile of vitiligo in children and adolescents. *An Bras Dermatol*. 2013;17:1096–1099.
14. Pajvani U, Ahmad N, Wiley A et al. The relationship between family medical history and childhood vitiligo. *J Am Acad Dermatol*. 2006;55: 238–244.
15. Mu EW, Cohen BE, Orlow SJ. Early-onset childhood vitiligo is associated with a more extensive and progressive course. *J Am Acad Dermatol*. 2015;73 :467–470.
16. A-Refu K. Vitiligo in children: A clinical-epidemiologic study in Jordan. *Pediatr Dermatol*. 2012;29:114–115.
17. Alikhan A, Felsten LM, Daly M et al. Vitiligo: A comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *J Am Acad Dermatol*. 2011;65:473–491.
18. Gan EY, Cario-André M, Pain C et al. Follicular vitiligo: A report of 8 cases. *J Am Acad Dermatol*. 2016;74:1178–1184.
19. Silverberg JI, Silverberg NB. Quality of life impairment in children and adolescents with vitiligo. *Pediatr Dermatol*. 2014;31:309–318.
20. Silverberg NB. Pediatric vitiligo. *Pediatr Clin North Am*. 2014;61:347–366.
21. van Geel N, Speeckaert M, Brochez L et al. Clinical profile of generalized vitiligo patients with associated autoimmune/autoinflammatory diseases. *J Eur Acad Dermatol Venereol*. 2014;28(6):741–746.
22. Iacovelli P, Sinagra JL, Vidolin AP et al. Relevance of thyroiditis and of other autoimmune diseases in children with vitiligo. *Dermatology*. 2005;210:26–30.
23. Kakourou T, Kanaka-Gantenbein C, Papadopoulou A et al. Increased prevalence of chronic autoimmune (Hashimoto's) thyroiditis in children and adolescents with vitiligo. *J Am Acad Dermatol*. 2005;53:220–223.
24. Kartal D, Borlu M, Çinar SL et al. Thyroid abnormalities in paediatric patients with vitiligo: Retrospective study. *Postepy Dermatol Alergol*. 2016;33(3):232–234.
25. Cho SB, Kim JH, Cho S et al. Vitiligo in children and adolescents: Association with thyroid dysfunction. *J Eur Acad Dermatol Venereol*. 2011;25:64–67.
26. Mazereeuw-Hautier J, Bezio S, Mahe E et al. Segmental and nonsegmental childhood vitiligo has distinct clinical characteristics: A prospective observational study. *J Am Acad Dermatol*. 2010;62:945–949.
27. Cohen BE, Mu EW, Orlow SJ. Comparison of childhood vitiligo presenting with or without associated halo nevi. *Pediatr Dermatol*. 2016;33:44–48.
28. Patrizi A, Bentivogli M, Raone B et al. Association of halo nevus/i and vitiligo in childhood: A retrospective observational study. *J Eur Acad Dermatol Venereol*. 2013;27(2):e148–e152.
29. Ezzedine K, Diallo A, Léauté-Labrèze C et al. Halo nevi association in nonsegmental vitiligo affects age at onset and depigmentation pattern. *Arch Dermatol*. 2012;148(4):497–502.
30. Bilgiç O, Bilgiç A, Akiş HK et al. Depression, anxiety and health-related quality of life in children and adolescents with vitiligo. *Clin Exp Dermatol*. 2011;36(4):360–365.
31. Krüger C, Panske A, Schallreuter KU. Disease-related behavioral patterns and experiences affect quality of life in children and adolescents with vitiligo. *Int J Dermatol*. 2014;53(1):43–50.
32. Catucci Boza J, Giongo N, Machado P et al. Quality of life impairment in children and adults with vitiligo: A cross-sectional study based on dermatology-specific and disease-specific quality of life instruments. *Dermatology*. 2016;232(5):619–625.
33. Amer AA, Mchepange UO, Gao XH et al. Hidden victims of childhood vitiligo: Impact on parents' mental health and quality of life. *Acta Derm Venereol*. 2015;95(3):322–325.
34. Manzoni AP, Weber MB, Nagatomi AR et al. Assessing depression and anxiety in the caregivers of pediatric patients with chronic skin disorders. *An Bras Dermatol*. 2013;88(6):894–899.
35. van Geel N, Speeckaert M, Chevolet I et al. Hypomelanoses in children. *J Cutan Aesthet Surg*. 2013;6(2):65–72.
36. Taieb A, Alomar A, Böhm M et al. Guidelines for the management of vitiligo: The European Dermatology Forum consensus. *Br J Dermatol*. 2013;168(1):5–19.
37. Kwinter J, Pelletier J, Khambalia A et al. High-potency steroid use in children with vitiligo: A retrospective study. *J Am Acad Dermatol*. 2007;56(2):236–241.
38. Ho N, Pope E, Weinstein M et al. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs. clobetasol propionate 0.05% in childhood vitiligo. *Br J Dermatol*. 2011;165(3):626–632.

39. Köse O, Arca E, Kurumlu Z. Mometasone cream versus pimecrolimus cream for the treatment of childhood localized vitiligo. *J Dermatolog Treat*. 2010;21(3):133–139.
40. Rodrigues M, Ezzedine K, Hamzavi I et al. Current and emerging treatments for vitiligo. *J Am Acad Dermatol*. 2017;77(1):17–29.
41. Wu CS, Yu CL, Wu CS, Lan CCE, Yu HS. Narrow-band ultraviolet-B stimulates proliferation and migration of cultured melanocytes. *Exp Dermatol*. 2004;13:755–763.
42. Nicolaidou E, Antoniou C, Stratigos A et al. Narrowband ultraviolet B phototherapy and 308-nm excimer laser in the treatment of vitiligo: A review. *J Am Acad Dermatol*. 2009;60(3):470–477.
43. Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *J Am Acad Dermatol*. 2000;42:245–253.
44. Koh MJ, Mok ZR, Chong WS. Phototherapy for the treatment of vitiligo in Asian children. *Pediatr Dermatol*. 2015;32(2):192–197.
45. Percivalle S, Piccinno R, Caccialanza M et al. Narrowband ultraviolet B phototherapy in childhood vitiligo: Evaluation of results in 28 patients. *Pediatr Dermatol*. 2012;29(2):160–165.
46. Nicolaidou E, Antoniou C, Stratigos AJ, Stefanaki C, Katsambas AD. Efficacy, predictors of response and long-term follow-up in vitiligo patients treated with narrow band UVB phototherapy. *J Am Acad Dermatol*. 2007;56:274–278.
47. Kanwar AJ, Dogra S. Narrow-band UVB for the treatment of generalized vitiligo in children. *Clin Exp Dermatol*. 2005;30(4):332–336.
48. Esfandiarpour I, Ekhlasi A, Farajzadeh S et al. The efficacy of pimecrolimus 1% cream plus narrow-band ultraviolet B in the treatment of vitiligo: A double-blind, placebo-controlled clinical trial. *J Dermatolog Treat*. 2009;20(1):14–18.
49. Majid I. Does topical tacrolimus ointment enhance the efficacy of narrowband ultraviolet B therapy in vitiligo? A left-right comparison study. *Photodermatol Photoimmunol Photomed*. 2010;26(5):230–234.
50. Dayal S, Sahu P, Gupta N. Treatment of childhood vitiligo using tacrolimus ointment with narrowband ultraviolet B phototherapy. *Pediatr Dermatol*. 2016;33(6):646–651.
51. Ezzedine K, Silverberg N. A practical approach to the diagnosis and treatment of vitiligo in children. *Pediatrics*. 2016;138(1):e20154126.
52. Cho S, Zheng Z, Park YK et al. The 308-nm excimer laser: A promising device for the treatment of childhood vitiligo. *Photodermatol Photoimmunol Photomed*. 2011;27(1):24–29.
53. Koh MJ, Mok ZR, Chong WS. Phototherapy for the treatment of vitiligo in Asian children. *Pediatr Dermatol*. 2015;32(2):192–197.
54. Hui-Lan Y, Xiao-Yan H, Jian-Yong F et al. Combination of 308-nm excimer laser with topical pimecrolimus for the treatment of childhood vitiligo. *Pediatr Dermatol*. 2009;26(3):354–356.
55. Hu JJ, Xu AE, Wu XG et al. Small-sized lesions of childhood vitiligo treated by autologous epidermal grafting. *J Dermatolog Treat*. 2012;23(3):219–223.
56. Sahni K, Parsad D, Kanwar AJ. Noncultured epidermal suspension transplantation for the treatment of stable vitiligo in children and adolescents. *Clin Exp Dermatol*. 2011;36(6):607–612.
57. Mulekar SV, Al Eisa A, Delvi MB et al. Childhood vitiligo: A long-term study of localized vitiligo treated by noncultured cellular grafting. *Pediatr Dermatol*. 2010;27(2):132–136.
58. Hong WS, Hu DN, Qian GP et al. Treatment of vitiligo in children and adolescents by autologous cultured pure melanocytes transplantation with comparison of efficacy to results in adults. *J Eur Acad Dermatol Venereol*. 2011;25(5):538–543.
59. Yao L, Li SS, Zhong SX et al. Successful treatment of vitiligo on the axilla in a 5-year-old child by cultured-melanocyte transplantation. *J Eur Acad Dermatol Venereol*. 2012;26(5):658–660.
1. van den Wijngaard R, Wankowicz-Kalinska A, Pals S, Weening J, Das P. Autoimmune melanocyte destruction in vitiligo. *Lab Invest*. 2001;81:1061–1067.
2. Njoo MD, Spuls PI, Bos JD, Westerhof W, Bossuyt PM. Nonsurgical repigmentation therapies in vitiligo: Meta-analysis of the literature. *Arch Dermatol*. 1998;134:1532–1540.
3. Schaffer JV, Bolognia JL. The treatment of hypopigmentation in children. *Clin Dermatol*. 2003;21:296–310.
4. Lotti T, Berti S, Moretti S. Vitiligo therapy. *Expert Opin Pharmacother*. 2009;10:2779–2785.
5. Whitton M, Pinart M, Batchelor JM et al. Evidence-Based Management of vitiligo: Summary of a Cochrane systematic review. *Br J Dermatol*. 2015; 174:962–969.
6. Taieb A, Alomar A, Böhm M et al. Guidelines for the management of vitiligo: The European Dermatology Forum consensus. *Br J Dermatol*. 2013;168:5–19.
7. Kwinter J, Pelletier J, Khambalia A, Pope E. High-potency steroid use in children with vitiligo: A retrospective study. *J Am Acad Dermatol*. 2007;56:236–241.
8. Kandil E. Treatment of vitiligo with 0-1 per cent betamethasone 17-valerate in isopropyl alcohol – A double-blind trial. *Br J Dermatol*. 1974;91:457–460.
9. Clayton R. A double-blind trial of 0–05% clobetasol proprionate in the treatment of vitiligo. *Br J Dermatol*. 1977;96:71–73.
10. Khalid M, Mujtaba G, Haroon TS. Comparison of 0.05% clobetasol propionate cream and topical Puvasol in childhood vitiligo. *Int J Dermatol*. 1995;34:203–205.
11. Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A

double-blind randomized trial of 0.1% tacrolimus vs. 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol*. 2003;139:581–585.
12. Kumaran MS, Kaur I, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol*. 2006;20:269–273.
13. Sanclemente G, Garcia JJ, Zuleta JJ, Diehl C, Correa C, Falabella R. A double-blind, randomized trial of 0.05% betamethasone vs. topical catalase/dismutase superoxide in vitiligo. *J Eur Acad Dermatol Venereol*. 2008;22:1359–1364.
14. Köse O, Arca E, Kurumlu Z. Mometasone cream versus pimecrolimus cream for the treatment of childhood localized vitiligo. *J Dermatolog Treat*. 2010;21:133–139.
15. Yaghoobi R, Omidian M, Bagherani N. Comparison of therapeutic efficacy of topical corticosteroid and oral zinc sulfate-topical corticosteroid combination in the treatment of vitiligo patients: A clinical trial. *BMC Dermatol*. 2011;11:7.
16. Kathuria S, Khaitan BK, Ramam M, Sharma VK. Segmental vitiligo: A randomized controlled trial to evaluate efficacy and safety of 0.1% tacrolimus ointment vs. 0.05% fluticasone propionate cream. *Indian J Dermatol Venereol Leprol*. 2012;78:68–73.
17. Iraji F, Banihashemi SH, Faghihi G, Shahmoradi Z, Tajmirriahi N, Jazi SB. A comparison of betamethasone valerate 0.1% cream twice daily plus oral simvastatin versus betamethasone valerate 0.1% cream alone in the treatment of Vitiligo patients. *Adv Biomed Res*. 2017;6:34.
18. Jung H, Chung H, Chang SE, Kang D-H, Oh E-S. FK506 regulates pigmentation by maturing the melanosome and facilitating their transfer to keratinocytes. *Pigment Cell Melanoma Res*. 2016;29:199–209.
19. Grimes PE, Soriano T, Dytoc MT. Topical tacrolimus for repigmentation of vitiligo. *J Am Acad Dermatol*. 2002;47:789–791.
20. Kanwar AJ, Dogra S, Parsad D. Topical tacrolimus for treatment of childhood vitiligo in Asians. *Clin Exp Dermatol*. 2004;29:589–592.
21. Silverberg NB, Lin P, Travis L et al. Tacrolimus ointment promotes repigmentation of vitiligo in children: A review of 57 cases. *J Am Acad Dermatol*. 2004;51:760–766.
22. Dawid M, Veensalu M, Grassberger M, Wolff K. Efficacy and safety of pimecrolimus cream 1% in adult patients with vitiligo: Results of a randomized, double-blind, vehicle-controlled study. *J Dtsch Dermatol Ges*. 2006;4:942–946.
23. Stinco G, Piccirillo F, Forcione M, Valent F, Patrone P. An open randomized study to compare narrow band UVB, topical pimecrolimus and topical tacrolimus in the treatment of vitiligo. *Eur J Dermatol*. 2009;19:588–593.
24. Lotti T, Buggiani G, Troiano M et al. Targeted and combination treatments for vitiligo. Comparative evaluation of different current modalities in 458 subjects. *Dermatol Ther*. 2008;21:S20–S26.
25. Radakovic S, Breier-Maly J, Konschitzky R et al. Response of vitiligo to once- vs. Twicedaily topical tacrolimus: A controlled prospective, randomized, observer-blinded trial. *J Eur Acad Dermatol Venereol*. 2009;23:951–953.
26. Hartmann A, Brocker EB, Hamm H. Occlusive treatment enhances the efficacy of tacrolimus 0.1% ointment in adult patients with vitiligo: Results of a placebo-controlled 12-month prospective study. *Acta Derm Venereol*. 2008;88:474–479.
27. Ostovari N, Passeron T, Lacour JP, Ortonne JP. Lack of efficacy of tacrolimus in the treatment of vitiligo in the absence of UV-B exposure. *Arch Dermatol*. 2006;142:252–253.
28. Speeckaert R, van Geel N. Vitiligo: An update on pathophysiology and treatment options. *Am J Clin Dermatol*. 2017;18:733–744.
29. Xu AE, Zhang DM, Wei XD, Huang B, Lu LJ. Efficacy and safety of tarcrolimus cream 0.1% in the treatment of vitiligo. *Int J Dermatol*. 2009;48:86–90.
30. Lo YH, Cheng GS, Huang CC, Chang WY, Wu CS. Efficacy and safety of topical tacrolimus for the treatment of face and neck vitiligo. *J Dermatol*. 2010;37:125–129.
31. Shim WH, Suh SW, Jwa SW et al. A pilot study of 1% pimecrolimus cream for the treatment of childhood segmental vitiligo. *Ann Dermatol*. 2013;25:168–172.
32. Kanwar AJ, Kumaran MS. Childhood vitiligo: Treatment paradigms. *Indian J Dermatol*. 2012;57:466–474.
33. Leone G, Pacifico A. Profile of clinical efficay and safety of topical tacalcitol. *Acta Biomed*. 2005;76:13–19.
34. Parsad D, Saini R, Nagpal R. Calcipotriol in vitiligo: Preliminary study. *Pediatr Dermatol*. 1999;16:317–320.
35. Travis LB, Silverberg NB. Calcipotriene and corticosteroid combination therapy for vitiligo. *Pediatr Dermatol*. 2004;21:495–498.
36. Gargoom AM, Duweb GA, Elzorghany AH, Benghazil M, Bugrein OO. Calcipotriol in the treatment of childhood citiligo. *Int J Clin Pharmacol Res*. 2004;24:11–14.
37. Rodríguez-Martín M, García Bustínduy M, Sáez Rodríguez M, Noda Cabrera A. Randomized, double-blind clinical trial to evaluate the efficacy of topical tacalcitol and sunlight exposure in the treatment of adult nonsegmental vitiligo. *Br J Dermatol*. 2009; 160:409–414.
38. Wat H, Dytoc M. Off-label uses of topical vitamin D in dermatology: A systematic review. *J Cutan Med Surg*. 2014;18:91–108.
39. Sarma N, Singh AK. Topical calcipotriol in childhood vitiligo: An Indian experience. *Int J Dermatol*. 2004;43:856–859.

