

The official journal of

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PIGMENT CELL & MELANOMA Research

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DOI: 10.1111/pcmr.12976

Volume 34, Issue 4, Pages 707–729

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REVIEW

The evolution of human skin pigmentation involved the interactions of genetic, environmental, and cultural variables

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Abstract

The primary biological role of human skin pigmentation is as a mediator of penetration of ultraviolet radiation (UVR) into the deep layers of skin and the cutaneous circulation. Since the origin of *Homo sapiens*, dark, protective constitutive pigmentation and strong tanning abilities have been favored under conditions of high UVR and represent the baseline condition for modern humans. The evolution of partly depigmented skin and variable tanning abilities has occurred multiple times in prehistory, as populations have dispersed into environments with lower and more seasonal UVR regimes, with unique complements of genes and cultural practices. The evolution of extremes of dark pigmentation and depigmentation has been rare and occurred only under conditions of extremely high or low environmental UVR, promoted by positive selection on variant pigmentation genes followed by limited gene flow. Over time, the evolution of human skin pigmentation has been influenced by the nature and course of human dispersals and modifications of cultural practices, which have modified the nature and actions of skin pigmentation genes. Throughout most of prehistory and history, the evolution of human skin pigmentation has been a contingent and non-deterministic process.

KEYWORDS

bottleneck, depigmentation, dispersal, eumelanin, folate, tanning, ultraviolet radiation, UVB, vasodilation, vitamin D

1 | INTRODUCTION

The evolution of mostly naked, darkly pigmented skin in the genus *Homo* is often not accorded the same importance in human prehistory as the evolution of a relatively large brain, a musculoskeletal system adapted for sustained, striding bipedal locomotion, and the manufacture and use of stone tools. This is mostly because, until recently, details of the evolution of the human integument were ignored or downplayed in the absence of direct fossil evidence. We now understand that the evolution of a skin interface, which facilitated sustained high levels of physical activity in a sunny and hot environment,

was a breakthrough in evolution that contributed to the ability of hominins to occupy, adapt to, and modify diverse terrestrial environments. Significant expansion of the knowledge bases in paleontology, archeology, genetics, genomics, and environmental physiology in recent decades has made possible a new focus on the central role of human skin and skin pigmentation in maintaining homeostasis and in ensuring individual survival and reproductive success. The lability of skin pigmentation, in particular, in relation to diverse environmental conditions has contributed to the ability of hominins to disperse and adapt to local circumstances over the long temporal span of human evolution. This facility was critical during most of prehistory when, in

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the absence of body coverings or built shelters, naked skin was the primary interface between the hominin body and the environment.

This review is focused primarily on the evolution of skin pigmentation during the history of anatomically modern people, *Homo sapiens*. Inferences about the characteristics of the skin and skin pigmentation in pre-*sapiens* *Homo* species are provided only in instances where interbreeding of these species with *H. sapiens* appears to have clearly influenced skin pigmentation in descendant populations of modern people. I have taken an historical and geographic approach here so that readers will achieve a comprehensive understanding of how skin pigmentation evolved in groups of people dispersing at different times into different environments, with different complements of genes, culturally determined behaviors, and material cultures. Skin pigmentation is one of the most thoroughly researched of complex phenotypic traits in humans, but this expanded knowledge base has allowed us to see just how much more needs to be done, especially in understanding the factors affecting the expression of skin pigmentation genes. The importance of skin pigmentation as a human phenotypic trait stems from its biological role in prehistory and its diverse social meanings in history; this review will focus on the former, not the latter.

Studying the evolution of human skin pigmentation is challenging because the trait has been influenced by a changing array of multiple variables over time. Identifying the genes and population genetic processes influencing human skin pigmentation is important, but not sufficient, for achieving a comprehensive understanding of the evolution of the trait. This is because human skin pigmentation is a highly contingent trait, which has changed under different combinations of genetic and cultural conditions over time and through space. It has been influenced by natural selection, population admixture, and population bottlenecks as hominins have dispersed into different biomes at various points in the past, but it has also been influenced by diverse cultural practices in different places and at different times in the past. In the last 20,000 years (kya), especially, skin pigmentation evolved under different combinations of genetic and cultural factors, as humans have dispersed relatively rapidly into diverse—including extreme—environments. Changes in skin pigmentation probably occurred rapidly in some cases as relatively small populations with restricted gene pools moved into extreme high latitude or island environments where selective pressures were strong. The skin pigmentation of some groups was also probably influenced by repeated bottlenecks and movements over many generations into diverse environments with different selective pressures, especially with respect to the nature and intensity of ultraviolet radiation (UVR). And, unlike other mammals, modern humans at specific places and times possessed unique patterns of diet, food procurement practices, body coverings, and use of the built environment that would have affected skin pigmentation phenotypes differentially to create unique and frequently highly localized biocultural adaptations. While making for considerable complexity, these phenomena render the study of the evolution of human skin pigmentation fascinating. Because of these considerations, this review differs from excellent recent reviews of this subject because it builds on information on

the nature and expression of skin pigmentation genes, the role of genetic epistasis, population genetics processes, and mechanisms of melanin production (Crawford et al., 2017; Feng et al., 2021; Hanel & Carlberg, 2020a; Lona-Durazo et al., 2019; Norton, 2019; Pavan & Sturm, 2019; Quillen et al., 2019; Rocha, 2020) and attempts to show how human skin pigmentation evolved in a complex and continually contingent manner in relation to changing complements of genes and changing backgrounds of geography and culture.

2 | NATURAL SELECTION AND THE SKIN OF EARLY HOMO SAPIENS

The genus *Homo* originated about 2.8 million years ago (mya) in Africa from a representative of the genus *Australopithecus* (Villmoare et al., 2015). The emerging consensus view is that the evolution of mostly naked skin in the human lineage probably occurred quite early in the history of the genus *Homo* in order to facilitate the evaporative cooling of eccrine sweat during extended periods of physical exertion in hot environments (Jablonski, 2004; Lieberman, 2011; Zihlman & Cohn, 1988). The onset and duration of this process are not known with certainty, but evidence provided by comparative study of patterns of neutral variation in the *MC1R* locus argues for a selective sweep having occurred approximately 1.2 mya ago that favored *MC1R* variants producing eumelanin-rich protective pigmentation on effectively naked skin (Rogers et al., 2004). Polymorphisms in other genes favoring enhanced eumelanin production may have been selected for early in the history of the genus *Homo* (Feng et al., 2021), but the time of origin of these variants cannot be fixed with certainty. The evolution of functionally naked skin was also associated with changes in epidermal barrier functions and the genes of the epidermal differentiation complex (Elias, 2005; Elias & Friend, 1975; Goodwin & de Guzman Strong, 2017).

The evolution of dark pigmentation early in the evolution of the genus *Homo* has been studied primarily from the perspective of identifying the nature and action of putative selective factors that accounted for the phenotype. The association of strong sunlight with dark skin was appreciated by scholars of Greek antiquity (Hippocrates, 1849) and examined as a likely cause-and-effect relationship in the seventeenth century by Robert Boyle, Benjamin Franklin, and John Hunter (Klaus, 1973). Recognition of the role played by UVR in this relationship owes to key insights made by Walter (1958), who was the first to demonstrate a high correlation between skin pigmentation and latitude as a proxy for UVR. This was followed up by studies that established that UVR had a higher correlation to skin pigmentation than environmental temperature, humidity, or other physical environmental parameters (Chaplin & Jablonski, 2002; Roberts & Kahlon, 1976). Critical consideration of selective factors responsible for the UVR-skin pigmentation relationship began with Blum's rejection of skin cancer as the likely primary driver of increased melanin content of the skin because of its limited effect on mortality (Blum, 1961). The most important result of Blum's contribution was his focus on the importance of survival,

reproductive success, and mechanisms of natural selection in defining adaptive traits, as opposed to identification of factors with negligible or unknowable selective value. Most of the hypotheses advanced for the evolution of skin pigmentation in the last 70 years have failed in this regard, for reasons fully described and reviewed elsewhere (Jablonski, 2004; Jablonski & Chaplin, 2000).

Two sets of hypotheses for the evolution of skin pigmentation that are not focused on the primacy of UVR intensity warrant mention here because they have stressed the importance of eumelanin in enhancing specific barrier functions of the skin. One set focused on the antimicrobial action of eumelanin in the epidermis and its heightened importance in combating parasitic and waterborne disease agents attacking the skin as being the likely agent for selection of darkly pigmented skin in the tropics (Mackintosh, 2001; Wassermann, 1965). Another set of hypotheses, championed by Elias and colleagues, has stressed the importance of increased melanization of the skin in enhancing the competence of the epidermal permeability barrier in desiccating terrestrial environments (Elias, Menon, Wetzel, & Williams, 2009, 2010; Elias & Williams, 2013). The explanatory power of these hypotheses to account for known patterns of human skin pigmentation and, in particular, the distribution of eumelanin-rich skin has been questioned on several grounds, including the fact that the skin of the lips and the volar surfaces of the hands and feet exhibits a near absence of eumelanin pigmentation in all people despite being subjected to some of the most rigorous physical and antimicrobial challenges of any skin on the body's surface (Jablonski & Chaplin, 2013). The weight of current evidence thus supports the theory that UVR is the primary selective agent which has influenced the evolution of human skin pigmentation.