40. Ermis O, Alpsoy E, Cetin L, Yilmaz E. Is the efficacy of psoralen plus ultraviolet a therapy for vitiligo enhanced by concurrent topical calcipotriol? A placebo-controlled double-blind study. *Br J Dermatol*. 2001;145:472–475.
41. Leone G, Pacifico A, Iacovelli P, Paro Vidolin A, Picardo M. Tacalcitol and narrow-band phototherapy in patients with vitiligo. *Clin Exp Dermatol*. 2006;31:200–205.
42. Yalçin B, Sahin S, Bükülmez G et al. Experience with calcipotriol as adjunctive treatment for vitiligo in patients who do not respond to PUVA alone: A preliminary study. *J Am Acad Dermatol*. 2001;44:634–637.
43. Ada S, Sahin S, Boztepe G, Karaduman A, Kölemen F. No additional effect of topical calcipotriol on narrow-band UVB phototherapy in patients with generalized vitiligo. *Photodermatol Photoimmunol Photomed*. 2005;21:79–83.
44. Baysal V, Yildirim M, Erel A, Kesici D. Is the combination of calcipotriol and PUVA effective in vitiligo? *J Eur Acad Dermatol Venereol*. 2003;17:299–302.
45. Schallreuter KU, Wood JM, Berger J. Low catalase levels in the epidermis of patients with vitiligo. *J Invest Dermatol*. 1991;97:1081–1085.
46. Schallreuter KU, Wood JM, Lemke KR, Levenig C. Treatment of vitiligo with a topical application of pseudocatalase and calcium in combination with short-term UVB exposure: A case study on 33 patients. *Dermatology*. 1995;190:223–229.
47. Schallreuter KU, Krüger C, Würfel BA, Panske A, Wood JM. From basic research to the bedside: Efficacy of topical treatment with pseudocatalase PC-KUS in 71 children with vitiligo. *Int J Dermatol*. 2008;47:743–753.
48. Yuksel EP, Aydin F, Senturk N, Canturk T, Turanli AY. Comparison of the efficacy of narrow band ultraviolet B and narrow band ultraviolet B plus topical catalase-superoxide dismutase treatment in vitiligo patients. *Eur J Dermatol*. 2009;19:341–344.
49. Bakis-Petsoglou S, Le Guay JL, Wittal R. A randomized, double-blinded, placebo-controlled trial of pseudocatalase cream and narrowband ultraviolet B in the treatment of vitiligo. *Br J Dermatol*. 2009;161:910–917.
50. Naini FF, Shooshtari AV, Ebrahimi B, Molaei R. The effect of pseudocatalase/superoxide dismutase in the treatment of vitiligo: A pilot study. *J Res Pharm Pract*. 2012;1:77–80.
51. Sanclemente G, Garcia JJ, Zuleta JJ, Diehl C, Correa C, Falabella R. A double-blind, randomized trial of 0.05% betamethasone vs. topical catalase/dismutase superoxide in vitiligo. *J Eur Acad Dermatol Venereol*. 2008;22:1359–1364.
52. Soliman M, Samy NA, Abo Eittah M, Hegazy M. Comparative study between excimer light and topical antioxidant versus excimer light alone for treatment of vitiligo. *J Cosmet Laser Ther*. 2016;18:7–11.
53. Parsad D, Pandhi R, Dogra S, Kumar B. Topical prostaglandin analog (PGE2) in vitiligo--a preliminary study. *Int J Dermatol*. 2002;41:942–945.
54. Kapoor R, Phiske MM, Jerajani HR. Evaluation of safety and efficacy of topical prostaglandin E2 in treatment of vitiligo. *Br J Dermatol*. 2009;160 :861–863.
55. Anbar TS, El-Ammawi TS, Abdel-Rahman AT, Hanna MR. The effect of latanoprost on vitiligo: A preliminary comparative study. *Int J Dermatol*. 2015;54:587–593.
56. Grimes PE. Bimatoprost 0.03% solution for the treatment of Nonfacial Vitiligo. *J Drugs Dermatol*. 2016;15:703–710.
57. Nordlund JJ, Halder R. Melagenina. An analysis of published and other available data. *Dermatologica*. 1990;181(1):1–4.
58. Zhao D, Li Y, Wang P et al. Melagenine modulates proliferation and differentiation of melanoblasts. *Int J Mol Med*. 2008;22:193–197.
59. Xu AE, Wei XD. Topical melagenine for repigmentation in twenty-two child patients with vitiligo on the scalp. *Chin Med J (Engl)*. 2004;117:199–201.
60. Miyares CM, Hollands Barca I, Miyares Diaz E, Pernas González A. Effectiveness of human placental extract with calcium (Melagenina Plus) for the treatment of vitiligo. *Medicina cutánea ibero-latino-americana*. 2009;37:207–212.
61. Liu J, Xu Y, Lin TK, Lv C, Elias PM, Man MQ. Topical histamine stimulates repigmentation of nonsegmental vitiligo by a receptor-dependent mechanism. *Skin Pharmacol Physiol*. 2017;30:139–145.
62. Handjani F, Aghaei S, Moezzi I, Saki N. Topical mycophenolate mofetil in the treatment of vitiligo: A pilot study. *Dermatol Pract Concept*. 2017;7:31–33.
63. Rothstein B, Joshipura D, Saraiya A et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;76: 1054–1060.e1.
64. Joshipura D, Alomran A, Zancanaro P, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: A 32-week open-label extension study with optional narrow-band ultraviolet B. *J Am Acad Dermatol*. 2018;78:1205–1207.e1.
65. Joshipura D, Plotnikova N, Goldminz A et al. Importance of light in the treatment of vitiligo with JAK-inhibitors. *J Dermatolog Treat*. 2018;29:98–99.
66. Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast-spreading disease. *Int J Dermatol*. 1993;32:753–757.
67. Kim SM, Lee HS, Hann SK. The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patients. *Int J Dermatol*. 1999;38:546–550.
68. Radakovic-Fijan S, Fürnsinn-Friedl AM, Hönigsmann H, Tanew A. Oral dexamethasone pulse treatment for vitiligo. *J Am Acad Dermatol*. 2001;44:814–817.

69. Lee Y, Seo YJ, Lee JH, Park JK. High-dose prednisolone and psoralen ultraviolet a combination therapy in 36 patients with vitiligo. *Clin Exp Dermatol*. 2007;32:499–501.
70. Lee J, Chu H, Lee H, Kim M, Kim DS, Oh SH. A retrospective study of methylprednisolone mini-pulse therapy combined with narrow-band UVB in non-segmental Vitiligo. *Dermatology*. 2016; 232(2):224–229.
71. Kanwar AJ, Mahajan R, Parsad D. Low-dose oral mini-pulse dexamethasone therapy in progressive unstable vitiligo. *J Cutan Med Surg*. 2013 Jul–Aug; 17(4):259–268.
72. Singh A, Kanwar AJ, Parsad D, Mahajan R. Randomized controlled study to evaluate the effectiveness of dexamethasone oral minipulse therapy versus oral minocycline in patients with active vitiligo vulgaris. *Indian J Dermatol Venereol Leprol*. 2014;80:29–35.
73. El Mofty M, Essmat S, Youssef R et al. The role of systemic steroids and phototherapy in the treatment of stable vitiligo: A randomized controlled trial. *Dermatol Ther*. 2016;29:406–412.
74. Dogra S, Kumar B. Repigmentation in vitiligo universalis: Role of melanocyte density, disease duration, and melanocytic reservoir. *Dermatol Online J*. 2005;11(3):30.
75. Pardue SL, Fite KV, Bengston L, Lamont SJ, Boyle ML 3rd, Smyth JR Jr. Enhanced integumental and ocular amelanosis following the termination of cyclosporine administration. *J Invest Dermatol*. 1987;88:758–761.
76. Sandra A, Pai S, Shenoi SD. Unstable vitiligo responding to methotrexate. *Indian J Dermatol Venereol Leprol*. 1998;64:309.
77. Alghamdi K, Khurrum H. Methotrexate for the treatment of generalized vitiligo. *Saudi Pharm J*. 2013;21:423–424.
78. Garza-Mayers AC, Kroshinsky D. Low-dose methotrexate for vitiligo. *J Drugs Dermatol*. 2017; 16:705–706.
79. Singh H, Kumaran MS, Bains A, Parsad D. A randomized comparative study of oral corticosteroid minipulse and low-dose oral methotrexate in the treatment of unstable vitiligo. *Dermatology*. 2015; 231:286–290.
80. Radmanesh M, Saedi K. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. *J Dermatolog Treat*. 2006;17(3):151–153.
81. Kim NH, Torchia D, Rouhani P, Roberts B, Romanelli P. Tumor necrosis factor-α in vitiligo: Direct correlation between tissue levels and clinical parameters. *Cutan Ocul Toxicol*. 2011;30:225–227.
82. Webb KC, Tung R, Winterfield LS et al. Tumour necrosis factor-α inhibition can stabilize disease in progressive vitiligo. *Br J Dermatol*. 2015; 173:641–650.
83. Rigopoulos D, Gregoriou S, Larios G, Moustou E, Belayeva-Karatza E, Kalogeromitros D. Etanercept in the treatment of vitiligo. *Dermatology*. 2007;215:84–85.
84. Alghamdi KM, Khurrum H, Taieb A, Ezzedine K. Treatment of generalized vitiligo with anti-TNF-α Agents. *J Drugs Dermatol*. 2012;11:534–539.
85. Maruthappu T, Leandro M, Morris SD. Deterioration of vitiligo and new onset of halo naevi observed in two patients receiving adalimumab. *Dermatol Ther*. 2013;26:370–372.
86. Alghamdi KM, Khurrum H, Rikabi A. Worsening of vitiligo and onset of new psoriasiform dermatitis following treatment with infliximab. *J Cutan Med Surg*. 2011;15:280–284.
87. Craiglow BG, King BA. Tofacitinib citrate for the treatment of Vitiligo: A pathogenesis-directed therapy. *JAMA Dermatol*. 2015;151:1110–1112.
88. Vu M, Heyes C, Robertson SJ, Varigos GA, Ross G. Oral tofacitinib: A promising treatment in atopic dermatitis, alopecia areata and vitiligo. *Clin Exp Dermatol*. 2017;42:942–944.
89. Parsad D, Pandhi R, Juneja A. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol*. 2003;28:285–287.
90. Szczurko O, Shear N, Taddio A, Boon H. Ginkgo biloba for the treatment of vitilgo vulgaris: An open label pilot clinical trial. *BMC Complement Altern Med*. 2011;11:21.
91. Dell'Anna ML, Mastrofrancesco A, Sala R et al. Antioxidants and narrow band-UVB in the treatment of vitiligo: A double-blind placebo controlled trial. *Clin Exp Dermatol*. 2007;32:631–636.
92. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: A randomized double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2007;21:942–950.
1. Silverberg JI, Silverberg NB. Association between vitiligo extent and distribution and quality-of-life impairment. *JAMA Dermatol*. 2013;149:159–164.
2. Ezzedine K, Lim HW, Suzuki T et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012;25:E1–13.
3. Behl PN, Bhatia RK. Treatment of vitiligo with autologous thin Thiersch's grafts. *Int J Dermatol*. 1973;12:329–331.
4. Kahn AM, Cohen MJ, Kaplan L, Highton A. Vitiligo: Treatment by dermabrasion and epithelial sheet grafting—A preliminary report. *J Am Acad Dermatol*. 1993;28:773–774.
5. McGovern TW, Bolognia J, Leffell DJ. Flip-top pigment transplantation: A novel transplantation procedure for the treatment of depigmentation. *Arch Dermatol*. 1999;135:1305–1307.

6. Krishnan A, Kar S. Smashed skin grafting or smash grafting—A novel method of vitiligo surgery. *Int J Dermatol*. 2012;51:1242–1247.
7. Mutalik S, Ginzburg A. Surgical management of stable vitiligo: A review with personal experience. *Dermatol Surg*. 2000;26:248–254.
8. Kovacs D, Abdel-Raouf H, Al-Khayyat M et al. Vitiligo: Characterization of melanocytes in repigmented skin after punch grafting. *J Eur Acad Dermatol Venereol*. 2015;29:581–590.
9. Li J, Fu WW, Zheng ZZ, Zhang QQ, Xu Y, Fang L. Suction blister epidermal grafting using a modified suction method in the treatment of stable vitiligo: A retrospective study. *Dermatol Surg*. 2011;37:999–1006.
10. Verma R, Grewal RS, Chatterjee M, Pragasam V, Vasudevan B, Mitra D. A comparative study of efficacy of cultured versus non cultured melanocyte transfer in the management of stable vitiligo. *Med J Armed Forces India*. 2014;70:26–31.
11. Holla AP, Kumar R, Parsad D, Kanwar A. Modified procedure of noncultured epidermal suspension transplantation: Changes are the core of vitiligo surgery. *J Cutan Aesthet Surg*. 2011;4:44–45.
12. Razmi TM, Parsad D. Cellular transplantation procedures in vitiligo: What is in a name? *Int J Dermatol*. 2018;57:e36–e7.
13. Silpa-Archa N, Griffith JL, Huggins RH et al. Long-term follow-up of patients undergoing autologous noncultured melanocyte-keratinocyte transplantation for vitiligo and other leukodermas. *J Am Acad Dermatol*. 2017;77:318–327.
14. van Geel N, Ongenae K, De Mil M, Haeghen YV, Vervaet C, Naeyaert JM. Double-blind placebo-controlled study of autologous transplanted epidermal cell suspensions for repigmenting vitiligo. *Arch Dermatol*. 2004;140:1203–1208.
15. Vanscheidt W, Hunziker T. Repigmentation by outer-root-sheath-derived melanocytes: Proof of concept in vitiligo and leucoderma. *Dermatology*. 2009;218:342–343.
16. Mohanty S, Kumar A, Dhawan J, Sreenivas V, Gupta S. Noncultured extracted hair follicle outer root sheath cell suspension for transplantation in vitiligo. *Br J Dermatol*. 2011;164:1241–1246.
17. Singh C, Parsad D, Kanwar AJ, Dogra S, Kumar R. Comparison between autologous noncultured extracted hair follicle outer root sheath cell suspension and autologous noncultured epidermal cell suspension in the treatment of stable vitiligo: A randomized study. *Br J Dermatol*. 2013;169:287–293.
18. Donaparthi N, Chopra A. Comparative study of efficacy of epidermal melanocyte transfer versus hair follicular melanocyte transfer in stable vitiligo. *Indian J Dermatol*. 2016;61:640–644.
19. Razmi TM, Parsad D, Kumaran SM. Combined epidermal and follicular cell suspension as a novel surgical approach for acral vitiligo. *J Am Acad Dermatol*. 2017;76:564–567.
20. Razmi TM, Kumar R, Rani S, Kumaran SM, Tanwar S, Parsad D. Combination of follicular and epidermal cell suspension as a novel surgical approach in difficult-to-treat vitiligo: A randomized clinical trial. *JAMA Dermatol*. 2018;154:301–308.
21. Shilpa K, Sacchidanand S, Savitha S, Ranjitha R, Lakshmi DV, Divya G. A study of the outcome of primary excision and closure technique in the management of lip leukoderma in 30 patients. *J Cutan Aesthet Surg*. 2016;9:20–26.
22. Tsuchiyama K, Wakao S, Kuroda Y et al. Functional melanocytes are readily reprogrammable from multilineage-differentiating stress-enduring (Muse) cells, distinct stem cells in human fibroblasts. *J Invest Dermatol*. 2013;133:2425–2435.
23. Li L, Fukunaga-Kalabis M, Yu H et al. Human dermal stem cells differentiate into functional epidermal melanocytes. *J Cell Sci*. 2010;123:853–860.
24. Zhou MN, Zhang ZQ, Wu JL et al. Dermal mesenchymal stem cells (DMSCs) inhibit skin-homing CD8+ T cell activity, a determining factor of vitiligo patients' autologous melanocytes transplantation efficiency. *PLOS ONE*. 2013;8:e60254.
25. Thakur V, Parsad D. Clinical Trial: A Novel Surgical Method in the Treatment of Unstable Vitiligo. Clinical Trial Identifier:NCT03013049. Available at https://clinicaltrials.gov/ct2/show/NCT03013049?cond=Vitiligo&cntry=IN&rank=1. Last accessed on April 25, 2018
26. Le Poole IC, Mehrotra S. Replenishing regulatory T cells to halt depigmentation in vitiligo. *J Investig Dermatol Symp Proc*. 2017;18:S38–S45.
27. Falabella R. Repigmentation of segmental vitiligo by autologous minigrafting. *J Am Acad Dermatol*. 1983;9:514–521.
28. Feetham HJ, Chan JL, Pandya AG. Characterization of clinical response in patients with vitiligo undergoing autologous epidermal punch grafting. *Dermatol Surg*. 2012;38:14–19.
29. Malakar S, Dhar S. Treatment of stable and recalcitrant vitiligo by autologous miniature punch grafting: A prospective study of 1,000 patients. *Dermatology*. 1999;198:133–139.
30. Babu A, Thappa DM, Jaisankar TJ. Punch grafting versus suction blister epidermal grafting in the treatment of stable lip vitiligo. *Dermatol Surg*. 2008;34:166–178; discussion 78.
31. Khandpur S, Sharma VK, Manchanda Y. Comparison of minipunch grafting versus split-skin grafting in chronic stable vitiligo. *Dermatol Surg*. 2005;31:436–441.
32. Gupta S, Jain VK, Saraswat PK. Suction blister epidermal grafting versus punch skin grafting in recalcitrant and stable vitiligo. *Dermatol Surg*. 1999;25:955–958.

33. Njoo MD, Westerhof W, Bos JD, Bossuyt PM. A systematic review of autologous transplantation methods in vitiligo. *Arch Dermatol*. 1998;134:1543–1549.
34. Olsson MJ, Juhlin L. Epidermal sheet grafts for repigmentation of vitiligo and piebaldism, with a review of surgical techniques. *Acta Derm Venereol*. 1997;77:463–466.
35. Lu N, Xu A, Wu X. Follow-up study of vitiligo patients treated with autologous epidermal sheet transplants. *J Dermatolog Treat*. 2014;25:200–204.
36. Majid I, Imran S. Ultrathin split-thickness skin grafting followed by narrowband UVB therapy for stable vitiligo: An effective and cosmetically satisfying treatment option. *Indian J Dermatol Venereol Leprol*. 2012;78:159–164.
37. Falabella R. Epidermal grafting. An original technique and its application in achromic and granulating areas. *Arch Dermatol*. 1971;104: 592–600.
38. Koga M. Epidermal grafting using the tops of suction blisters in the treatment of vitiligo. *Arch Dermatol*. 1988;124:1656–1658.
39. Budania A, Parsad D, Kanwar AJ, Dogra S. Comparison between autologous noncultured epidermal cell suspension and suction blister epidermal grafting in stable vitiligo: A randomized study. *Br J Dermatol*. 2012;167:1295–1301.
40. Gou D, Currimbhoy S, Pandya AG. Suction blister grafting for vitiligo: Efficacy and clinical predictive factors. *Dermatol Surg*. 2015;41:633–639.
41. Na GY, Seo SK, Choi SK. Single hair grafting for the treatment of vitiligo. *J Am Acad Dermatol*. 1998;38:580–584.
42. Mapar MA, Safarpour M, Mapar M, Haghighizadeh MH. A comparative study of the mini-punch grafting and hair follicle transplantation in the treatment of refractory and stable vitiligo. *J Am Acad Dermatol*. 2014;70:743–747.
43. Brysk MM, Newton RC, Rajaraman S et al. Repigmentation of vitiliginous skin by cultured cells. *Pigment Cell Res*. 1989;2:202–207.
44. Falabella R, Escobar C, Borrero I. Transplantation of *in vitro*-cultured epidermis bearing melanocytes for repigmenting vitiligo. *J Am Acad Dermatol*. 1989;21:257–264.
45. Lerner AB, Halaban R, Klaus SN, Moellmann GE. Transplantation of human melanocytes. *J Invest Dermatol*. 1987;89:219–224.
46. Chen YF, Yang PY, Hu DN, Kuo FS, Hung CS, Hung CM. Treatment of vitiligo by transplantation of cultured pure melanocyte suspension: Analysis of 120 cases. *J Am Acad Dermatol*. 2004;51:68–74.
47. Gauthier Y, Surleve-Bazeille JE. Autologous grafting with noncultured melanocytes: A simplified method for treatment of depigmented lesions. *J Am Acad Dermatol*. 1992;26:191–194.
48. van Geel N, Goh BK, Wallaeys E, De Keyser S, Lambert J. A review of non-cultured epidermal cellular grafting in vitiligo. *J Cutan Aesthet Surg*. 2011;4:17–22.
49. Mulekar SV. Long-term follow-up study of 142 patients with vitiligo vulgaris treated by autologous, non-cultured melanocyte-keratinocyte cell transplantation. *Int J Dermatol*. 2005;44:841–845.
50. Mulekar SV, Al Issa A, Al Eisa A. Treatment of vitiligo on difficult-to-treat sites using autologous noncultured cellular grafting. *Dermatol Surg*. 2009;35:66–71.
51. Toossi P, Shahidi-Dadras M, Mahmoudi Rad M, Fesharaki RJ. Non-cultured melanocyte-keratinocyte transplantation for the treatment of vitiligo: A clinical trial in an Iranian population. *J Eur Acad Dermatol Venereol*. 2011;25:1182–1186.
52. Anbar T, Westerhof W, Abdel-Rahman A, El-Khayyat M, El-Metwally Y. Treatment of periungual vitiligo with erbium-YAG-laser plus 5-flurouracil: A left to right comparative study. *J Cosmet Dermatol*. 2006;5:135–139.
53. Olsson MJ, Juhlin L. Leucoderma treated by transplantation of a basal cell layer enriched suspension. *Br J Dermatol*. 1998;138:644–648.
54. van Geel N, Ongenae K, De Mil M, Naeyaert JM. Modified technique of autologous noncultured epidermal cell transplantation for repigmenting vitiligo: A pilot study. *Dermatol Surg*. 2001;27:873–876.
55. Mulekar SV, Ghwish B, Al Issa A, Al Eisa A. Treatment of vitiligo lesions by ReCell vs. conventional melanocyte-keratinocyte transplantation: A pilot study. *Br J Dermatol*. 2008;158:45–49.
56. Goh BK, Chua XM, Chong KL, de Mil M, van Geel NA. Simplified cellular grafting for treatment of vitiligo and piebaldism: The "6-well plate" technique. *Dermatol Surg*. 2010;36:203–207.
57. Sahni K, Parsad D, Kanwar AJ, Mehta SD. Autologous noncultured melanocyte transplantation for stable vitiligo: Can suspending autologous melanocytes in the patients' own serum improve repigmentation and patient satisfaction? *Dermatol Surg*. 2011;37:176–182.
58. Kumar R, Parsad D, Singh C, Yadav S. Four compartment method: A simplified and cost-effective method of noncultured epidermal cell suspension for the treatment of vitiligo. *Br J Dermatol*. 2014;170:581–585.
59. Benzekri L, Gauthier Y. The first transepidermal transplantation of non-cultured epidermal suspension using a dermarolling system in vitiligo: A sequential histological and clinical study. *Pigment Cell Melanoma Res*. 2017;30:493–497.
1. Ling TC, Clayton TH, Crawley J et al. British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen-ultraviolet A therapy 2015. *Br J Dermatol*. January 2016;174(1):24–55.

2. Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Arch Dermatol*. December 1997;133(12): 1525–1528.
3. Whitton ME, Pinart M, Batchelor J, Leonardi-Bee J, González U, Jiyad Z, Eleftheriadou V, Ezzedine K. Interventions for vitiligo. *Cochrane Database Syst Rev*. February 2015;24(2):CD003263.
4. Weichenthal M, Schwarz T. Phototherapy: How does UV work? *Photodermatol Photoimmunol Photomed*. October 2005;21:260–266.
5. De Francesco V, Stinco G, Laspina S, Parlangeli ME, Mariuzzi L, Patrone P. Immunohistochemical study before and after narrow band (311 nm) UVB treatment in vitiligo. *Eur J Dermatol*. May 2008–June;18(3):292–296.
6. Eleftheriadou V. Setting priorities and reducing uncertainties for the treatment of vitiligo. *PhD thesis*. The University of Nottingham; 2013.
7. Mysore V. Targeted phototherapy. *Indian J Dermatol Venereol Leprol*. 2009;75:119–125.
8. Koek M, Buskens E, van Weelden H, et al. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: Pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). *Br Med J*. 2009; 338:b1542.
9. Taieb A, Alomar A, Böhm M et al. Vitiligo European Task Force. Guidelines for the management of vitiligo: The European Dermatology Forum consensus. *Br J Dermatol*. January 2013;168:5–b1519.
10. Anbar TS, Westerhof W, Abdel-Rahman AT, El-Khayyat MA. Evaluation of the effects of NB-UVB in both segmental and non-segmental vitiligo affecting different body sites. *Photodermatol Photoimmunol Photomed*. June 2006;22:157–163.
11. Diffey BL, Farr PM. The challenge of follow-up in narrowband ultraviolet B phototherapy. *Br J Dermatol*. August 2007;157:344–349.
12. Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *J Am Acad Dermatol*. February 2000;42:245–255.
13. Parsad D, Kanwar AJ, Kumar B. Psoralen–ultraviolet A vs. narrow-band ultraviolet B phototherapy for the treatment of vitiligo. *J Eur Acad Dermatol Venereol*. February 2006; 20:175–177.
14. Yones SS, Palmer RA, Garibaldinos TM, Hawk JLM. Randomized double-blind trial of treatment of vitiligo efficacy of psoralen–UV-A therapy vs narrowband–UV-B therapy. *Arch Dermatol*. May 2007;143(5):578–584.
15. Bae JM, Jung HM, Hong BY, Lee JH, Choi WJ, Lee JH, Kim GM. Phototherapy for vitiligo: A systematic review and meta-analysis. *J Am Acad Dermatol*. July 2017; 153(7):666–674.
16. Nicolaidou E, Antoniou C, Stratigos AJ, Stefanaki C, Katsambas AD. Efficacy, predictors of response, and long-term follow-up in patients with vitiligo treated with narrowband UVB phototherapy. *J Am Acad Dermatol*. February 2007;56(2):274–278.
17. Sitek JC, Loeb M, Ronnevig JR. Narrowband UVB therapy for vitiligo: does the repigmentation last? *J Eur Acad Dermatol Venereol*. August 2007;21(7):891–896.
18. Studniberg HM, Weller P. PUVA, UVB, psoriasis, and non-melanoma skin cancer. *J Am Acad Dermatol*. December 1993;29(6):1013–1022.
19. Weischer M, Blum A, Eberhard F et al. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Derm Venereol*. 2004;84(5):370–374.
20. Man I, Crombie I, Dawe R, Ibbotson S, Ferguson J. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: Early follow-up data. *Br J Dermatol*. April 2005;152(4):755–757.
21. Hearn R, Kerr A, Rahim K, Ferguson J, Dawe R. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol*. September 2008; 159(4):931–935.
22. Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. *J Invest Dermatol*. March 2005;124(3): 505–513.
23. Jin Y, Birlea SA, Fain PR et al. Common variants in FOXP1 are associated with generalized vitiligo. *Nat Genet*. July 2010;42(7):576–578.
24. Lotti TM, Menchini G, Andreassi L. UV-B radiation microphototherapy. An elective treatment for segmental vitiligo. *J Eur Acad Dermatol Venereol*. September 1999; 13(2):102–108.
25. Menchini G, Tsoureli-Nikita E, Hercogova J. Narrow-band UV-B micro-phototherapy: A new treatment for vitiligo. *J Eur Acad Dermatol Venereol*. March 2003;17(2):171–177.
26. Majid I. Efficacy of targeted narrowband ultraviolet B therapy in vitiligo. *Indian J Dermatol*. September 2014; 59(5):485–489.
27. Shanmuga SC, Srinivas CR. Fractional-targeted phototherapy. *Indian Dermatol Online J*. December 2014; 5(Suppl 2):S104–S105.
28. Yang Y, Cho H, Ryou J, Lee M. Clinical study of repigmentation patterns with either narrow-band ultraviolet B (NBUVB) or 308 nm excimer laser treatment in Korean vitiligo patients. *Intern J Dermatol*. February 2010; 49:317–323.
29. Chimento SM, Newland M, Ricotti C, Nistico S, Romanelli P. A pilot study to determine the safety and efficacy of monochromatic excimer light in the treatment of vitiligo. *J Drugs Dermatol*. March 2008; 7(3):258–263.

30. Park K, Liao W, Murase J. A review of monochromatic excimer light in vitiligo. *British Journal of Dermatology*. 2012;167:468–478.
31. Leone G, Iacovelli P, Paro Vidolin A, Picardo M. Monochromatic excimer light 308 nm in the treatment of vitiligo: A pilot study. *J Eur Acad Dermatol Venereol*. August 2003;17:531–537.
32. Hofer A, Hassan A, Legat F, Kerl H, Wolf P. The efficacy of excimer laser (308 nm) for vitiligo at different body sites. *J Eur Acad Dermatol Venereol*. August 2006;20:558–564.
33. AlGhamdi KM, Kumar A, Moussa NA. Low-level laser therapy: A useful technique for enhancing the proliferation of various cultured cells. *Lasers Med Sci*. January 2012;27:237–249.
34. Yu HS, Wu CS, Yu CL, Kao YH, Chiou MH. Helium–neon laser irradiation stimulates migration and proliferation in melanocytes and induces repigmentation in segmental-type vitiligo. *J Investig Dermatol*. January 2003;120(1):56–264.
35. Sassi F, Cazzaniga S, Tessari G, Chatenoud L, Reseghetti A, Marchesi L, Girolomoni G, Naldi L. Randomized controlled trial comparing the effectiveness of 308-nm excimer laser alone or in combination with topical hydrocortisone 17-butyrate cream in the treatment of vitiligo of the face and neck. *Br J Dermatol*. October 2008;159:1186–1191.
36. Naylor M, Elmets C, Jaracz E, Rico JM. Non-melanoma skin cancer in patients with atopic dermatitis treated with topical tacrolimus. *J Dermatol Treatm*. July 2009; 16(3):149–153.
37. Rath N, Kar HK, Sabhnani S. An open labeled, comparative clinical study on efficacy and tolerability of oral minipulse of steroid (OMP) alone, OMP with PUVA and broad/narrow band UVB phototherapy in progressive vitiligo. *Indian J Dermatol Venereol Leprol*. August 2008;74(4):357–360.
1. Cohen BE, Elbuluk N, Mu EW, Orlow SJ. Alternative systemic treatments for vitiligo: A review. *Am J Clin Dermatol*. 2015;16(6):463–474.
2. Dell'Anna MLEK, Hamzavi I, Harris J, Parsad D, Taieb A, Picardo M. Vitiligo. *Nature Reviews Disease Primers*. 2015;1(1):1–16.
3. Frisoli ML, Harris JE. Vitiligo: Mechanistic insights lead to novel treatments. *J Allergy Clin Immunol*. September 2017;140(3):654–662.
4. Harris JE. Cellular stress and innate inflammation in organ-specific autoimmunity: Lessons learned from vitiligo. *Immunol Rev*. 2016;269(1):11–25.
5. Lotti T, Gianfaldoni S, Valle Y, Rovesti M, Feliciano C, Satolli F. Controversial issues in vitiligo patients: A review of old and recent treatments. *Dermatol Ther*. 2019;32(1):e12745.
6. Rashighi M, Harris JE. Vitiligo pathogenesis and emerging treatments. *Dermatol Clin*. April 2017;35(2):257–e12265.
7. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE; Vitiligo Working Group. Current and emerging treatments for vitiligo. *J Am Acad Dermatol*. July 2017;77(1):17–29.
8. Spritz RA. Six decades of vitiligo genetics: Genome-wide studies provide insights into autoimmune pathogenesis. *J Invest Dermatol*. 2012;132(2):268–273.
9. Faas L, Venkatasamy R, Hider RC, Young AR, Soumyanath A. *In vivo* evaluation of piperine and synthetic analogues as potential treatments for vitiligo using a sparsely pigmented mouse model. *Br J Dermatol*. May 2008;158(5):941–950.
10. Shafiee A, Hoormand M, Shahidi-Dadras M, Abadi A. The effect of topical piperine combined with narrowband UVB on vitiligo treatment: A clinical trial study. *Phytother Res*. September 2018;32(9):1812–1817.
11. Yan R, Yuan J, Chen H et al. Fractional Er:YAG laser assisting topical betamethasone solution in combination with NB-UVB for resistant non-segmental vitiligo. *Lasers Med Sci*. 2017;32:1571–1577.
12. Kim HJ, Hong ES, Cho SH et al. Fractional Carbon Dioxide Laser as an "Add-on" treatment for vitiligo: A meta-analysis with systematic review. *Acta Derm Venereol*. 2018;98:180–184.
13. Lotti T, Tchernev G, Wollina U et al. Successful treatment with UVA 1 laser of non-responder vitiligo patients. *Open Access Maced J Med Sci* 2018;6:43–45.
14. Goren A, Salafia A, McCoy J, Keene S, Lotti T. Novel topical cream delivers safe and effective sunlight therapy for vitiligo by selectively filtering damaging ultraviolet radiation. *Dermatol Ther*. 2014;27(4):195–197.
15. Shalbaf M, Gibbons NC, Wood JM et al. Presence of epidermal allantoin further supports oxidative stress in vitiligo. *Exp Dermatol*. 2008;17(9):761–770.
16. Dell'Anna ML, Mastrofrancesco A, Sala R et al. Antioxidants and narrow band-UVB in the treatment of vitiligo: A double-blind placebo controlled trial. *Clin Exp Dermatol*. 2007;32(6):631–636.
17. Parsad D, Pandhi R, Juneja A. Effectiveness of oral ginkgo biloba in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol*. 2003;28(3):285–287.
18. Szczurko O, Shear N, Taddio A, Boon H. Ginkgo biloba for the treatment of vitiligo vulgaris: An open label pilot clinical trial. *BMC Complement Altern Med*. 2011;11:21.
19. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral *Polypodium leucotomos* extract: A randomized double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2007;21(7):942–950.
20. Grimes PE, Hamzavi I, Lebwohl M, Ortonne JP, Lim HW. The efficacy of afamelanotide and narrowband UV-B phototherapy for repigmentation of vitiligo. *JAMA Dermatol*. 2013;149(1):68–73.

21. Rashighi M, Harris JE. Interfering with the IFN-gamma/CXCL10 pathway to develop new targeted treatments for vitiligo. *Ann Transl Med*. 2015;3(21):343.
22. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol*. 2015;72(2):221–236. quiz 37-8.
23. Rashighi M, Agarwal P, Richmond JM et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med*. 2014;6(223):223ra23.
24. Wang XX, Wang QQ, Wu JQ, Jiang M, Chen L, Zhang CF, Xiang LH. Increased expression of CXCR3 and its ligands in vitiligo patients and CXCL10 as a potential clinical marker for vitiligo. *Br J Dermatol*. 2016;174(6):1318–1326.
25. Villarino AV, Kanno Y, Ferdinand JR, O'Shea JJ. Mechanisms of JAK/STAT signaling in immunity and disease. *J Immunol*. 2015;194(1):21–27.
26. Craiglow BG, King BA. Tofacitinib citrate for the treatment of vitiligo: A pathogenesis-directed therapy. *JAMA Dermatol*. 2015;151(10):1110–1112.
27. Harris JE, Rashighi M, Nguyen N et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J Am Acad Dermatol*. 2016;74(2):370–371.
28. Rothstein B, Joshipura D, Sarayia A et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;76:1054–1060.
29. Tufts Medical Center. *ClinicalTrials.gov [Internet]*. Bethesda (MD): National Library of Medicine (US); Topical Ruxolitinib for the Treatment of Vitiligo. Available from https://clinicaltrials.gov/ct2/show/NCT02809976 NLM Identifier: NCT02809976 [2000-[cited June 29, 2016]
30. Moreland L, Bate G, Kirkpatrick P. Abatacept. *Nat Rev Drug Discov*. 2006;5(3):185–186.
31. Weber J. Immune checkpoint proteins: A new therapeutic paradigm for cancer—Preclinical background: CTLA-4 and PD-1 blockade. *Semin Oncol*. 2010;37(5):430–439.
32. Speerchaert R, van Geel N. Targeting CTLA-4, PD-L1 and IDO to modulate immune responses in vitiligo. *Exp Dermatol*. 2017;26:630–636.
33. Kumar P, Bhari N, Tembhre MK, Mohanty S, Arava S, Sharma VK, Gupta S. Study of efficacy and safety of noncultured, extracted follicular outer root sheath cell suspension transplantation in the management of stable vitiligo. *Int J Dermatol*. February 2018;57(2):245–249.
1. Sparagana SP, Roach ES. Tuberous sclerosis complex. *CurrOpin Neurol*. April 2000;13(2):115–119.
2. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann NY Acad Sci*. 1991;615:125–127.
3. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *Lancet*. 1998;351:1490.
4. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet*. 2008;23:372(9639):657–1468.
5. Rosset C, Netto CBO, Ashton-Prolla P. TSC1 and TSC2 gene mutations and their implications for treatment in tuberous sclerosis complex: A review. *Genet Mol Biol*. 2017;40(1):69–79.
6. Caban C, Khan N, Hasbani DM, Crino PB. Genetics of tuberous sclerosis complex: Implications for clinical practice. *Appl Clin Genet*. 2016;10:1–8. doi:10.2147/TACG.S90262
7. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. October 2013;49(4):243–254.
8. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: Advances in diagnosis, genetics and management. *J Am Acad Dermatol*. 2007;57:189–202.
9. Ebrahimi-Fakhari D, Mann LL, Poryo M et al. Incidence of tuberous sclerosis and age at first diagnosis: New data and emerging trends from a national, prospective surveillance study. *Orphanet J Rare Dis*. July 17, 2018;13(1):117.
10. de Vries PJ, Whittemore VH, Leclezio L et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. *Pediatr Neurol*. 2014;52(1):25–135.
11. Kohrman MH. Emerging treatments in the management of tuberous sclerosis complex. *Pediatr Neurol*. May 2012;46(5):267–275.
12. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: Revised clinical diagnostic criteria. *J Child Neurol*. 1998;13:624–628.
13. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: A population study. *Br J Dermatol*. 1996;135(1):1–5.
14. Northrup H, Koenig MK, Pearson DA et al. Tuberous Sclerosis Complex. July 13, 1999 [Updated July 12, 2018]. In: Adam MP, Ardinger HH, Pagon RA et al. eds. *GeneReviews*. Seattle (WA): University of Washington, Seattle; 1993–2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1220/
15. Wataya-Kaneda M, Tanaka M, Hamasaki T, Katayama I. Trends in the prevalence of tuberous sclerosis complex manifestations: An epidemiological study of 166 Japanese patients. *PLOS ONE*. 2013;8:e63910.
16. Seibert D, Hong CH, Takeuchi F et al. Recognition of tuberous sclerosis in adult women: Delayed presentation with life-threatening consequences. *Ann Intern Med*. 2011;154:806–e63813.
17. Cardis MA, DeKlotz CMC. Cutaneous manifestations of tuberous sclerosis complex and the paediatrician's role. *Arch Dis Child*. September 2017;102(9):858–863.