The distribution and intensity of the different wavelengths of UVR vary over terrestrial surfaces according to time of day, season, geographical latitude, altitude, cloud cover, and other factors (Diffey, 1991). Individual exposure to UVR depends on the intensity of the ambient UVR in a given location, the fraction of ambient exposure received at a given anatomical site, and the timing and nature of outdoor activity (Diffey, 1999). In assessing the effects of UVR on the skin and weighing the relative importance of these effects on the evolution of skin pigmentation, it is important to appreciate that humans in prehistory exhibited different lifestyles and patterns of UVR exposure than modern people. While this may seem self-evident, it is rarely taken into account.

The relative importance of different selective factors in the evolution of human skin pigmentation depends on their potential effects on reproductive success. A potential selective agent like UVR may damage connective tissue and DNA, for instance, but if the effects of the damage do not adversely affect the individual's reproductive success, or if the number of individuals adversely affected is small, then its evolutionary impact is diminished. In this connection, the patterns of life history, longevity, and demographics observed in modern people cannot be assumed for early members of the genus *Homo* or even prehistoric *H. sapiens*. A recent proposal advancing the importance of skin cancer as a selective agent in the evolution of human skin pigmentation that was based on an assumption

of widespread longevity and the importance of grandparental care of offspring needs thus needs to be questioned (Osborne & Hames, 2014). It is also important to choose suitable modern human models or model systems when framing theoretical discussions of the evolution of skin pigmentation because choices of inappropriate model systems result can result in misleading conclusions. An important case in point is another hypothesis proposing protection against skin cancer as the primary selective agent favoring the evolution of permanent dark skin pigmentation. In this study, high rates of fatal skin cancers in depigmented people with albinism living in high UVR environments were presented as evidence that the most important function of eumelanin was protection against UVR-induced damage to DNA and its connection to diminished reproductive success and premature death (Greaves, 2014). This hypothesis was based on the assumption that ancestral hominins had lightly pigmented or depigmented skin and that modern people mostly or entirely lacking eumelanin in their integument might a suitable model for the ancestral human state. The notion that very lightly pigmented people or individuals with albinism could serve as models for understanding the selective forces operating on the skin of early hominins is wrong. All living catarrhine primates, including the closest living ape relatives of humans, have intact pigmentary systems and can develop facultative pigmentation through tanning of non-hairy exposed skin or have permanently melanized exposed skin (Jablonski & Chaplin, 2014b). In the human lineage, lightly pigmented skin and depigmented skin due to albinism are highly derived, not ancestral, conditions. The manifold protective effects of eumelanin in the skin, especially with respect to mitigation of UVR damage and prevention of carcinogenesis, have been thoroughly researched and reviewed elsewhere (Abdel-Malek, 2009; Hennessy, Oh, Diffey, et al., 2005; Swope & Abdel-Malek, 2018; Tadokoro et al., 2003; Young et al., 2017). More germane in the context of this review is discussion of the likely selective value of different degrees of eumelanin pigmentation on health and potential reproductive success. In this context, we cannot assume that the appearance, genetic composition, sun exposure habits, or UVR skin reactions of humans today are the same as those of our ancestors in prehistory. Choice of appropriate models for ancestral or ancient hominin appearance, physiology, or behavior must be done with great care and will always involve uncertainty because of the many kinds of variables involved. Consideration of the evolutionary significance of eumelanin-rich skin pigmentation in the human lineage must be informed by this principle.

2.1 | Folate-dependent processes and their role in the evolution of eumelanin-rich pigmentation