18. Sehgal VN, Srivastava G. Hereditary hypo/de-pigmented dermatoses: An overview. *Int J Dermatol*. 2008;47:1041–1050.
19. Jimbow K. Tuberous sclerosis and guttate leukodermas. *SeminCutan Med Surg*. 1997;16:30–35.
20. Jozwiak S, Schwarz RA, Janniger CK et al. Skin lesions in children with tuberous sclerosis complex: Their prevalence, natural course, and diagnostic significance. *Int J Dermatol*. 1998;37:911–917.
21. Wataya-Kaneda M, Ohno Y, Fujita Y et al. Sirolimus gel treatment vs placebo for facial angiofibromas in patients with tuberous sclerosis complex: A randomized clinical trial. *JAMA Dermatol*. July 1, 2018;154(7):781–788.
22. Sasongko TH, Ismail NF, Zabidi-Hussin Z. Rapamycin and rapalogs for tuberous sclerosis complex. *Cochrane Database Syst Rev*. July 13, 2016;7:CD011272.
23. Balestri R, Neri I, Patrizi A, Angileri L, Ricci L, Magnano M. Analysis of current data on the use of topical rapamycin in the treatment of facial angiofibromas in tuberous sclerosis complex. *J Eur Acad Dermatol Venereol*. January 2015;29(1):14–20.

1. Federico JR, Krishnamurthy K. *Albinism. StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; January 2018 – July 28, 2018.
2. Orlow SJ. Albinism: An update. *Semin Cutan Med Surg*. 1997;16(1):24–29.
3. Oetting WS. Albinism. *Curr Opin Pediatr*. 1999;11(6):565–571.
4. Suzuki T, Tomita Y. Recent advances in genetic analyses of oculocutaneous albinism types 2 and 4. *J Dermatol Sci*. 2008;51(1):1–9.
5. Kubasch AS, Meurer M. Oculocutaneous and ocular albinism. *Hautarzt*. 2017;68(11):867–875.
6. Toro C, Nicoli ER, Malicdan MC, Adams DR, Introne WJ. Chediak-Higashi syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, ed. *GeneReviews [Internet]*. Seattle (WA): University of Washington, Seattle; 1993–2018. March 3, 2009 [updated July 5, 2018].
7. Ramrath K, Stolz W. Disorders of melanin pigmentation/amelanosis and hypomelanosis/albinism, Chapter 65. In: Burgdorf WHC, Plewig G, Wolf HH, Landthaler M. ed. *Braun-Falco's Dermatology*. 3rd ed. Springer Verlag, Munchen, Germany; 2009, pp. 969–971.
8. Kamaraj B, Purohit R. Mutational analysis of oculocutaneous albinism: A compact review. *Biomed Res Int*. 2014;2014:905472.
9. Mártinez-García M, Montoliu L. Albinism in Europe. *J Dermatol*. 2013;40(5):319–24.
10. Khordadpoor-Deilamani F, Akbari MT, Karimipoor M, Javadi G. Sequence analysis of tyrosinase gene in ocular and oculocutaneous albinism patients: introducing three novel mutations. *Mol Vis*. 2015;21:730–735. eCollection 2015.
11. Dotta L, Parolini S, Prandini A, Tabellini G, Antolini M, Kingsmore SF, Badolato R. Clinical, laboratory and molecular signs of immunodeficiency in patients with partial oculo-cutaneous albinism. *Orphanet J Rare Dis*. October 17, 2013;8:168.
12. Kirkwood BJ. Albinism and its implications with vision. *Insight*. 2009;34(2):13–166.
13. Montoliu L, Grønskov K, Wei AH, Martínez-García M, Fernández A, Arveiler B, Morice-Picard F, Riazuddin S, Suzuki T, Ahmed ZM, Rosenberg T, Li W. Increasing the complexity: New genes and new types of albinism. *Pigment Cell Melanoma Res*. 2014;27(1):11–18.
14. Onojafe IF, Adams DR, Simeonov DR, Zhang J, Chan CC, Bernardini IM, Sergeev YV, Dolinska MB, Alur RP, Brilliant MH, Gahl WA, Brooks BP. Nitisinone improves eye and skin pigmentation defects in a mouse model of oculocutaneous albinism. *J. Clin. Invest*. 2011;121(10):3914–3923.
15. Emadi SE, Juma Suleh A, Babamahmoodi F, Ahangarkani F, Betty Chelimo V, Mutai B, Raeeskarami SR, Ghanadan A, Emadi SN. Common malignant cutaneous conditions among albinos in Kenya. *Med J Islam Repub Iran*. 2017;31:3.
16. Mabula JB, Chalya PL, Mchembe MD, Jaka H, Giiti G, Rambau P, Masalu N, Kamugisha E, Robert S, Gilyoma JM. Skin cancers among albinos at a university teaching hospital in Northwestern Tanzania: A retrospective review of 64 cases. *BMC Dermatol*. 2012;12:5.

1. Dessinioti C, Stratigos AJ, Rigopoulus D, Katsambas AD. A review of genetic disorders of hypopigmentation: Lessons learned from the biology of melanocytes. *Exp Dermatol*. 2009;18:741–749.
2. Scheinfeld NS. Syndromic albinism: A review of genetics and phenotypes. *Dermatol Online J*. December 2003;9(5):5.
3. Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: Report of two cases with histochemical studies. *Blood*. 1959;14:162–169.
4. Data provided by Orphanet (www.orpha.net), the European website providing information about orphan drugs and rare diseases.
5. "HPS most prevalent in persons from northwest Puerto Rico, where the disorder affects one of every 1.800 individuals," according to the data published by NORD, the National Organisation of Rare Disorders, https://rarediseases.org/rare-diseases/hermansky-pudlak-syndrome/
6. Berber I, Erkurt MA, Kuku I et al. Hermansky-Pudlak syndrome: A case report. *Case Rep Hematol*. 2014;2014:249195–6.
7. Ramsay M, Colman MA, Stevens G et al. The tyrosinase-positive oculocutaneous albinism locus maps to chromosome 15q11.2-q12. *Am J Hum Genet*. 1992;51:879–884.

8. Pierson DM, Ionescu D, Qing G et al. Pulmonary fibrosis in Hermansky-Pudlak syndrome: A case report and review. *Respiration*. 2006;73(3):382–395.
9. El-Chemaly S, Young LR. Hermansky-Pudlak syndrome. *Clin Chest Med*. 2016;37(3):505–511.
10. Huizing M, Malicdan MCV, Gochuico BR et al. Hermansky-Pudlak syndrome. In: Adam MP, Ardinger HH, Pagon RA et al. eds. *GeneReviews*. Seattle (WA): University of Washington, Seattle; 2000:1993–2018. https://www.ncbi.nlm.nih.gov/sites/books/NBK1287/
11. Oshima J, Martin GM, Hisama FM. Werner syndrome. In: Adam MP, Ardinger HH, Pagon RA et al., eds. *GeneReviews*. Seattle (WA): University of Washington, Seattle, 2002:1993–2018. https://www.ncbi.nlm.nih.gov/books/NBK1514/
12. Chediak MM. New leukocyte anomaly of constitutional and familial character. *Rev Hematol*. 1952;7:362–367.
13. Higashi O. Congenital gigantism of peroxidase granules: The first case ever reported of qualitative abnormity of peroxidase. *Tohoku J Exp Med*. 1954;59:315–332.
14. Sato A. Chédiak and Higashi's disease: Probable identity of a new leucocytal anomaly (Chédiak) and congenital gigantism of peroxidase granules (Higashi) Tohoku. *J Exp Med*. 1995;61:201–210.
15. Beguez-Cesar AB. Neutropenia crónica maligna familiar con granulaciones atípicas de los leucocitos. *Boletín de la Sociedad Cubana de Pediatría*. 1943;15:900–922.
16. Ajitkumar A, Ramphul K. Chediak Higashi syndrome. [Updated June 10, 2018]. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2018. https://www.ncbi.nlm.nih.gov/books/NBK507881/
17. Toro C, Nicoli ER, Malicdan MC et al. Chediak-Higashi syndrome. In: Adam MP, Ardinger HH, Pagon RA et al. eds. GeneReviewsSeattle (WA): University of Washington, Seattle; 2009:1993–2018. https://www.ncbi.nlm.nih.gov/books/NBK5188/
18. Solomons HD. Hermansky-Pudlak/Chediak-Higashi syndromes. *Cardiovasc J Afr*. 2012;23(6):312.
19. Dotta L, Parolini S, Prandini A et al. Clinical, laboratory and molecular signs of immunodeficiency in patients with partial oculo-cutaneous albinism. *Orphanet J Rare Dis*. 2013;8:168. Published October 17, 2013.
20. Valente NY, Machado MC et al. Polarized light microscopy of hair shafts aids in the differential diagnosis of Chédiak-Higashi and Griscelli-Prunieras syndromes. *Clinics (Sao Paulo)*. August 2006;61(4):327–332.
21. Umeda K, Adachi S. Allogeneic hematopoietic stem cell transplantation for Chediak-Higashi syndrome, *Pediatr Transplant*. March 2016;20(2):271–275.
22. Goding CR. Melanocytes: the new black. *Int J Biochem Cell Biol*. 2007;39:275–279.
23. Griscelli C, Prunieras M. Pigment dilution and immunodeficiency: A new syndrome. *Int J Dermatol*. December 1978;17(10):788–791.
24. Cağdaş D, Ozgür TT, Asal GT, Tezcan I, Metin A, Lambert N, de Saint Basile G, Sanal O. Griscelli syndrome types 1 and 3: Analysis of four new cases and long-term evaluation of previously diagnosed patients. *Eur J Pediatr*. October 2012;171(10):1527–1531.
25. Tardieu M, Rostasy K. Neurological expression of genetic immunodeficiencies and of opportunistic infections. In: *Handbook of Clinical Neurology*. 2013;112:1219–1227. doi:10.1016/B978-0-444-52910-7.00044-1.
26. Ménasché G, Ho CH, Sanal O, Feldmann J, Tezcan I, Ersoy F, Houdusse A, Fischer A, de Saint Basile G. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). *J Clin Invest*. 2003;112:450–456.
27. Bizario JC, Feldmann J, Castro FA, Ménasché G, Jacob CM, Cristofani L, Casella EB, Voltarelli JC, de Saint-Basile G, Espreafico EM. Griscelli syndrome: Characterization of a new mutation and rescue of T-cytotoxic activity by retroviral transfer of RAB27A gene. *J Clin Immunol*. July 2004;24(4):397–410.
28. Van Gele M, Dynoodt P, Lambert J. Griscelli syndrome: A model system to study vesicular trafficking. *Pigment Cell Melanoma Res*. 2009;22:268–282.
1. Huang A, Glick SA. Piebaldism in history—"The Zebra People." *JAMA Dermatol*. 2016;152(11):1261.
2. Debbarh FZ, Mernissi FZ. Piebaldisme: A rare genodermatosis. *Pan Afr Med J*. 2017;27:221.
3. Dessinioti C, Stratigos AJ, Rigopoulos D, Katsambas AD. A review of genetic disorders of hypopigmentation: Lessons learned from the biology of melanocytes. *Exp Dermatol*. 2009;18(9):741–1269.
4. Perez-Losada J, Sanchez-Martin M, Rodriguez-Garcia A et al. Zinc-finger transcription factor SLUG contributes to the function of the stem cell factor c-kit signaling pathway. *Blood*. 2002;100(4):1274–1286.
5. Tomita Y, Suzuki T. Genetics of pigmentary disorders. *Am J Med Genet C Semin Med Genet*. 2004;131c(1):75–81.
6. Spritz RA. The molecular basis of human piebaldism. *Pigment Cell Res*. 1992;5(5 Pt 2):340–343.
7. Fleischman RA, Gallardo T, Mi X. Mutations in the ligand-binding domain of the kit receptor: An uncommon site in human piebaldism. *J Invest Dermatol*. 1996;107(5):703–706.
8. Sanchez-Martin M, Perez-Losada J, Rodriguez-Garcia A et al. Deletion of the SLUG (SNAI2) gene results in human piebaldism. *Am J Med Genet A*. 2003;122a(2):125–132.
9. Agarwal S, Ojha A. Piebaldism: A brief report and review of the literature. *Indian Dermatol Online J*. 2012;3(2):144–147.
10. Oiso N, Fukai K, Kawada A, Suzuki T. Piebaldism. *J Dermatol*. 2013;40(5):330–335.

11. Arase N, Wataya-Kaneda M, Oiso N et al. Repigmentation of leukoderma in a piebald patient associated with a novel c-KIT gene mutation, G592E, of the tyrosine kinase domain. *J Dermatol Sci*. 2011;64(2):147–149.
12. Frances L, Betlloch I, Leiva-Salinas M, Silvestre JF. Spontaneous repigmentation in an infant with piebaldism. *Int J Dermatol*. 2015;54(6):e244–e246.
13. Spritz RA, Itin PH, Gutmann DH. Piebaldism and neurofibromatosis type 1: Horses of very different colors. *J Invest Dermatol*. 2004;122(2): xxxiv–xxxv.
14. Sarma N, Chakraborty S, Bhanja DC, Bhattachraya SR. Piebaldism with non-intertriginous freckles: What does it mean? *Indian J Dermatol Venereol Leprol*. 2014;80(2):163–165.
15. Chiu YE, Dugan S, Basel D, Siegel DH. Association of piebaldism, multiple cafe-au-lait macules, and intertriginous freckling: Clinical evidence of a common pathway between KIT and Sprouty-related, Ena/vasodilator-stimulated phosphoprotein homology-1 domain containing protein 1 (SPRED1). *Pediatr Dermatol*. 2013;30(3):379–382.
16. Jia WX, Xiao XM, Wu JB et al. A novel missense KIT mutation causing piebaldism in one Chinese family associated with cafe-au-lait macules and intertriginous freckling. *Ther Clin Risk Manag*. 2015;11:635–638.
17. Nagaputra JC, Koh MJA, Brett M, Lim ECP, Lim HW, Tan EC. Piebaldism with multiple cafe-au-lait-like hyperpigmented macules and inguinal freckling caused by a novel KIT mutation. *JAAD Case Rep*. 2018;4(4):318–321.
18. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat*. 2010;31(4):391–406.
19. Smith SD, Kelley PM, Kenyon JB, Hoover D. Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF. *J Med Genet*. 2000;37(6):446–448.
20. Sleiman R, Kurban M, Succaria F, Abbas O. Poliosis circumscripta: Overview and underlying causes. *J Am Acad Dermatol*. 2013;69(4):625–633.
21. Jacob AN, Kandpal G, Gill N, Kandpal RP. Toward expression mapping of albinism-deafness syndrome (ADFN) locus on chromosome Xq26. *Somat Cell Mol Genet*. 1998;24(2):135–140.
22. Shiloh Y, Litvak G, Ziv Y et al. Genetic mapping of X-linked albinism-deafness syndrome (ADFN) to Xq26.–q27.I. *Am J Hum Genet*. 1990;47(1):20–27.
23. Bansal L, Zinkus TP, Kats A. Poliosis with a rare association. *Pediatr Neurol*. 2018;83:62–63.
24. Ghoshal B, Sarkar N, Bhattacharjee M, Bhattacharjee R. Glycogen storage disease 1a with piebaldism. *Indian Pediatr*. 2012;49(3):235–236.
25. Herman KL, Salman K, Rose LI. White forelock in Marfan's syndrome: An unusual association, with review of the literature. *Cutis*. 1991;48(1):82–84.
26. Herranz P, Borbujo J, Martinez W, Vidaurrazaga C, Diaz R, Casado M. Rubinstein-Taybi syndrome with piebaldism. *Clin Exp Dermatol*. 1994;19(2):170–172.
27. Hann SK, Lee HJ. Segmental vitiligo: Clinical findings in 208 patients. *J Am Acad Dermatol*. 1996;35(5 Pt 1):671–674.
28. Greco A, Fusconi M, Gallo A et al. Vogt-Koyanagi-Harada syndrome. *Autoimmun Rev* 2013;12(11): 1033–1038.
29. Andrade A, Pithon M. Alezzandrini syndrome: Report of a sixth clinical case. *Dermatology*. 2011;222(1):8–9.
30. Elston DM, Clayton AS, Meffert JJ, McCollough ML. Migratory poliosis: A forme fruste of alopecia areata? *J Am Acad Dermatol*. 2000;42(6):1076–1077.
31. Jalalat SZ, Kelsoe JR, Cohen PR. Alopecia areata with white hair regrowth: Case report and review of poliosis. *Dermatol Online J*. 2014;20(9).
32. Lett KS, Deane JS. Eyelash poliosis in association with sarcoidosis. *Eye (Lond)*. 2005;19(9):1015–1017.
33. Bernardes TF, Bonfioli AA. Blepharitis. *Semin Ophthalmol*. 2010;25(3):79–83.
34. Dunn CL, Harrington A, Benson PM, Sau P, James WD. Melanoma of the scalp presenting as poliosis circumscripta. *Arch Dermatol*. 1995;131(5):618–619.
35. Kwon IH, Cho YJ, Lee SH et al. Poliosis circumscripta associated with neurofibroma. *J Dermatol*. 2005;32(6):446–449.
36. Suga Y, Ikejima A, Matsuba S, Ogawa H. Medical pearl: DHA application for camouflaging segmental vitiligo and piebald lesions. *J Am Acad Dermatol*. 2002;47(3):436–438.
37. Thomas I, Kihiczak GG, Fox MD, Janniger CK, Schwartz RA. Piebaldism: An update. *Int J Dermatol*. 2004;43(10):716–719.
38. Njoo MD, Nieuweboer-Krobotova L, Westerhof W. Repigmentation of leucodermic defects in piebaldism by dermabrasion and thin split-thickness skin grafting in combination with minigrafting. *Br J Dermatol*. 1998;139(5):829–833.
39. Olsson MJ, Juhlin L. Long-term follow-up of leucoderma patients treated with transplants of autologous cultured melanocytes, ultrathin epidermal sheets and basal cell layer suspension. *Br J Dermatol*. 2002;147(5):893–904.
40. Lommerts JE, Meesters AA, Komen L et al. Autologous cell suspension grafting in segmental vitiligo and piebaldism: A randomized controlled trial comparing full surface and fractional CO_2 laser recipient-site preparations. *Br J Dermatol*. 2017;177(5):1293–1298.
1. Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and noseroot with pigmentary anomalies of the iris and head hair and with congenital deafness; Dystopia canthi medialis et punctorum lacrimalium lateroversa, hyperplasia supercilii medialis et radicis nasi, heterochromia iridum totaliis sive partialis,