Research conducted first in the 1970s suggested that eumelanin in the skin may be protective against degradation of folate (Branda & Eaton, 1978). Appreciation of the centrality of folate in regulating DNA synthesis and repair grew rapidly in subsequent years, especially after the connection between folate deficiencies and the then common class of birth defects, neural tube defects, became widely

recognized on the basis of epidemiological and experimental studies (Bower & Stanley, 1989; Elwood, 1983; Fleming & Copp, 1998; MRC Vitamin Study Research Group, 1991). Folate, primarily in the form of 5-methyltetrahydrofolate (5-MTHF), is used at the cellular level for DNA production, the cysteine cycle, and regulation of homocysteine. Knowledge of the specific actions, enzymatic and genetic regulation, and environmental sensitivity of folate grew quickly in light of increasing appreciation of the vitamin's extensive clinical significance (Branda & Blicksenderfer, 1993; Giovannucci et al., 1995; Lucock & Daskalakis, 2000; Lucock et al., 2001; Mastropaolo & Wilson, 1993). Appreciation of the importance of folate to DNA production and cell proliferation during embryogenesis and spermatogenesis and its likely sensitivity to UVR lead to initial formulations of a hypothesis about the protective effect of eumelanin pigmentation with respect to successful pregnancy outcomes (Jablonski, 1992, 1999). This work was further elaborated when it became possible to examine patterns of human skin pigmentation (as provided in reports of standardized skin reflectance measurements taken from indigenous peoples) relative to levels of remotely sensed UVR as measured by the NASA Total Ozone Mapping Spectrometer 7 (TOMS-7) satellite (McPeters et al., 1996). The TOMS-7 and subsequent NASA satellites revolutionized the study of the effects of UVR on biological systems because they provided standardized, global, spatially continuous and gridded data that made it possible to assess the potential for biological damage due to solar irradiation, given the column ozone amount and cloud conditions on any day, for most places on earth (Langston et al., 2017). The demonstration that human skin pigmentation was more highly correlated to UVB than to latitude (Jablonski & Chaplin, 2000) or environmental parameters such as total solar irradiance, temperature, humidity, or rainfall. Chaplin (2004) indicated that UVR was the most important environmental determinant of skin pigmentation.

The nature of the specific protective effect of eumelanin in the epidermis and its effects of evolutionary fitness depends fundamentally on where the pigment is localized in the skin. Different wavelengths of UVR penetrate the skin to different depths of the epidermis and dermis, depending on the skin site, the amount and location of eumelanin, and the degree of keratinization of the skin (Meinhardt et al., 2008). Eumelanin is concentrated within keratinocytes in the stratum basale of the epidermis and in this position can afford considerable protection against damage by UVR, especially UVB (Fajuyigbe et al., 2018; Fajuyigbe & Young, 2016). The stratum corneum itself affords some protection against UVB, but the degree of protection afforded depends on the thickness of individual layers, the number of layers, the degree of hydration of epidermis (Bruls et al., 1984). The protective effect of stratum corneum itself is more significant with respect to UVB shielding in skin with less eumelanin content, but the magnitude of this effect is variable and, overall, minor compared to that of eumelanin itself (Hennessy et al., 2005; Kaidbey et al., 1979; Olivarius et al., 1997).

Most of the attention paid to the UVB shielding effects of eumelanin has been concerned with the sparing of damage to DNA and mitigation of carcinogenesis because of the pigment's significant

UVR absorptive abilities, which slow the formation of highly mutagenic cyclobutane pyrimidine dimers (CPD) (Fajuyigbe et al., 2018). The localization of most eumelanin in the stratum basale also serves to protect the capillary bed of the dermis from UVR, especially UVB. Penetration of UVA into the stratum basale is considerably greater and potentially more harmful in lightly pigmented skin (Meinhardt et al., 2008). Attention in this connection has been paid primarily to the cosmetic effects of UVA on the breakdown of connective tissues in the dermis (Battie et al., 2014), but the demonstrated effects of UVA on vasodilation of arteries in the capillary bed of the dermis (Liu et al., 2014) suggest that control of blood pressure may be of more fundamental importance.

Evidence for the hypothesis that permanent dark pigmentation in hominin skin was an adaptation to protect against UVR-induced degradation of folate in the skin was originally based on direct effects on fertility such as potential embryo loss or faulty spermatogenesis (Jablonski & Chaplin, 2000). These effects are hard to demonstrate in living human subjects or through retrospective epidemiological studies. Folate levels and folate metabolism are affected by primary folate deficiency, non-folate B-vitamin nutrient deficiencies, and genetic variations that influence cellular folate accumulation and utilization (Perry et al., 2004; Stover, 2009), and these factors were generally not considered in 20th-century surveys of folate levels within and between populations. The clearest epidemiological demonstration of the possible folate-sparing effect of dark pigmentation against UVR challenge came from a study demonstrating the lower prevalence of NTDs in darkly pigmented as opposed to lightly pigmented South Africans, despite the greater affluence and presumed better diet of the latter group (Buccimazza et al., 1994). Experimental studies of the effects of UVA and UVB on serum and red cell folate conducted *in vitro* and *in vivo* have yielded mixed results and have been difficult to interpret because of inconsistencies in experimental conditions and folate assay standardization (Borradaile et al., 2014; Borradaile & Kimlin, 2012; Fukuwatari et al., 2009; Gambichler et al., 2001; Juzeniene et al., 2009; Wolf & Kenney, 2019), but most studies have found depletion of folate to varying degrees, depending on the wavelength and duration of UVR exposure, the pre-exposure folate level, and the species of folate being assayed. Experimental demonstration of a decline in epidermal 5-MTHF following UVA exposure in individuals with lightly pigmented but not darkly pigmented skin (Hasoun et al., 2015) is potentially more significant because it indicates the importance of UVR-induced folate depletion in the skin after a short UVR exposure and possible systemic depletion following prolonged exposure.