albinismus circumscriptus (leucismus, polioss) et surditas congenita (surdimutitas). *Am J Hum Genet*. September 1951;3(3):195.
2. Zaman A, Capper R, Baddoo W. Waardenburg syndrome: More common than you think! *Clin Otolaryngol*. February 2015;40(1):44–48.
3. Farrer LA, Grundfast KM, Amos J, Arnos KS, Asher JH, Beighton P, Diehl SR, Fex J, Foy C, Friedman TB, Greenberg J. Waardenberg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: First report of the WS consortium. *Am J Hum Genet*. May 1992;50(5):902.
4. Tamayo ML, Gelvez N, Rodriguez M, Florez S, Varon C, Medina D, Bernal JE. Screening program for Waardenburg syndrome in Colombia: Clinical definition and phenotypic variability. *Am J Med Genet A*. April 15, 2008;146(8):1026–1031.
5. Milunsky, JM. Waardenburg syndrome type I. InGeneReviews® [Internet] 2017 May 4. University of Washington, Seattle. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1531/, accessed on December 2018.
6. Hageman MJ, Delleman JW. Heterogeneity in Waardenburg syndrome. *Am J Hum Genet*. September 1977;29(5):468.
7. Read AP, Newton VE. Waardenburg syndrome. *J Med Genet*. August 1, 1997;34(8):656–665.
8. U.S. National Library of Medicine, National Institutes of Health. Genetics Home Reference: Your guide to understanding genetic conditions. Available from: https://ghr.nlm.nih.gov/condition/waardenburg-syndrome, accessed on December 2018.
9. Bronner ME, LeDouarin NM. Development and evolution of the neural crest: An overview. *Dev Biol*. June 1, 2012;366(1):2–9.
10. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat*. April 2010;31(4):391–406.
11. Pilon N. Pigmentation-based insertional mutagenesis is a simple and potent screening approach for identifying neurocristopathy-associated genes in mice. *Rare Dis*. January 1, 2016;4(1):4483–4496.
12. Takeda K, Takahashi NH, Shibahara S. Neuroendocrine functions of melanocytes: Beyond the skin-deep melanin maker. *Tohoku J Exp Med*. 2007;211(3):201–221.
13. Bondurand N, Pingault V, Goerich DE, Lemort N, Sock E, Caignec CL, Wegner M, Goossens M. Interaction among SOX10, PAX3 and MITF, three genes altered in Waardenburg syndrome. *Hum Mol Genet*. August 12, 2000;9(13):1907–1917.
14. Wang Q, Fang WH, Krupinski J, Kumar S, Slevin M, Kumar P. PAX genes in embryogenesis and oncogenesis. *J Cell Mol Med*. December 1, 2008;12(6a):2281–2294.
15. Shibahara S, Takeda K, Yasumoto KI, Udono T, Watanabe KI, Saito H, Takahashi K. Microphthalmia-associated transcription factor (MITF): multiplicity in structure, function, and regulation. In *Journal of Investigative Dermatology Symposium Proceedings* November 1, 2001 (Vol. 6, No. 1, pp. 99–104). Elsevier.
16. Sánchez-Martín M, Rodríguez-García A, Pérez-Losada J, Sagrera A, Read AP, Sánchez-García I. SLUG (SNAI2) deletions in patients with Waardenburg disease. *Hum Mol Genet*. December 1, 2002;11(25):3231–3236.
17. Ito Y, Inoue N, Inoue YU, Nakamura S, Matsuda Y, Inagaki M, Ohkubo T, Asami J, Terakawa YW, Kohsaka S, Goto YI. Additive dominant effect of a SOX10 mutation underlies a complex phenotype of PCWH. *Neurobiol Dis*. August 1, 2015;80:1–4.
18. Pla P, Larue L. Involvement of endothelin receptors in normal and pathological development of neural crest cells. *Int J Dev Biol*. June 1, 2003;47(5):315–325.
19. Doubaj Y, Pingault V, Elalaoui SC, Ratbi I, Azouz M, Zerhouni H, Ettayebi F, Sefiani A. A novel mutation in the endothelin B receptor gene in a Moroccan family with Shah-Waardenburg syndrome. *Mol Syndromol*. 2015;6(1):44–49.
20. Charrier B, Pilon N. Toward a better understanding of enteric gliogenesis. *Neurogenesis*. January 1, 2017;4(1):1283–1293.
21. Bergeron KF, Nguyen CM, Cardinal T, Charrier B, Silversides DW, Pilon N. Upregulation of the Nr2f1-A830082K12Rik gene pair in murine neural crest cells results in a complex phenotype reminiscent of Waardenburg syndrome type 4. *Dis Model Mech*. 2016 Nov 1;9(11):1283–93.
22. Issa S, Bondurand N, Faubert E et al. EDNRB mutations cause Waardenburg syndrome type II in the heterozygous state. *Hum Mutat*. 2017, 38(5):581–593.
23. Huggins RH, Janusz CA, Schwartz RA. Vitiligo: A sign of systemic disease. *Indian J Dermatol Venereol Leprol*. January 1, 2006;72(1):68.
24. Que SK, Weston G, Suchecki J, Ricketts J. Pigmentary disorders of the eyes and skin. *Clin Dermatol*. March 1, 2015;33(2):147–158.
25. Watanabe S, Matsudera S, Yamaguchi T, Tani Y, Ogino K, Nakajima M, Yamaguchi S, Sasaki K, Suzumura H, Tsuchioka T. Waardenburg syndrome with isolated deficiency of myenteric ganglion cells at the sigmoid colon and rectum. *Pediatr Rep*. May 24, 2018;10(2).
26. Seiberg M. Age-induced hair greying—The multiple effects of oxidative stress. *Int J Cosmetic Sci*. December 2013;35(6):532–538.
27. Karaman A, Aliagaoglu C. Waardenburg syndrome type 1. *Dermatol Online J*. January 1, 2003;12(3).
28. Pardono E, van Bever Y, van den Ende J, Havrenne PC, Iughetti P, Maestrelli SR, Costa FO, Richieri-Costa A, Frota-Pessoa O, Otto PA. Waardenburg syndrome: Clinical differentiation between types I and II. *Am J Med Genet A*. March 15, 2003;117(3):223–235.
29. Kumar P. Synophrys: Epidemiological study. *Int J Trichology*. July 2017;9(3):105.

1. Casala AM, Alezzandrini AA. Vitiligo, poliosis unilateral con retinitis pigmentaria y hypoacusia. *Arch Argent Dermatol*. 1959;9:449.
2. Alezzandrini AA. Unilateral manifestations of tapeto-retinal degeneration, vitiligo, poliosis, grey hair and hypoacousia. *Ophthalmologica*. 1964;147:409–419.
3. Ziprkowski L, Krakowski A, Adam A et al. Partial albinism and deaf-mutism due to a recessive sex-linked gene. *Arch Derm*. October 1962;86:530–539.
4. Margolis E. A new hereditary syndrome: Sex-linked deaf-mutism associated with total albinism. *Acta Genet*. 1962;12:12–19.
5. Cross HE, McKusick VA, Breen W. A new oculocerebral syndrome with hypopigmentation. *J Pediatr*. March 1967;70:398–406.
6. Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: Report of two cases with histochemical studies. *Blood*. February 1959;14:162–169.
7. Pierson DM, Ionescu D, Qing G et al. Pulmonary fibrosis in Hermansky-Pudlak syndrome. A case report and review. *Respir Int Rev Thorac Dis*. 2006;73:382–395.
8. Christensen S, Wagner L, Colema MM. et al. The lived experience of having a rare medical disorder: Hermansky-Pudlak syndrome. *Chronic Illn*. March 2017;13(1):62–72.
9. Vici CD, Sabetta G, Gambarara M et al. Agenesis of the corpus callosum, combined immunodeficiency, bilateral cataract, and hypopigmentation in two brothers. *Am J Med Genet*. January 1988;29(1):1–8.
10. Cullup T, Kho AL, Dionisi-Vici C et al. Recessive mutations in EPG5 cause Vici syndrome, a multisystem disorder with defective autophagy. *Nat Genet*. January 2013;45(1):83–87.
11. Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. *Curr Opin Hematol*. January 2008;15(1):22–29.
12. Griscelli C, Durandy A, Guy-Grand D et al. A syndrome associating partial albinism and immunodeficiency. *Am J Med*. October 1978;65:691–702.
13. Andrade A, Pithon M. Alezzandrini syndrome: Report of a sixth clinical case. *Dermatology*. February 2011;222(1):8–9.
14. Chabchoub E, Cogulu O, Durmaz B et al. Oculocerebral hypopigmentation syndrome maps to chromosome 3q27.1q29. *Dermatology*. 2011;223(4): 306–310.
15. Asztalos ML, Schafemak KT, Gray J et al. Hermansky-Pudlak syndrome: Report of two patients with updated genetic classification and management recommendations. *Pedriatr Dermatol*. November 2017;34(6):638–646.
16. Byrne S, Dionisi-Vici C, Smith L et al. Vici syndrome: A review. *Orphanet J Rare Dis*. February 29, 2016;11:21.
17. Kumar M, Sackey K, Schmalstieg F et al. Griscelli syndrome: Rare neonatal syndrome of recurrent hemophagocytosis. *J Pediatr Hematol Oncol*. October 2001;23(7):464–468.
18. Shiloh Y, Litvak G, Ziv Y et al. Genetic mapping of X-linked albinism-deafness syndrome (ADFN) to Xq26.3-q27.I. *Am J Hum Genet*. July 2006;47(1):20–27.
19. Gahl WA, Brantly M, Kaiser-Kupfer MI et al. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (Hermansky-Pudlak syndrome). *N Engl J Med*. April 30, 1998;338(18):1258–1264.
20. Byrne S, Jansen L, U-King Im JM et al. EPG-related Vici syndrome: A paradigm of neurodevelopmental disorders with defective autophagy. *Brain*. March 2016;139(Pt 3):765–781.
21. Barrat FJ, Auloge L, Pastural E et al. Genetic and physical mapping of the Chediak-Higashi syndrome on chromosome 1q42-43. *Am J Hum Genet*. 1996 Spt;59(3):625–632.
22. Durchfort N, Verhoef S, Vaughn MB et al. The enlarged lysosomes in beige J cells result from decreased lysosome fission and not increased lysosome fusion. *Traffic*. January 2012;13(1):108–119.
23. Menasche G, Ho Chen, Sanal O et al. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F exon deletion (GS1). *J Clin Invest*. August 2003;112(3):450–456.
24. Pollazzon M, Grosso S, Papa FT et al. A 9.3 Mb microdeletion of 3q27.3q29 associated with psychomotor and growth delay, tricuspid valve dysplasia and bifid thumb. *Eur J Med Genet*. March 2009–June;52(2–3):131–133.
25. De Jong G, Fryns JP. Oculocerebral syndrome with hypopigmentation (Cross syndrome): The mixed pattern of hair pigmentation as an important diagnostic sign. *Genet Couns*. 1991;2(3):151–155.
26. Garay SM, Gardella JE, Fazzini EP et al. Hermansky-Pudlak syndrome. Pulmonary manifestations of a ceroid storage disorder. *Am J Med*. May 1979;66(5):737–747.
27. Karim MA, Suzuki K, Fukai K et al. Apparent genotype-phenotype correlation in childhood, adolescent, and adult Chediak-Higashi syndrome. *Am J Med Genet*. February 2002;108(1):16–22.
28. Mehta RS, Smith RE. Hemophagocytic lymphohistiocytosis (HLH): A review of literature. *Med Oncol*. December 2013;30(4):740.
29. Minocha P, Choudhary R, Agrawal A et al. Griscelli syndrome subtype 2 with hemophagocytic lympho-histiocytosis: A case report and review of literature. *Intractable Rare Dis Res*. February 2017;6(1):76–79.
30. Dotta L, Parolini S, Prandini A et al. Clinical, laboratory and molecular signs of immunodeficiency in patients with partial oculo-cutaneous albinism. *Orphanet J Rare Dis*. October 2013; 17;8:168.

31. Huggins RH, Janusz CA, Schwartz RA. Vitiligo: A sign of systemic disease. *Indian J Dermatol Venereol Leprol*. January 2006–February;72(1):68–71.
32. Bhatnagar A, Kanwar AJ, Parsad D et al. Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: An open prospective study. *J Eur Acad Dermatol Venereol*. May 2007;21(5):638–642.
1. Happle R. Mosaicism in human skin. *Understanding Nevi, Nevoid Skin Disorders, and Cutaneous Neoplasia*. Springer; 2014.
2. Celia Moss. Mosaicism and linear lesion. In: Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology*. Vol 1. 4th ed. Elsevier; 2018:1004–1025.
3. Happle R. The McCune Albright syndrome: A lethal gene surviving by mosaicism. *Clin Genet*. 1986;29:321–324.
4. Kurek KC, Luks VL, Ayturk UM et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *Am J Hum Genet*. 2012;90:1108–1115.
5. Happle R. The molecular revolution in cutaneous biology: Era of mosaicism. *J Invest Dermatol*. 2017;137:e73–e77.
6. Lindhurst MJ, Sapp JC, Teer JK et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med*. 2011;365:611–619.
7. Lara-Corrales I, Moazzami M, García-Romero MT et al. Mosaic neurofibromatosis type 1 in children: A single-institution experience. *J Cutan Med Surg*. 2017;21:379–382.
8. Bessis D, Malinge MC, Girard C. Isolated and unilateral facial angiofibromas revealing a type 1 segmental postzygotic mosaicism of tuberous sclerosis complex with c.4949_4982del TSC2 mutation. *Br J Dermatol*. 2018;178:e53–e54.
9. Nagao-Watanabe M, Fukao T, Matsui E et al. Identification of somatic and germline mosaicism for a keratin 5 mutation in epidermolysis bullosa simplex in a family of which the proband was previously regarded as a sporadic case. *Clin Genet*. 2004;66:236e8.
10. Happle R. Segmental forms of autosomal dominant skin disorders: Different types of severity reflect different states of zygosity. *Am J Med Genet*. 1996; 66:241–242.
11. Happle R. The concept of type 2 segmental mosaicism, expanding from dermatology to general medicine. *J Eur Acad Dermatol Venereol*. 2018;32:1075–1088.
12. Siegel DH. Cutaneous mosaicism: A molecular and clinical review. *Adv Dermatol*. 2008;24:223–244.
13. Geiman TM, Robertson KD. Chromatin remodeling histone modifications, and DNA methylation-how does it all fit together? *J Cell Biochem*. 2002;87:117–125.
14. Blaschko A. *Die Nervenverteilung in der Haut in ihre Beziehung zu den Erkrankungen der Haut*. Vienna, Austria and Leipzig, Germany: Wilhelm Braunmuller; 1901.
15. Happle R, Assim A. The lines of Blaschko on the head and neck. *J Am Acad Dermatol*. 2001;44:6125.
16. Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. *Arch Dermatol*. 1993;129:1460–1470.
17. Ito M. Studies of melanin XI. Incontinentia pigmenti achromians: A singular case of nevus depigmentosus systematicus bilateralis. *Tohoky J Exp Med* 1952; 55(Suppl):57–59.
18. Lee HS, Chun YS, Hann SK. Nevus depigmentosus: Clinical features and histopathologic characteristics in 67 patients. *J Am Acad Dermatol*. 1999;40:21–26.
19. Kim SK, Kang HY, Lee ES, Kim YC. Clinical and histopathologic characteristics of nevus depigmentosus. *J Am Acad Dermatol*. 2006;55:423–428.
20. Cohen J 3rd, Shahrokh K, Cohen B. Analysis of 36 cases of Blaschkoid dyspigmentation: Reading between the lines of Blaschko. *Pediatr Dermatol*. 2014;31:471–476.
21. Hogeling M, Fieden IJ. Segmental pigmentation disorder. *Br J Dermatol*. 2010;162:1337–1341.
22. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. *Arch Dermatol*. 1996;132:1167–1170.
23. Kromann AB, Ousager LB, Ali IKM, Aydemir N, Bygum A. Pigmentary mosaicism: A review of original literature and recommendations for future handling. *Orphanet J Rare Dis*. 2018;13:39.
24. Mirzaa GM, Campbell CD, Solovieff N et al. Association of MTOR mutations with developmental brain disorders, including megalencephaly, focal cortical dysplasia, and pigmentary mosaicism. *JAMA Neurol*. 2016;73:836–845.
25. Torchia D, Happle R. Segmental hypomelanosis and hypermelanosis arranged in a checkerboard pattern are distinct naevi: Flag-like hypomelanotic naevus and flag-like hypermelanotic naevus. *J Eur Acad Dermatol Venereol*. 2015;29:2088–2099.
26. Asch S, Sugarman JL. Epidermal nevus syndromes: New insights into whorls and swirls. *Pediatr Dermatol*. 2018;35:21–29.
27. Garcias-Ladaria J, Cuadrado Rosón M, Pascual-López M. Epidermal nevi and related syndromes—Part 1: Keratinocytic nevi. *Actas Dermosifiliogr*. 2018;109:677–686.
28. Laura FS. Epidermal nevus syndrome. *Handb Clin Neurol*. 2013;111:349–368.
29. Fusco F, Bardaro T, Fimiani G et al. Molecular analysis of the genetic defect in a large cohort of IP patients and identification of novel NEMO mutations interfering with NF-kappaB activation. *Hum Mol Genet*. 2004;13:1763–1773.
30. Greene-Roethke C. Incontinentia pigmenti: A summary review of this rare ectodermal dysplasia with neurologic manifestations, including treatment protocols. *J Pediatr Health Care*. 2017;31:e45–e52.