Appreciation of the central importance of folate on human health through its effects of DNA synthesis and methylation (Stover, 2009) has been augmented in the last 20 years by research demonstrating direct effects of folate on vascular function. These effects are pertinent to the evolution of skin pigmentation because of the role played by folate (as 5-MTHF and as its further derivative, tetrahydrobiopterin, or BH₄) in improving nitric oxide (NO)-mediated endothelial function and affecting vasodilation, blood pressure, and thermoregulation (Alexander et al., 2013; Ng et al., 2009; Stanhewicz et al., 2012,

2015). UVA triggers cutaneous vasodilation, probably by releasing NO from preexisting stores of nitrite in the dermis (Liu et al., 2014). The discovery that lower NO levels contributed to attenuated vasodilation in response to local heating of the skin of older individuals and that these responses could be restored by folate administration (Kenney, 2017) led to studies aimed at discovering the likely molecular mechanisms whereby folate improved NO bioavailability and protected endothelial function (Stanhewicz & Kenney, 2017). Recent findings indicating that acute UVB exposure attenuated NO-mediated vasodilation of the cutaneous microvasculature via degradation of 5-MTHF led to the pursuit of studies examining the effects of skin pigmentation, age, and folate status on vasodilation and thermoregulation (Wolf & Kenney, 2019). Available evidence indicates that folate degradation in response to UVR exposure is likely dose-dependent and requires relatively large doses, repeated prolonged exposures, or both to observe reductions in serum or red blood cell folate (Wolf & Kenney, 2019). These environmental conditions would have been met in the early history of the genus *Homo* when hominins were active in the sun or at least exposed to strong, equatorial sunlight for most daylight hours without the benefit of body coverings.

The sum of the effects of UVR-induced folate loss on hominins cannot be accurately estimated, but there is little doubt that lowered fertility due to embryo loss and impaired spermatogenesis combined with impairments of vasodilation and temperature regulation would have represented direct and severe selective pressures favoring conservation of folate through increased eumelanin in the functionally naked skin of early *Homo*. This does not mean that early *Homo* had “dark skin,” but that selection favoring enhanced eumelanin pigmentation in the skin was evolving early in the evolution of the genus, along with polymorphisms in genes affecting folate metabolism. Because folate metabolism is regulated by several enzymes, including methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase (*MTR*), and methionine synthase reductase (*MTRR*), and because the activity of these enzymes varies according to different *functional polymorphisms*, these polymorphisms appear to have evolved in response to seasonal availability of folate and levels of UVR (Jones et al., 2018; Lucock et al., 2010, 2017). It is thus probable that multiple mechanisms, including enhanced eumelanin pigmentation and conservation of folate through modification of enzymatically controlled metabolism, evolved in the face of seasonally dependent variations in folate availability and UVR levels.

2.2 | Vitamin D and skin pigmentation

The importance of vitamin D in connection with the evolution of human skin pigmentation was first introduced by Murray (Murray, 1934) and later elaborated by Loomis (Loomis, 1967). These were based, at that time, on the recognition of the physiological importance of vitamin D in the growth and maintenance of the skeleton and understanding that production of vitamin D could be catalyzed only by specific wavelengths of UVR, from about 290–320 nm, in the UVB range. Loomis originally opined that “white skins” had evolved

to maximize cutaneous photoconversion of 7-dehydrocholesterol (7-DHC) into vitamin D under low UVB conditions at high latitudes and that “black skins” had evolved to protect against vitamin D toxicity due to potential overproduction of vitamin D at low latitudes under high UVB conditions (Loomis, 1967). Research into the mechanisms of cutaneous vitamin D synthesis by Holick and colleagues provided evidence that the process was tightly photochemically controlled and that the eumelanin content of the skin determined the rate of conversion of 7-DHC to previtamin D₃ (pre-D). (Clemens et al., 1982; Holick et al., 1980, 1981). This body of research demonstrated that increased eumelanin content of the skin could not be implicated in preventing vitamin D toxicity, but that depigmented skin facilitated cutaneous vitamin D production because of the fact that eumelanin competes with 7-DHC for UVB photons (Holick et al., 1981). This research laid the groundwork for subsequent studies establishing the nature and genetic basis of the selective forces acting on the evolution of skin pigmentation in populations dispersing into and inhabiting regions of lower and more highly seasonal UVB (Beleza, Santos, et al., 2013; Gozdzik et al., 2008; Hanel & Carlberg, 2020a; Izagirre et al., 2006; Jablonski & Chaplin, 2000, 2010; Makova & Norton, 2005).

The body of research pertaining to the importance of vitamin D in bone metabolism and many cellular and immunological processes is now immense and is reviewed elsewhere (Lips, 2006, 2007; Lips et al., 2014; Sassi et al., 2018). Issues raised about the strength of natural selection acting to reduce eumelanin pigmentation in order to enhance cutaneous vitamin D synthesis (Elias et al., 2009; Elias & Williams, 2013, 2016; Robins, 2009) have been countered by considerable evidence. The claim that loss of eumelanin and enhancement of cutaneous vitamin D production did not significantly improve the reproductive success of hominins dispersing to high latitudes (Robins, 2009) was called into question by challenging incorrect assertions, including the claim that, even at the highest latitudes, stored vitamin D alone is sufficient to meet physiological needs during months when the UVB in sunlight is insufficient to catalyze cutaneous vitamin D production (Chaplin & Jablonski, 2009, 2013). Other claims centering around reduction in epidermal eumelanin having been selected for altered epidermal barrier functions have also been found deficient. These have focused on the significance of reduced levels of the protein filaggrin in the stratum corneum, leading to enhanced cutaneous synthesis of pre-D and also on the argument that reduction in eumelanin production was favored by natural selection because of the importance of conserving energy (Elias & Williams, 2013). These explanations failed to demonstrate any significant evolutionary advantage for reduction of filaggrin (Jablonski & Chaplin, 2013), and further study of variation in loss of function genes affecting filaggrin in the epidermis failed to demonstrate a relationship between genetic variants and latitude (as a surrogate for UVB and cutaneous vitamin D synthesis potential) (Eaaswarkhanth et al., 2016).

A key consideration in understanding the evolution of skin pigmentation in people living under high and less seasonally variable UVR conditions—generally within the tropics—is the degree to which eumelanin pigmentation actually slows the cutaneous biosynthesis

of vitamin D. Recent experimental work done by Young and colleagues on human subjects has demonstrated that darkly pigmented individuals (Fitzpatrick type VI according to study protocols) exhibited a melanin vitamin D inhibition factor of 1.3–1.4 relative to lightly pigmented individuals (Fitzpatrick type II) (Young et al., 2020). They reasoned that this significant, but relatively modest, inhibitory effect may have been due to the fact that photoconversion of 7-DHC into pre-D occurs mostly in the stratum granulosum and stratum spinosum of the epidermis, above the heavily melanized layers of the basal epidermis (Young et al., 2020).

Vitamin D serves many critical functions in the body, and deficiency in the vitamin increases susceptibility to a range of developmental, chronic, and infectious diseases via its effects on the epigenome and on the expression of many genes on nearly all organs and tissue types in the body (Bora & Cantorna, 2017; Bustamante et al., 2020; Caccamo et al., 2018; Carlberg, 2019; Sassi et al., 2018). The recognition that vitamin D improves endothelial function by signaling for the transcription of endothelial nitric oxide synthase (eNOS) and thereby acting to preserve production of NO and healthy peripheral vascular function augments our understanding of the vitamin's consummate importance in human physiology and has potentially great consequences for our understanding of the evolution of skin pigmentation (Wolf et al., 2020; Wolf & Kenney, 2019). Vitamin D is produced in the upper epidermis through UVB-induced catalysis of 7-DHC into pre-D, and it is required in the dermis to preserve NO production required for healthy vasodilation. This important function of vitamin D probably accounts for the intriguing finding of reduced all-cause mortality in a large cohort of lightly pigmented Scandinavian women reported by Lindqvist and colleagues (Lindqvist et al., 2020). The role of vitamin D's role in eNOS signaling, control of vasodilation, and regulation of blood pressure warrants further investigation in an evolutionary context with respect to the evolution of skin pigmentation under low UVR conditions (Wolf et al., 2020). It is also of potentially great relevance in clinical contexts with respect to the importance of low and carefully controlled doses of natural UVR sufficient to produce vitamin D and maintain healthy vasodilation and blood pressure (Alfredsson et al., 2020; Wolf et al., 2020). This consideration is of particular concern in habitually indoor-dwelling people, older people with attenuated cutaneous vitamin D production abilities, and darkly pigmented people living in low UVR environments.