31. Peltomäki P, Knuutila S, Ritvanen A et al. Pallister-Killian syndrome: Cytogenetic and molecular studies. *Clin Genet*. 1987;31:399–405.
32. Karaman B, Kayserili H, Ghanbari A, Uyguner ZO, Toksoy G, Altunoglu U, Basaran S. Pallister-Killian syndrome: clinical, cytogenetic and molecular findings in 15 cases. *Mol Cytogenet*. 2018;11:45. Published online August 17, 2018. doi:10.1186/s13039-018-0395-z.
33. Wilkens A, Liu H, Park K, Campbell LB, Jackson M, Kostanecka A, Pipan M, Izumi K, Pallister P, Krantz ID. Novel clinical manifestations in Pallister-Killian syndrome: Comprehensive evaluation of 59 affected individuals and review of previously reported cases. *Am J Med Genet A*. 2012;158A:3002–3017.
34. Dhar SU, Robbins-Furman P, Levy ML, Patel A, Scaglia F. Tetrasomy 13q mosaicism associated with phylloid hypomelanosis and precocious puberty. *Am J Med Genet A*. 2009;149A:993–996.
35. Happle R. Phylloid hypomelanosis and mosaic trisomy 13: A new etiologically defined neurocutaneous syndrome. *Hautarzt*. 2001;52:3–5.
36. Braverman N, Lin P, Moebius FF et al. 1999. Mutations in the gene encoding 3 beta-hydroxysteroid-delta 8, delta 7-isomerase cause X-linked dominant Conradi-Hünermann syndrome. *Nat. Genet*. 22:291–294.
37. Clements SE, Mellerio JE, Holden St et al. PORCN gene mutation and the protean nature of focal dermal hypoplasia. *Br J Dermatol*. 2009;160:1103–1109.
38. Lim YH, Moscato Z, Choate KA. Mosaicism in cutaneous disorders. *Annu Rev Genet*. 2017;51:123–141.
39. Bachoo S, Gibbons RJ. Germline and gonosomal mosaicism in the ATR-X syndrome. *Eur J Hum Genet*. 1999;7:933–936.
40. Sachdev NM, Maxwell SM, Besser AG, Grifo JA. Diagnosis and clinical management of embryonic mosaicism. *Fertil Steril*. 2017;107:6–11.
1. Saleem MD, Oussedik E, Picardo M et al. Acquired disorders with hypopigmentation: A clinical approach to diagnosis and treatment. *J Am Acad Dermatol*. 2019;80:1233–1250.e10. doi: 10.1016/j.jaad.2018.07.070
2. Vachiramon V, Thadanipon K. Postinflammatory hypopigmentation. *Clin Exp Dermatol*. 2011;36:708–714. doi: 10.1111/j.1365-2230.2011.04088.x.
3. Tey HL. Approach to hypopigmentation disorders in adults. *Clin Exp Dermatol*. 2010;35:829–834. doi: 10.1111/j.1365-2230.2010.03853.x.
4. Passeron T, Ortonne J. Vitiligo and other disorders of hypopigmentation. In: Callen J, ed. *Dermatology* by Jean L. Bolognia, Julie V. Schaffer, and Lorenzo Cerroni, 4th ed. China: Elsevier; 2018:1103–1106.
5. Nicolaidou E, Katsambas AD. Pigmentation disorders: Hyperpigmentation and hypopigmentation. *Clin Dermatol*. 2014;32:66–72.
6. Patel AB, Kubba R, Kubba A. Clinicopathological correlation of acquired hypopigmentary disorders. *Indian J Dermatol Venereol Leprol*. 2013;79:376–382.
7. Disturbances of Pigmentation. In: James W, ed. *Andrews' Diseases of the Skin: Clinical Dermatology*, 12th ed. China: Elsevier; 2016:856, 870.
8. Hartmann A, Bröcker EB, Becker JC. Hypopigmentary skin disorders: Current treatment options and future directions. *Drugs*. 2004;64:89–107.
9. Ruiz-Maldonado R, Orozco-Covarrubias ML. Post-inflammatory hypopigmentation and hyperpigmentation. *Semin Cutan Med Surg*. 1997;16:36–43.
10. Mollet I, Ongenae K, Naeyaert JM. Origin, clinical presentation, and diagnosis of hypomelanotic skin disorders. *Dermatol Clin*. 2007;25:363–371, ix. doi: 10.1016/j.det.2007.04.013.
11. Plensdorf S, Livieratos M, Dada N. Pigmentation disorders: Diagnosis and management. *Am Fam Physician*. 2017;96:797–804.
12. Tey HL. A practical classification of childhood hypopigmentation disorders. *Acta Derm Venereol*. 2010;90:6–11.
13. Engin RI, Cayir Y. Pigmentation disorders: A short review. *Pigment Disord*. 2015;2:6. doi: 10.4172/2376-0427.1000189.
14. Kuriyama S, Kasuya A, Fujiyama T et al. Leukoderma in patients with atopic dermatitis. *J Dermatol*. 2015;42:215–218.
15. Sugita K, Izu K, Tokura Y. Vitiligo with inflammatory raised borders, associated with atopic dermatitis. *Clin Exp Dermatol*. 2006;31:80–82.
16. Lopez I, Ahmed A, Pandya AG. Topical PUVA for post-inflammatory hypopigmentation. *J Eur Acad Dermatol Venereol*. 2011;25:742–743.
17. Connective tissue diseases. In: James W, ed. *Andrews' Diseases of the Skin: Clinical Dermatology*, 12th ed. China: Elsevier; 2016:153–162.
18. Amorim GM, Niemeyer-Corbellini JP, Quintella DC et al. Hypopigmented mycosis fungoides: A 20-case retrospective series. *Int J Dermatol*. 2018;57:306–312.
19. Castano E, Glick S, Wolgast L et al. Hypopigmented mycosis fungoides in childhood and adolescence: A long-term retrospective study. *J Cutan Pathol*. 2013;40:924–934.
20. Furlan FC, Sanches JA. Hypopigmented mycosis fungoides: A review of its clinical features and pathophysiology. *An Bras Dermatol*. 2013;88:954–960.
1. Balevi A, Üstüner P, Kakşi SA et al. Narrow-band UV-B phototherapy: An effective and reliable treatment alternative for extensive and recurrent pityriasis versicolor. *J Dermatolog Treat* 2018;29(3):252–255.
2. Gobbato AA, Babadópulos T, Gobbato CA et al. A randomized double-blind, non-inferiority Phase II trial, comparing dapaconazoletosylate 2% cream with ketoconazole 2% cream in the treatment of pityriasis versicolor. *Expert Opin Investig Drugs* 2015;24(11):1399–1407.
3. Santana JO, Azevedo FL, Campos Filho PC. Pityriasis versicolor: Clinical-epidemiological characterization of patients in the urban area of Buerarema-BA, Brazil. *An Bras Dermatol* 2013;88(2):216–221.

4. Prohic A, JovovicSadikovic T, Krupalija-Fazlic M et al. *Malassezia* species in healthy skin and in dermatological conditions. *Int J Dermatol* 2016; 55(5):494–504.
5. Elshabrawy WO, Saudy N, Sallam M. Molecular and phenotypic identification and speciation of *Malassezia* yeasts isolated from Egyptian patients with pityriasis versicolor. *J ClinDiagn Res* 2017;11(8):DC12–DC17.
6. Lee KH, Kim YG, Bang D et al. Scanning electron microscopy of *Malassezia furfur* in tinea versicolor. *Yonsei Med J* 1989;30(4):334–338.
7. Romero-Sandoval K, Costa AA, Teixeira Sousa MG et al. Recurrent and disseminated pityriasis versicolor: A novel clinical form consequent to *Malassezia*-host interaction?. *Med Hypotheses* 2017;109:139–144.
8. Ibekwe PU, Ogunbiyi AO, Besch R et al. The spectrum of *Malassezia* species isolated from students with pityriasis versicolor in Nigeria. *Mycoses* 2015;58(4):203–208.
9. Gaitanis G, Magiatis P, Hantschke M et al. The *Malassezia* genus in skin and systemic diseases. *ClinMicrobiol Rev* 2012;25(1):106–141.
10. Pakran J, Riyaz N. Interesting effect of *Malassezia* spp. infection on dermatoses of other origins. *Int J Dermatol* 2011;50(12):1518–1521.
11. Rad F, Nik-Khoo B, Yaghmaee R et al. Terbinafin 1% cream and ketoconazole 2% cream in the treatment of pityriasis versicolor: A randomized comparative clinical trial. *Pak J Med Sci* 2014;30(6):1273–1276.
12. Rasi A, Naderi R, Behzadi AH et al. *Malassezia* yeast species isolated from Iranian patients with pityriasis versicolor in a prospective study. *Mycoses* 2010;53(4):350–355.
13. Boralevi F, Marco-Bonnet J, Lepreux S et al. Hyperkeratotic head and neck *Malassezia* dermatosis. *Dermatology* 2006;212(1):36–40.
14. Kallini JR, Riaz F, Khachemoune A. Tinea versicolor in dark-skinned individuals. *Int J Dermatol* 2014;53(2):137–141.
15. Prohic A, Ozegovic L. *Malassezia* species isolated from lesional and non-lesional skin in patients with pityriasis versicolor. *Mycoses* 2007;50(1):58–63.
16. Gupta AK, Kogan N, Batra R. Pityriasis versicolor: A review of pharmacological treatment options. *Expert OpinPharmacother* 2005;6(2):165–178.
17. Kröger S, Neuber K, Gruseck E et al. Pityrosporumovale extracts increase interleukin-4, interleukin-10 and IgE synthesis in patients with atopic eczema. *ActaDermVenereol* 1995;75(5):357–360.
18. Darling MJ, Lambiase MC, Young RJ. Tinea versicolor mimicking pityriasisrubra pilaris. *Cutis* 2005;75(5):265–267.
19. Mostafa WZ, Assaf MI, Ameen IA et al. Hair loss in pityriasis versicolor lesions: A descriptive clinicopathological study. *J Am AcadDermatol* 2013;69(1):e19–e23.
20. Gaitanis G, Velegraki A, Frangoulis E et al. Identification of *Malassezia* species from patient skin scales by PCR-RFLP. *ClinMicrobiol Infect* 2002;8(3):162–173.
21. Zawar V, Chuh A. Case report on *Malassezia* infection of palms and fingernails—Speculations on cause for therapeutic failure in pityriasis versicolor. *J Eur Acad Dermatol Venereol* 2009;(2):171–172.
22. Nasarre J, Umbert P, Herrero E et al. Therapeutic efficacy and safety of the new antimycotic sertaconazole in the treatment of pityriasis versicolor. *Arzneimittelforschung* 1992;42(5A):764–767.
23. Cruz RCDS, Bührer-Sékula S, Penna MLF et al. Leprosy: Current situation, clinical and laboratory aspects, treatment history and perspective of the uniform multidrug therapy for all patients. *An Bras Dermatol* 2017;92(6):761–773.
24. Reibel F, Cambau E, Aubry A. Update on the epidemiology, diagnosis, and treatment of leprosy. *Med Mal Infect* 2015;45(9):383–393.
25. Daniel OJ, Adejumo OA, Oritogun KS et al. Spatial distribution of leprosy in Nigeria. *Lepr Rev* 2016;87(4):476–485.
26. Wang N, Wang Z, Wang C et al. Prediction of leprosy in the Chinese population based on a weighted genetic risk score. *PLoS Negl Trop Dis* 2018;12(9):e0006789.
27. Campos de Carvalho J, Araújo MG, Alves Coelho-Dos-Reis JG et al. Phenotypic and functional features of innate and adaptive immunity as putative biomarkers for clinical status and leprosy reactions. *Microb Pathogpii* 2018;S0882-4010(18)30305-X.
28. Centers for Disease Control and Prevention (CDC). Hansen's disease (Leprosy). Available at: https://www.cdc.gov/leprosy/about/about.html. Accessed on March 20, 2019.
29. Suryawati N, Saputra H. Erythema nodosum leprosum presenting as Sweet's syndrome-like reaction in a borderline lepromatous leprosy patient. *Int J Mycobacteriol*. April 2018–June;7(2):191–194.
30. World Health Organization (WHO). Leprosy. Available at: https://www.who.int/lep/disease/en/. Accessed on March 20, 2019.
31. Narang T, Vinay K, Kumar S et al. A critical appraisal on pure neuritic leprosy from India after achieving WHO global target of leprosy elimination. *Lepr Rev* 2016;87(4):456–463.
32. Secchin-De-Andrade PJ, De Andrea Vilas-Boas, Hacker M et al. Corticosteroid therapy in borderline tuberculoid leprosy patients co-infected with HIV undergoing reversal reaction: A clinical study. *Lepr Rev* 2016;87(4):516–525.
33. Gupta S, Bhatt S, Bhargava SK et al. High resolution sonographic examination: A newer technique to study ulnar nerve neuropathy in leprosy. *Lepr Rev* 2016;87(4):464–475.

34. Hattori M, Motegi S, Amano H et al. Borderline lepromatous leprosy: Cutaneous manifestation and type 1 reversal reaction. *Acta DermVenereol* 2016;96(3):422–423.
35. Rocha RH, Emerich PS, Diniz LM et al. Lucio's phenomenon: Exuberant case report and review of Brazilian cases. *An Bras Dermatol* 2016;91(5 suppl 1): 60–63.
36. Rao PN. Global leprosy strategy 2016–2020: Issues and concerns. *Indian J Dermatol Venereol Leprol*. January 2017–February ;83(1):4–6.
37. Centers for Disease Control and Prevention (CDC). Leprosy. Laboratory Diagnostics. Available at: https://www.cdc.gov/leprosy/health-care-workers/laboratory-diagnostics.html. Accessed on March 20, 2019.
38. World Health Organization (WHO). Guidelines for the diagnosis, treatment and prevention of leprosy. Executive summary. Available at: http://www.searo.who.int/entity/global_leprosy_programme/approved-guidelines-leprosy-executives-summary.pdf?ua=1. Assessed on March 20, 2019.
39. Thapa M, Sendhil Kumaran M, Narang T et al. A prospective study to validate various clinical criteria used in classification of leprosy: A study from a tertiary care center in India. *Int J Dermatol* 2018;57(9):1107–1113.
40. World Health Organization (WHO). *Onchocerciasis—Fact Sheet*. WHO, 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/onchocerciasis. Accessed on September 9, 2018.
41. Veraldi S. Oncocercosi. In: *Dermatologia di importazione*, 2nd edition (Veraldi S and Caputo R, eds). Milano: Poletto Editore, 2000: 203–209.
42. Basáñez MG, Pion SD, Churcher TS et al. River blindness: A success story under threat? *PLoS Med* 2006;3:e371.
43. The Australian Society for Parasitology. *Onchocerca*. The Australian Society for Parasitology, 2018. Available at: http://parasite.org.au/para-site/text/onchocerca-text.html. Accessed on September 9, 2018.
44. Saint André AV, Blackwell NM, Hall LR et al. The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. *Science* 2002;295:1892–1895.
45. Hall LR, Pearlman E. Pathogenesis of onchocercal keratitis (River blindness). *Clin Microbiol Rev* 1999;12:445–453.
46. McKechnie NM, Gürr W, Yamada H et al. Antigenic mimicry: *Onchocerca volvulus* antigen-specific T cells and ocular inflammation. *Invest Ophthalmol Vis Sci* 2002;43:411–418.
47. Stingl P. Onchocerciasis: Developments in diagnosis, treatment and control. *Int J Dermatol* 2009;48:393–396.
48. Van Laethem Y, Lopes C. Treatment of onchocerciasis. *Drugs*. 1996;52:861–869.
49. Hoerauf A, Specht S, Marfo-Debrekyei Y et al. Efficacy of 5-week doxycycline treatment on adult *Onchocerca volvulus*. *Parasitol Res* 2009;104: 437–447.
50. Giacani L, Lukehart SA. The endemic treponematoses. *ClinMicrobiol Rev*. 2014;27:89–115.
51. Turner TB, Hollander DH. *Biology of the Treponematoses*. Geneva: World Health Organization, 1957.
52. Mitjà O, Hays R, Ipai A et al. Osteoperiostitis in early yaws: Case series and literature review. *Clin Infect Dis* 2011;52:771–774.
53. Mitjà O, Šmajs D, Bassat Q. Advances in the diagnosis of endemic treponematoses: Yaws, bejel, and pinta. *PLoS Negl Trop Dis*. 2013;7:e2283.
54. Hasselmann CM. Comparative studies on the histopathology of syphilis, yaws, and pinta. *Br J Venereal Dis* 1957;33:5–e2212.
55. Fuchs J, Milbradt R, Pecher SA. Tertiary pinta: Case reports and overview. *Cutis* 1993;51:425–430.
56. Garner MF, Backhouse JF, Daskolopolous G, Walsh JL. Treponema pallidum haemagglutination test for yaw; comparison with the TPI and FTA-ABS tests. *Br J Vener Dis* 1972;48:479–482.
57. Menke HE, Veldkamp J, Brunings EA et al. Comparison of cardiolipin and treponemal tests in the serodiagnosis of yaws. *Br J Vener Dis* 1979;55:102–104.
58. Jafari Y, Peeling RW, Shivkumar S et al. Are *Treponema pallidum* specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PLOS ONE* 2013;8:e54695.
59. Yin YP, Chen XS, Wei W et al. A dual point-of-care test shows good performance in simultaneously detecting non-treponemal and treponemal antibodies in patients with syphilis—A multi-site evaluation study in China. *Clin Infect Dis* 2013;56:659–665.
60. World Health Organization (WHO). Yaws. Available at: https://www.who.int/news-room/fact-sheets/detail/yaws. Accessed on March 20, 2019.
61. Hook EW 3rd. Syphilis. *Lancet* 2017;389:1550–1557.
62. Freitas DMM, Azevedo A, Pinheiro G, Ribeiro R. Psoriasiform papules, condylomalata, lung nodules and hepatitis: The enormous variability of secondary syphilis manifestations. *BMJ Case Rep*. 2017;2017:pii: bcr-2017–219408. doi: 10.1136/bcr-2017–219408.
63. Eyer-Silva WA, Martins CJ, Silva GARD et al. Secondary syphilis presenting as leukoderma syphiliticum: Case report and review. *Rev Inst Med Trop Sao Paulo* 2017;59: e74.
64. Janier M, HegyiV, Dupin N et al. 2014 European guideline on the management of syphilis. *J Eur Acad Dermatol Venereol* 2014;28:1581–1e93.
65. WHO. *Guidelines for the Treatment of* Treponema pallidum *(Syphilis)*. Geneva: World Health Organization, 2016.
66. Stamm LV. Syphilis: Antibiotic treatment and resistance. *Epidemiol Infect* 2015;143:1567–1574.