The manifest importance of vitamin D in human physiology implies that complex, genetically based mechanisms for establishing and maintaining vitamin D sufficiency have evolved in the course of human evolution. Modification of the production and packaging of eumelanin in the skin affects the penetration of UVB into the epidermis and the physical potential for photoconversion of 7-DHC into pre-D, but levels of vitamin D can and are affected by many other processes and pathways. Advances in genomics and archeogenomics have made possible a significant shift in our understanding of these processes in recent years, to the extent that there is now greater appreciation of how the evolution of genetic variants associated with vitamin D metabolism and signaling has evolved in concert

with skin pigmentation. As modern populations have dispersed and undergone bottlenecks and admixture, variant genes encoding for proteins responsible for photoconversion of 7-DHC into pre-D (Kuan et al., 2013) and governing transport, metabolism, and signaling of vitamin D, including *DHCR7*, *GC*, *CYP2R1*, and *CYP24A1* (Hanel & Carlberg, 2020a, 2020b), have undergone changes in frequency appeared and become common. Genetic changes affecting vitamin D metabolism rather than skin pigmentation have been particularly important (Hanel & Carlberg, 2020a, 2020b), especially at extreme northern high latitudes where levels of UVB are low and highly seasonal, creating conditions for only short and sporadic cutaneous photosynthesis of vitamin D (Chaplin & Jablonski, 2013; Jablonski & Chaplin, 2010). Lastly, the nature of the genetic changes occurring was being mediated by numerous lifestyle variables (including diet, typical body coverings and kinds of shelter, and patterns of daily activity) which affected vitamin D status and would have contributed to individual survival and reproductive success. Thus, consideration of the contingent nature of biocultural compromises in different places and at different times is essential to the study of the evolution of human skin pigmentation and human health (Chaplin & Jablonski, 2013). Genetically driven changes in skin pigmentation favoring less integumental eumelanin were only one factor in the "adaptive equation" contributing to healthy vitamin D status.

2.3 | Likely skin pigmentation of early *Homo sapiens*

The probable loss of most body hair during the early evolution of the genus *Homo* left the body highly vulnerable to the effects of UVR, as well as to many other potentially harmful physical, chemical, and biological agents. The evolution of protective eumelanin-rich constitutive pigmentation in the tropical-dwelling, African ancestors of all modern people was probably a step-by-step process involving many genetic loci. Early in the history of skin pigmentation genomics, considerable attention was focused on the primacy of a selective sweep affecting the *MC1R* locus to eliminate variation and establish permanent dark pigmentation in the human lineage (Rana et al., 1999; Rogers et al., 2004). Since those early studies, the field of skin pigmentation genomics has been revolutionized by the development of high-throughput sequencing technologies coupled with the application of genome-wide association studies (GWAS) for identifying multiple genes associated with human skin pigmentation and the execution of genome-wide scans of natural selection. These developments have made possible the identification of many genes contributing to skin pigmentation, and the degree to which they have been acted upon by natural selection (Feng et al., 2021). For many loci of interest, application of coalescent studies on specific derived alleles has made possible estimation of when was the most recent common ancestor of existing derived alleles first occurred.

Based on these studies, it is possible to estimate that multiple derived alleles contributed to the evolution of dark pigmentation in ancestral *H. sapiens*. These include two derived alleles of the major