1. Saleem MD, Oussedik E, Schoch JJ et al. Acquired disorders with depigmentation: A systematic approach to vitiliginoid conditions. *J Am Acad Dermatol*. 2018. pii: S0190-9622(18)32506-4. doi:10.1016/j.jaad.2018.03.063. [Epub ahead of print].
2. Teulings HE, Willemsen KJ, Glykofridis et al. The antibody response against MART-1 differs in patients with melanoma-associated leucoderma and vitiligo. *Pigment Cell Melanoma Res*. 2014;27:1086–1096.
3. Vyas R, Selph J, Gerstenblith MR. Cutaneous manifestations associated with melanoma. *Semin Oncol*. 2016; 43: 384–389.
4. Teulings HE, Lommerts JE, Wolkerstorfer A et al. Vitiligo-like depigmentations as the first sign of melanoma: A retrospective case series from a tertiary vitiligo centre. *Br J Dermatol*. 2017;176:503–506.
5. Lommerts JE, Teulings HE, Ezzedine K et al. Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field. *J Am Acad Dermatol*. 2016;75:1198–1204.
6. Passeron T, Ortonne J. Vitiligo and Other Disorders of Hypopigmentation. In: Callen J, editor. *Dermatology by Jean L. Bolognia, Julie V. Schaffer, and Lorenzo Cerroni*, 4th ed. China: Elsevier, 2018:1108–1109.
7. Ben-Betzalel G, Baruch EN, Boursi B et al. Possible immune adverse events as predictors of durable response to BRAF inhibitors in patients with BRAF V600-mutant metastatic melanoma. *Eur J Cancer*. 2018;101:229–235.
8. Naveh HP, Rao UN, Butterfield LH. Melanoma-associated leukoderma—Immunology in black and white? *Pigment Cell Melanoma Res*. 2013;26:796–804.
9. Spring IR, de Wet J, Jordaan HF et al. Complete spontaneous regression of a metastatic acral melanoma with associated leukoderma. *JAAD Case Rep*. 2017;3:524–528.
10. Quaglino P, Marenco F, Osella-Abate S et al. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Ann Oncol*. 2010;21:409–414.
11. Ezzedine K, Lim HW, Suzuki T et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012;25:E1–13.
12. González R, Torres-López E. Immunological basis of melanoma-associated vitiligo-like depigmentation. *Actas Dermosifiliogr*. 2014;105:122–127.
1. Aouthmany M, Weinstein M, Zirwas MJ, Brodell RT. The natural history of halo nevi: A retrospective case series. *J Am Acad Dermatol*. 2012;67:582–586.
2. Weyant G, Chung C, Helm K. Halo nevus: Review of the literature and clinicopathologic findings. *Int J Dermatol*. 2015;54:30–447.
3. Haliasos EC, Kerner M, Jaimes N et al. Dermoscopy for the pediatric dermatologist; Part III: Dermoscopy of melanocytic lesions. *Pediatr Dermatol*. 2012; doi:10.1111/pde.12041.
4. Zalaudek I, Manzo M, Ferrara G, Argenziano G. A new classification of melanocytic nevi based on dermoscopy. *Expert Rev Dermatol*. 2008;3:477–489.
5. Van Geel N, Speeckaert R, Lambert J et al. Halo naevi with associated vitiligo-like depigmentations: Pathogenetic hypothesis. *J Eur Acad Dermatol Venereol*. 2012;26: 755–761.
6. MacKie RM. Disorders of the cutaneous melanocyte: halo naevus. In: Burns T, Breathnach S, Cox N, Griffith C, eds. *Rook's Textbook of Dermatology*. Vol 2. 7th ed. Oxford, England: Blackwell Scientific Publications, 2004: 1–39.
7. Herd RM, Hunter JA. Familial halo naevi. *Clin Exp Dermatol*. 1998;23:68–69.
8. Kuet K, Goodfield M. Multiple halo naevi associated with tocilizumab. *Clin Exp Dermatol*. 2014;39:717–719.
9. Thivi Maruthappu T, Leandro M, Morris M. Deterioration of vitiligo and new onset of halo naevi observed in two patients receiving adalimumab. *Dermatologic Therapy* 2013;26:370–372.
10. Rabinovitz HS, Barnhill R. Benign melanocytic neoplasms: halo nevus. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. Vol 2. 3rd ed. Elsevier, 2012;1851–1880.
11. Larre Borges A, Zalaudek I, Longo C et al. Melanocytic nevi with special features: Clinical-dermoscopic and reflectance confocal microscopic-findings. *J Eur Acad Dermatol Venereol*. 2014;28:833–845.
12. Kerr OA, Schlofield O. Halo congenital nevi. *Pediatr Dermatol*. 2003;20:541–542.
13. Harvell JD, Meehan SA, LeBoit PE. Spitz's nevi with halo reaction: A histopathologic study of 17 cases. *J Cutan Pathol*. 1997;24:611–619.
14. Zeff RA, Freitag A, Grin CM, Grant-Kels JM. The immune response in halo nevi. *J Am Acad Dermatol*. 1997;37:620–624.
15. Mooney MA, Barr RJ, Buxton MG. Halo nevus or halo phenomenon? A study of 142 cases. *J Cutan Pathol*. 1995;22: 342–348.
16. Kolm I, Di Stefani A, Hofmann-Wellenhof R et al. Dermoscopy patterns of halo nevi. *Arch Dermatol*. 2006;142:1627–1632.
17. Schwartz RJ, Vera K, Navarrete N, Lobos P. *In vivo* reflectance confocal microscopy of halo nevus. *J Cutan Med Surg*. 2013;17:33–38.
18. Argenziano G, Soyer HP, Chimenti S et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the Internet. *J Am Acad Dermatol*. 2003;48:679–693.
19. Zalaudek I, Argenziano G, Ferrara G et al. Clinically equivocal melanocytic skin lesions with features of regression: A dermoscopic-pathological study. *Br J Dermatol*. 2004;150:64–71.

20. De Vijlder HC, Westerhof W, Schreuder GM et al. Difference in pathogenesis between vitiligo vulgaris and halo nevi associated with vitiligo is supported by an HLA study. *Pigment Cell Res*. 2004;17: 270–274.
21. Van Geel N, Vandenhaute S, Speeckaert R et al. Prognostic value and clinical significance of halo naevi regarding vitiligo. *Br J Dermatol*. 2011;164:743–749.
22. Schallreuter KU, Kothari S, Elwary S et al. Molecular evidence that halo in Sutton's naevus is not vitiligo. *Arch Dermatol Res*. 2003;295:223–228.
23. Kim HS, Goh BK. Vitiligo after halo formation around congenital melanocytic nevi. *Pediatr Dermatol*. 2009;26: 755–756.
24. Itin PH, Lautenschlager S. Acquired leukoderma in congenital pigmented nevus associated with vitiligo depigmentation. *Pediatr Dermatol*. 2002;19: 73–75.
25. Stierman SC, Tierney E, Shwayder TA. Halo congenital nevocellular nevi associated with extralesional vitiligo: Case series with review of the literature. *Pediatr Dermatol*. 2009;26: 414–424.
26. Ezzedine K, Diallo A, Leaute-Labreze C et al. Halo naevi and leukotrichia are strong predictors of the passage to mixed vitiligo in a subgroup of segmental vitiligo. *BrJ Dermatol*. 2012;166:539–544.
27. Ezzedine K, Diallo A, Léauté-Labrèze C et al. Halo nevi association in nonsegmental vitiligo affects age at onset and depigmentation pattern. *Arch Dermatol*. 2012;148:497–502.
28. Patrizi A, Bentivogli M, Raone B et al. Association of halo nevus/i and vitiligo in childhood: A retrospective observational study. *J Eur Acad Dermatol Venereol*. 2013;27:e148–e152.
29. van Geel NA, Mollet IG, De Schepper S et al. First histopathological and immunophenotypic analysis of early dynamic events in a patient with segmental vitiligo associated with halo nevi. *Pigment Cell Melanoma Res*. 2010;23:375–384.
30. Cohen BE, Mu EW, Orlow SJ. Comparison of childhood vitiligo presenting with or without associated halo nevi. *Pediatr Dermatol*. 2016;33:44–48.
1. Nicolaidou E, Katsambas AD. Pigmentation disorders: Hyperpigmentation and hypopigmentation. *Clin Dermatol*. January 2014–February;32(1):66–72.
2. Ross JS, Schenkein DP, Pietrusko R et al. Targeted therapies for cancer 2004. *Am J Clin Pathol*. October 2004;122(4):598–609.
3. Dai J, Belum VR, Wu S et al. Pigmentary changes in patients treated with targeted anticancer agents: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;77(5):902–910.e2.
4. Belum VR, Washington C, Pratilas CA et al. Dermatologic adverse events in pediatric patients receiving targeted anticancer therapies: A pooled analysis. *Pediatr Blood Cancer*. 2015;62(5):798–806.
5. Arora B, Kumar L, Sharma A et al. Pigmentary changes in chronic myeloid leukemia patients treated with imatinibmesylate. *Ann Oncol*. 2004;15(2):358–359.
6. Mariani S, Abruzzese E, Basciani S et al. Reversible hair depigmentation in a patient treated with imatinib. *Leuk Res*. 2011;35(6):e64–e66.
7. Valeyrie L, Bastuji-Garin S, Revuz J et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: A prospective study of 54 patients. *J Am Acad Dermatol*. 2003;48:201–206.
8. Balagula Y, Pulitzer MP, Maki RG, Myskowski PL. Pigmentary changes in a patient treated with imatinib. *J Drugs Dermatol*. 2011;10:1062.
9. Han H, Yu YY, Wang YH. Imatinibmesylate-induced repigmentation of vitiligo lesions in a patient with recurrent gastrointestinal stromal tumors. *J Am Acad Dermatol*. 2008;59:S80–S83.
10. Brazzelli V, Grasso V, Barbaccia V et al. Hair depigmentation and vitiligo-like lesions in a leukaemic paediatric patient during chemotherapy with dasatinib. *Acta Derm Venereol*. 2012;92:218–219.
11. Fujimi A, Ibata S, Kanisawa Y et al. Reversible skin and hair depigmentation during chemotherapy with dasatinib for chronic myeloid leukemia. *J Dermatol*. January 2016;43(1):106–107.
12. Goyal S, Shah S, Khan AJ et al. Evaluation of acute locoregional toxicity in patients with breast cancer treated with adjuvant radiotherapy in combination with pazopanib. *ISRN Oncol*. 2012;2012:896202.
13. Sideras K, Menefee ME, Burton JK et al. Profound hair and skin hypopigmentation in an African American woman treated with the multi-targeted tyrosine kinase inhibitor pazopanib. *J Clin Oncol*. July 1, 2010;28(19):e312–e313.
14. Hartmann JT, Kanz L. Sunitinib and periodic hair depigmentation due to temporary c-KIT inhibition. *Arch Dermatol*. 2008;144:1525–1526.
15. Al Enazi MM, Kadry R, Mitwali H. Skin depigmentation induced by sunitinib treatment of renal cell carcinoma. *J Am Acad Dermatol*. November 2009;61(5):905–906.
16. Hussain SZ, Asghar A, Ikram M, Islam N. Development of skin hypopigmentation in a patient with metastatic papillary carcinoma thyroid treated with Sorafenib. *BMC Endocrine Disorders*. 2013;13:29.
17. Freeman-Keller M, Kim Y, Cronin H et al. Nivolumab in resected and unresectable metastatic melanoma: Characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. February 15, 2016;22(4):886–894.
18. Hua C, Boussemart L, Mateus C et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol*. 2016;152:45–51.
19. Larsabal M, Marti A, Jacquemin C et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol*. May 2017;76(5):863–870.

20. Teulings HE, Limpens J, Jansen SN et al. Vitiligo-like depigmentation in patients with stage III–IV melanoma receiving immunotherapy and its association with survival: A systematic review and meta-analysis. *J Clin Oncol*. 2015;33:773–781.
21. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. January 11, 2018;378(2):158–168.
22. Wolner ZJ, Marghoob AA, Pulitzer MP et al. A case report of disappearing pigmented skin lesions associated with pembrolizumab treatment for metastatic melanoma. *Br J Dermatol*. January 2018;178(1):265–269.
23. Nakamura Y, Tanaka R, Asami Y et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: A multi-institutional retrospective study. *J Dermatol*. February 2017;44(2):117–122.
24. Yin ES, Totonchy MB, Leventhal JS. Nivolumab-associated vitiligo-like depigmentation in a patient with acute myeloid leukemia: A novel finding. *JAAD Case Rep*. 2017 2;3(2):90–92.
25. Imfinzi significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer. AstraZeneca; May 12, 2017. https://www.astrazeneca.com/media-centre/press-releases/2017. Accessed July 31, 2017.
26. Martín-García RF, del R Camacho N, Sánchez JL. Chloroquine-induced, vitiligo-like depigmentation. *J Am Acad Dermatol*. June 2003;48(6):981–983.
27. Donovan JC, Price VH. Images in clinical medicine. Chloroquine-induced hair hypopigmentation. *N Engl J Med*. 2010;363:372.
28. Bae JM, Choi KH, Jung HM et al. Subsequent vitiligo after hematopoietic stem cell transplantation: A nationwide population-based cohort study from Korea. *J Am Acad Dermatol*. March 2017;76(3):459–463.
29. Zuo RC, Naik HB et al. Risk factors and characterization of vitiligo and alopecia areata in patients with chronic graft-vs-host disease. *JAMA Dermatol*. 2015;151(1):23–32.
30. Tan AW, Koh LP, Goh BK. Leucoderma in chronic graft-versus-host disease: Excellent repigmentation with noncultured cellular grafting. *Br J Dermatol*. 2011;165(2):435–437.
31. Mimouni D, David M, Feinmesser M et al. Vitiligo-like leucoderma during photochemotherapy for mycosis fungoides. *Br J Dermatol*. 2001;145:1008–1014.
32. Zhu H, Hu J, Chen L et al. J. The 12-year follow-up of survival, chronic adverse effects, and retention of arsenic in patients with acute promyelocytic leukemia. *Blood*. 2016 15;128(11):1525–1528.
33. Holla AP, Kumar R, Parsad D, Kanwar A. Proton pump inhibitor induced depigmentation in vitiligo. *J Cutan Aesthet Surg*. January 2011;4(1):46–47.
34. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol*. 2006;54:1–15.
35. Weaver J. Postmarketing safety review—PID D010141. Drugs: Topical corticosteroids. FDA Web site. July 9, 2001. Available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3999B1_21_Weaver-Memo%2007-09-01.pdf. Accessed on May 5, 2019.
36. Gupta AK, Rasmussen JE. Perilesional linear atrophic streaks associated with intralesional corticosteroid injections in a psoriatic plaque. *Pediatr Dermatol*. 1987;4:259–260.
37. Shah CP, Rhee D, Garg SJ. Eyelid cutaneous hypopigmentation after sub-tenon triamcinolone injection after retinal detachment repair. *Retin Cases Brief Rep*. 2012 Summer;6(3):271–272.
38. Salvatierra AR, Alweis R. Permanent hypopigmentation after triamcinolone injection for tennis elbow. *J Commun Hosp Int Med Perspect*. July 6, 2016;6(3):31814.
39. Kwon HH, Cho KH. Induction of vitiligo-like hypopigmentation after imiquimod treatment of extramammary Paget's disease. *Ann Dermatol*. 2012;24:482–484.
40. Burnett CT, Kouba DJ. Imiquimod-induced depigmentation: Report of two cases and review of the literature. *Dermatol Surg*. 2012;38:1872–1875.
41. Kim NH, Lee JB, Yun SJ. Development of vitiligo-like depigmentation after treatment of lentigo maligna melanoma with 5% imiquimod cream. *Ann Dermatol*. August 2018;30(4):454–457.
42. Mashiah J, Brenner S. Possible mechanisms in the induction of vitiligo-like hypopigmentation by topical imiquimod. *Clin Exp Dermatol*. 2008;33:74–76.
43. Hatzis J, Gourgiotou K, Tosca A, Stratigos J. Vitiligo as a reaction to topical treatment with diphencyprone. *Dermatologica*. 1988;177:146–148.
44. Nasca MR, Micali G, Pulvirenti N et al. Transient leucoderma appearing in an untreated area following contact immunotherapy for alopecia areata. *Eur J Dermatol*. March 1998;8(2):125–126.
45. Ganzetti G, Simonetti O, Campanati A et al. Phototherapy as a useful therapeutic option in the treatment of diphenylcyclopropenone-induced vitiligo. *Acta Derm Venereol*. November 2010;90(6):642–643.
46. Ghasri P, Gattu S, Saedi N, Ganesan AK. Chemical leukoderma after the application of a transdermal methylphenidate patch. *J Am Acad Dermatol*. June 2012;66(6):e237–e238.
47. Center for Drug Evaluation and Research. FDA Drug Safety Communication: FDA reporting permanent skin color changes associated with use of Daytrana patch (methylphenidate transdermal system) for treating ADHD. U.S. Food and Drug Administration, FDA. www.fda.gov/Drugs/DrugSafety/ucm452244.htm.

48. Prakash N, Chand P. Chemical leukoderma: A rare adverse effect of the rotigotine patch. *Mov Disord Clin Pract*. 2017;4(5):781–783.
49. Yadav S, Gupta S, Kumar R, Dogra S. Streaky hypopigmentation following lignocaine injection: An unusual side effect. *J Cutan Aesthet Surg*. January 2012;5(1):61–62.
50. Harben DJ, Cooper PH, Rodman OG. Thiotepa-induced leukoderma. *Arch Dermatol*. 1979;115(8):973–974.
51. Zackheim HS, Epstein EH Jr, McNutt NS et al. Topical carmustine (BCNU) for mycosis fungoides and related disorders: A 10-year experience. *J Am Acad Dermatol*. 1983;9(3):363–374.
52. Vine K, Meulener M, Shieh S, Silverberg NB. Vitiliginous lesions induced by amyl nitrite exposure. *Cutis*. March 2013;91(3):129–136.
53. Kim SW, Han TY, Lee JH et al. A case of vitiligo associated with paraffin injection. *Annals of Dermatology*. 2014;26(6):775–776.
54. Coghe G, Atzori L, Frau J et al. Localized pigmentation disorder after subcutaneous pegylated interferon beta-1a injection. *Mult Scler*. February 2018;24(2):231–233.
55. Roehm PC, Perry JD, Girkin CA, Miller NR. Prevalence of periocular depigmentation after repeated botulinum toxin a injections in African American patients. *J Neuroophthalmol*. March 1999;19(1):7–9.
1. Ruiz-Maldonado R, Orozco-Covarrubias ML. Postinflammatory hypopigmentation and hyperpigmentation. *Semin Cutan Med Surg*. 1997;16:36–43.
2. Dubey SK, Misra K, Tiwari A, Bajaj AK. Chemically induced pigmentary changes of human skin, interaction of some azo dyes with human DNA. *J Pharmacol Toxicol*. 2006;1:234–247.
3. Ortonne JP, Bahadoran P, Fitzpatrick TB et al. Hypomelanoses and hypermelanoses. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's Dermatology in General Medicine*. New York: McGraw-Hill, 2003:836–881.
4. Bonamonte D, Vestita M, Romita P et al. Chemical leukoderma. *Dermatitis*. 2016;27(3):90–99.
5. Ghosh SK, Bandyopadhyay D. Chemical leukoderma induced by colored strings. *J Am Acad Dermatol*. 2009;61(5):909–910.
6. Benn EKT, Alexis A, Mohamed N et al. Skin bleaching and dermatologic health of African and Afro-Caribbean populations in the US: New directions for methodologically rigorous, multidisciplinary, and culturally sensitive research. *Dermatology and Therapy*. 2016;6(4):453–459.
7. Nordlund JJ, Grimes PE, Ortonne JP. The safety of hydroquinone. *J Eur Acad Dermatol Venereol*. 2006;20:781–787.
8. Mohamed M, Toumi A, Soua Y et al. Confetti leukoderma following application of mequinol: A case report. *J Clin Dermatol Ther*. 2018;4:028.
9. Yoshikawa M, Sumikawa Y, Hida T et al. Clinical and epidemiological analysis in 149 cases of rhododendrol-induced leukoderma. *J Dermatol*. 2017;44(5):582–587.
10. Peregrino CP, Moreno MV, Miranda SV et al. Mercury levels in locally manufactured Mexican skin-lightening creams. *Int J Environ Res Public Health*. 2011;8(6):2516–2523.
11. Zhu W, Gao J. The use of botanical extracts as topical skin-lightening agents for the improvement of skin pigmentation disorders. *J Investig Dermatol Symp Proc*. 2008;13(1):20–24.
12. Madhogaria S, Ahmed I. Leucoderma after use of a skin-lightening cream containing kojic dipalmitate, liquorice root extract and *Mitracarpus scaber* extract. *Clin Exp Dermatol*. 2010;35(4):e103–e105.
13. Gye J, Nam CH, Kim JS et al. Chemical leucoderma induced by homemade lemon toner. *Australas J Dermatol*. 2014;55(1):90–92.
14. Sitheeque M, Ariyawardana A, Jayasinghe R, Tilakaratne W. Depigmentation of oral mucosa as the earliest possible manifestation of oral submucous fibrosis in Sri Lankan preschool children. *J Investig Clin Dent*. November 2010;1(2):156–159.
15. Redmond RW, Rajadurai A, Udayakumar D et al. Melanocytes are selectively vulnerable to UVA-mediated bystander oxidative signaling. *J Invest Dermatol*. 2013;134(4):1083–1090.
16. Vachiramon V, Thadanipon K. Postinflammatory hypopigmentation. *Clin Exp Dermatol*. 2011;36(7):708–714.
17. Chadwick S, Heath R, Shah M. Abnormal pigmentation within cutaneous scars: A complication of wound healing. *Indian J Plast Surg*. 2012;45(2):403–411.
18. Danielsen L, Rasmussen OV. Dermatological findings after alleged torture. *Torture*. 2006;16(2):108–127.
19. Eryilmaz T, Tuncer S, Uygur S, Ayhan S. Finger tip defect after cryotherapy. *Dermatol Surg* 2009;35:550–551.
20. Sachs C, Lehnhardt M, Daigeler A, Goertz O. The triaging and treatment of cold-induced injuries. *Dtsch Arztebl Int*. 2015;112(44):741–747.
21. Damevska K, Duma S, Pollozhani N. Median canaliform dystrophy of Heller after cryotherapy. *Pediatr Dermatol*. 2017;34(6):726–727.
22. Greenhalgh DG. A primer on pigmentation. *J Burn Care Res*. 2015;36(2):247–257.
23. Cil Y. Second-degree skin burn after intense pulsed light therapy with EMLA cream for hair removal. *Int J Dermatol*. 2009;48(2):206–207.
1. Cummings KI, Cottel WI. Idiopathic guttate hypomelanosis. *Arch Dermatol*. 1966;93(2):184–186.
2. Juntongjin P, Laosakul K. Idiopathic guttate hypomelanosis: A review of its etiology, pathogenesis, findings, and treatments. *Am J Clin Dermatol*. 2016;17(4):403–411.
3. Brown F, Crane JS. *Idiopathic Guttate Hypomelanosis*. Stat Pearls. Treasure Island, FL: StatPearls Publishing, 2018.

4. Shin MK, Jeong KH, Oh IH et al. Clinical features of idiopathic guttate hypomelanosis in 646 subjects and association with other aspects of photoaging. *Int J Dermatol*. 2011;50(7):798–805.
5. Kumarasinghe SP. 3-5 second cryotherapy is effective in idiopathic guttate hypomelanosis. *J Dermatol*. 2004;31(5):437–439.
6. Kim SK, Kim EH, Kang HY et al. Comprehensive understanding of idiopathic guttate hypomelanosis: Clinical and histopathological correlation. *Int J Dermatol*. 2010;49(2):162–166.
7. Kaya TI, Yazici AC, Tursen U et al. Idiopathic guttate hypomelanosis: Idiopathic or ultraviolet induced? *Photodermatol Photoimmunol Photomed*. 2005;21(5):270–271.
8. Friedland R, David M, Feinmesser M et al. Idiopathic guttate hypomelanosis-like lesions in patients with mycosis fungoides: A new adverse effect of phototherapy. *J Eur Acad Dermatol Venereol*. 2010;24(9):1026–1030.
9. Kakepis M, Havaki S, Katoulis A et al. Idiopathic guttate hypomelanosis: An electron microscopy study. *J Eur Acad Dermatol Venereol*. 2015;29(7):1435–1438.
10. Falabella R, Escobar C, Giraldo N et al. On the pathogenesis of idiopathic guttate hypomelanosis. *J Am Acad Dermatol*. 1987;16(1 Pt 1):35–44.
11. Arrunategui A, Trujillo RA, Marulanda MP et al. HLA-DQ3 is associated with idiopathic guttate hypomelanosis, whereas HLA-DR8 is not, in a group of renal transplant patients. *Int J Dermatol*. 2002;41(11):744–747.
12. Gilhar A, Pillar T, Eidelman S et al. Vitiligo and idiopathic guttate hypomelanosis. Repigmentation of skin following engraftment onto nude mice. *Arch Dermatol*. 1989;125(10):1363–1366.
13. Rani S, Kumar R, Kumarasinghe P et al. Melanocyte abnormalities and senescence in the pathogenesis of idiopathic guttate hypomelanosis. *Int J Dermatol*. 2018;57(5):559–565.
14. Wilson PD, Lavker RM, Kligman AM. On the nature of idiopathic guttate hypomelanosis. *Acta Derm Venereol*. 1982;62(4):301–306.
15. Ortonne JP, Perrot H. Idiopathic guttate hypomelanosis. Ultrastructural study. *Arch Dermatol*. 1980;116(6):664–668.
16. Pagnoni A, Kligman AM, Sadiq I et al. Hypopigmented macules of photodamaged skin and their treatment with topical tretinoin. *Acta Derm Venereol*. 1999;79(4):305–310.
17. Ploysangam T, Dee-Ananlap S, Suvanprakorn P. Treatment of idiopathic guttate hypomelanosis with liquid nitrogen: Light and electron microscopic studies. *J Am Acad Dermatol*. 1990;23(4 Pt 1):681–684.
18. Ankad BS, Beergouder SL. Dermoscopic evaluation of idiopathic guttate hypomelanosis: A preliminary observation. *Indian Dermatol Online J*. 2015;6(3):164–167.
19. Morrison B, Burden-Teh E, Batchelor JM et al. Quality of life in people with vitiligo: A systematic review and meta-analysis. *Br J Dermatol*. 2017;177(6):e338–e39.
20. Asawanonda P, Sutthipong T, Prejawai N. Pimecrolimus for idiopathic guttate hypomelanosis. *J Drugs Dermatol*. 2010;9(3):238–239.
21. Rerknimitr P, Disphanurat W, Achariyakul M. Topical tacrolimus significantly promotes repigmentation in idiopathic guttate hypomelanosis: A double-blind, randomized, placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2013;27(4):460–464.
22. Arbache S, Roth D, Steiner D et al. Activation of melanocytes in idiopathic guttate hypomelanosis after 5-fluorouracil infusion using a tattoo machine: Preliminary analysis of a randomized, split-body, single blinded, placebo controlled clinical trial. *J Am Acad Dermatol*. 2018;78(1):212–215.
23. Wambier CG, Perillo de Farias Wambier S, Pereira Soares MT et al. 5-fluorouracil tattooing for idiopathic guttate hypomelanosis. *J Am Acad Dermatol*. 2018;78(4):e81–e82.
24. Ravikiran SP, Sacchidanand S, Leelavathy B. Therapeutic wounding—88% phenol in idiopathic guttate hypomelanosis. *Indian Dermatol Online J*. 2014;5(1):14–18.
25. Gupta K, Tripathi S, Kaur M. Evaluation of placental extracts as an adjuvant therapy to phenol in treatment of idiopathic guttate hypomelanolsis. *J Clinical Diagn Res*. 2016;10(8):Wc01–Wc03.
26. Gordon JR, Reed KE, Sebastian KR et al. Excimer light treatment for idiopathic guttate hypomelanosis: A pilot study. *Dermatol Surg*. 2017;43(4):553–557.
27. Shin J, Kim M, Park SH et al. The effect of fractional carbon dioxide lasers on idiopathic guttate hypomelanosis: A preliminary study. *J Eur Acad Dermatol Venereol*. 2013;27(2):e243–e246.
28. Goldust M, Mohebbipour A, Mirmohammadi R. Treatment of idiopathic guttate hypomelanosis with fractional carbon dioxide lasers. *J Cosmet Laser Ther*. 2013.
29. Rerknimitr P, Chitvanich S, Pongprutthipan M et al. Non-ablative fractional photothermolysis in treatment of idiopathic guttate hypomelanosis. *J Eur Acad Dermatol Venereol*. 2015;29(11):2238–2242.
30. Chitvanich S, Rerknimitr P, Panchaprateep R et al. Combination of non-ablative fractional photothermolysis and 0.1% tacrolimus ointment is efficacious for treating idiopathic guttate hypomelanosis. *J Dermatolog Treat*. 2016;27(5):456–460.
31. Laosakul K, Juntongjin P. Efficacy of tip cryotherapy in the treatment of idiopathic guttate hypomelanosis (IGH): A randomized, controlled, evaluator-blinded study. *J Dermatolog Treat*. 2017;28(3):271–275.
32. Hexsel DM. Treatment of idiopathic guttate hypomelanosis by localized superficial dermabrasion. *Dermatol Surg*. 1999;25(11):917–918.

33. Guillet G, Helenon R, Gauthier Y et al. Progressive macular hypomelanosis of the trunk: Primary acquired hypopigmentation. *J Cutan Pathol*. 1988;15(5):286–289.
34. Elmariah SB, Kundu RV. Progressive macular hypomelanosis. *J Drugs Dermatol*. 2011;10(5):502–506.
35. Relyveld GN, Menke HE, Westerhof W. Progressive macular hypomelanosis: An overview. *Am J Clin Dermatol*. 2007;8(1):13–19.
36. Desai S, Owen J. Progressive macular hypomelanosis: An update. *Pigment Int*. 2014;1(2):52–55.
37. Borelli D. [Cutis "trunci variata." A new genetic dermatosis]. *Medicina Cutanea Ibero-Latino-Americana*. 1987;15(4):317–319.
38. Westerhof W, Relyveld GN, Kingswijk MM et al. *Propionibacterium acnes* and the pathogenesis of progressive macular hypomelanosis. *Arch Dermatol*. 2004;140(2):210–214.
39. Relyveld GN, Westerhof W, Woudenberg J et al. Progressive macular hypomelanosis is associated with a putative *Propionibacterium* species. *J Invest Dermatol*. 2010;130(4):1182–1184.
40. Barnard E, Liu J, Yankova E et al. Strains of the *Propionibacterium acnes* type III lineage are associated with the skin condition progressive macular hypomelanosis. *Sci Rep*. 2016;6:31968.
41. Cavalcanti SM, de Franca ER, Lins AK et al. Investigation of *Propionibacterium acnes* in progressive macular hypomelanosis using real-time PCR and culture. *Int J Dermatol*. 2011;50(11):1347–1352.
42. Relyveld GN, Kingswijk MM, Reitsma JB et al. Benzoyl peroxide/clindamycin/UVA is more effective than fluticasone/UVA in progressive macular hypomelanosis: A randomized study. *J Am Acad Dermatol*. 2006;55(5):836–843.
43. Cavalcanti SM, Querino MC, Magalhaes V et al. The use of lymecycline and benzoyl peroxide for the treatment of progressive macular hypomelanosis: A prospective study. *Anais Brasileiros de Dermatol*. 2011;86(4):813–814.
44. Relyveld GN, Dingemans KP, Menke HE et al. Ultrastructural findings in progressive macular hypomelanosis indicate decreased melanin production. *J Eur Acad Dermatol Venereol*. 2008;22(5):568–574.
45. Kumarasinghe SP, Tan SH, Thng S et al. Progressive macular hypomelanosis in Singapore: A clinico-pathological study. *Int J Dermatol*. 2006;45(6):737–742.
46. Errichetti E, Stinco G. Dermoscopy in general dermatology: A practical overview. *Dermatol Ther*. 2016;6(4):471–507.
47. Errichetti E, Stinco G. Dermoscopy of idiopathic guttate hypomelanosis. *J Dermatol*. 2015;42(11):1118–1119.
48. Pflederer RT, Wuennenberg JP, Foote C et al. Use of Wood's lamp to diagnose progressive macular hypomelanosis. *J Am Acad Dermatol*. 2017;77(4):e99–e100.
49. Wu XG, Xu AE, Song XZ et al. Clinical, pathologic, and ultrastructural studies of progressive macular hypomelanosis. *Int J Dermatol*. 2010;49(10):1127–1132.
50. Xu P, Tan C. Dermoscopy of poikilodermatous mycosis fungoides (MF). *J Am Acad Dermatol*. 2016;74(3):e45–e47.
51. Ankad BS, Sakhare PS. Dermoscopy of borderline tuberculoid leprosy. *Int J Dermatol*. 2018;57(1):74–76.
52. Jha A, Sonthalia S, Lallas A. Dermoscopy of post kala-azar dermal leishmaniasis. *Indian Dermatol Online J*. 2018;9(1):78–79.
53. Santos JB, Almeida OLS, Silva LMD et al. Eficácia da combinação tópica de peróxido de benzoíla 5% e clindamicina 1% para o tratamento da hipomelanose macular progressiva: um estudo randomizado, duplo-cego, placebo-controlado. *Anais Brasileiros de Dermatol*. 2011;86:50–54.
54. Duarte I, Nina BI, Gordiano MC et al. Progressive macular hypomelanosis: An epidemiological study and therapeutic response to phototherapy. *Anais Brasileiros de Dermatol*. 2010;85(5):621–624.
55. Kim MB, Kim GW, Cho HH et al. Narrowband UVB treatment of progressive macular hypomelanosis. *J Am Acad Dermatol*. 2012;66(4):598–605.
56. Chung YL, Goo B, Chung WS et al. A case of progressive macular hypomelanosis treated with narrow-band UVB. *J Eur Acad Dermatol Venereol*. 2007;21(7):1007–1009.
57. Menke H, Relyveld G, Westerhof W. Comment on the letter by Chung et al. about progressive macular hypomelanosis. *J Eur Acad Dermatol Venereol*. 2008;22(8):1029–1030.
58. Kim YJ, Lee DY, Lee JY et al. Progressive macular hypomelanosis showing excellent response to oral isotretinoin. *J Dermatol*. 2012;39(11):937–938.
59. Damevska K, Pollozhani N, Neloska L et al. Unsuccessful treatment of progressive macular hypomelanosis with oral isotretinoin. *Dermatol Ther*. 2017;30(5).

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com