facilitator superfamily domain-containing protein 12 (*MFSD12*), which appeared at or near the time of origin of *H. sapiens*, about 0.3 mya (Crawford et al., 2017; Feng et al., 2021). Other candidate loci, including multiple alleles of the DNA damage-binding protein 1 (*DDB1*), may also have been present in early *H. sapiens* because of their presence at high frequencies in modern African and in some non-European populations today (Crawford et al., 2017; Feng et al., 2021) (Figure 1), thus suggesting that derived alleles were carried in one of the populations that dispersed along the southern and southeast Asian coasts and into Melanesia. Detailed examination of the geographical pattern of variation in one of these alleles, rs7948623 (T), further suggests that it may have been under positive selection, resulting in further skin darkening, in regions of the world including East Africa, parts of South Asia, and Melanesia with extremely high environmental UVR (Feng et al., 2021). The key point is that the ancestor of all *H. sapiens* had darkly pigmented, but not necessarily maximally darkly pigmented, skin (Chaplin, 2004; Hanel & Carlberg, 2020a). In Africa today, and among many South Asians and Melanesians, there is great variation in the darkness of “darkly pigmented” skin that appears to be due to variations in UVR intensity (Chaplin, 2004; Jablonski & Chaplin, 2014a). Genomic studies of the last two decades have revealed that the genetic “palette” of skin pigmentation gene variants is great and that many combinations of multiple variant genes have contributed to the complex pattern of skin pigmentation phenotypes and genotypes observed today. Under more highly seasonal UVR regimes, the evolution of enhanced tanning abilities and genes contributing to rapid development of facultative pigmentation has been favored (Quillen et al., 2019). Despite the manifest importance and relevance of tanning genetics to skin cancer dynamics and skin esthetics, relatively little genomics-based research on the topic has been done, especially in African and indigenous American populations. Although advances in evolutionary skin pigmentation genetics have been enormous, there is an urgent need to validate candidate skin pigmentation variants using GWAS and scans of natural selection, using functional experiments in vitro and in vivo (Feng et al., 2021).

3 | SKIN PIGMENTATION EVOLUTION IN RELATION TO DISPERSALS, GENES, AND CULTURE IN PREHISTORY

The processes affecting the evolution of human skin pigmentation have changed in relative importance over time. In the last 100,000 years (100 kya), *H. sapiens* has gone from being an exclusively African species to a global one. The nature and speed of major dispersals of modern humans varied according to many geographic, demographic, technological, and cultural variables. With gains in technological competence and, especially, with the domestication of animals used for food and transportation, humans became more mobile and had better abilities to buffer themselves against the exigencies of the environment because they could control more aspects of personal nutrition and bodily protection through technology and cultural practices. Through time, and especially since the beginning of history *sensu stricto* about five thousand years ago, culturally based preferences for skin color (including sexual selection and social selection) have also influenced regional trends in the skin pigmentation. For all of these reasons, there has probably never been a time or place in the history of our species when skin pigmentation has been in equilibrium.

The following review of the history of skin pigmentation in the major regions of the world is, perforce, speculative because of the multiplicity of variables being considered. The level of detail presented here falls far short of that covered in global reviews of human dispersals that have examined the details of human movements from the perspectives of genomics, genetics, and population genetics (James et al., 2019; Nielsen et al., 2017; Posth et al., 2016). Nonetheless, they form a basis for discussion and future research.

3.1 | Africa

The earliest history of *H. sapiens* occurred in Africa and has been reconstructed through a combination of sparse fossil evidence and inferences from archeogenomics (Galway-Witham & Stringer, 2018;

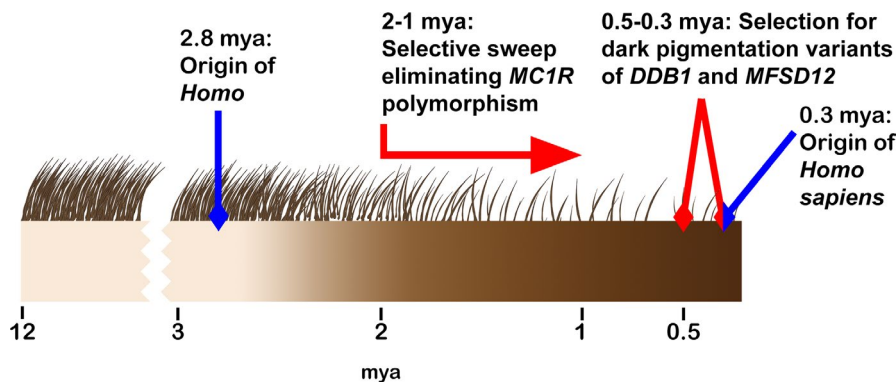


FIGURE 1 The “hairy timeline of human evolution” illustrating, schematically, the evolution of body hair and skin color in pre-*Homo sapiens* members of the human lineage. Prior to the evolution of early members of the genus *Homo*, about 2.8 mya, hominin skin, was lightly pigmented (but tannable) and covered with dark hair. The evolution of mostly hairless bodies beginning about 2 mya inaugurated a selective sweep eliminating *MC1R* polymorphism, after which time selection for dark pigmentation variants of *DDB1* and *MFSD12* persists through the time of origin of *H. sapiens*, about 0.3 mya

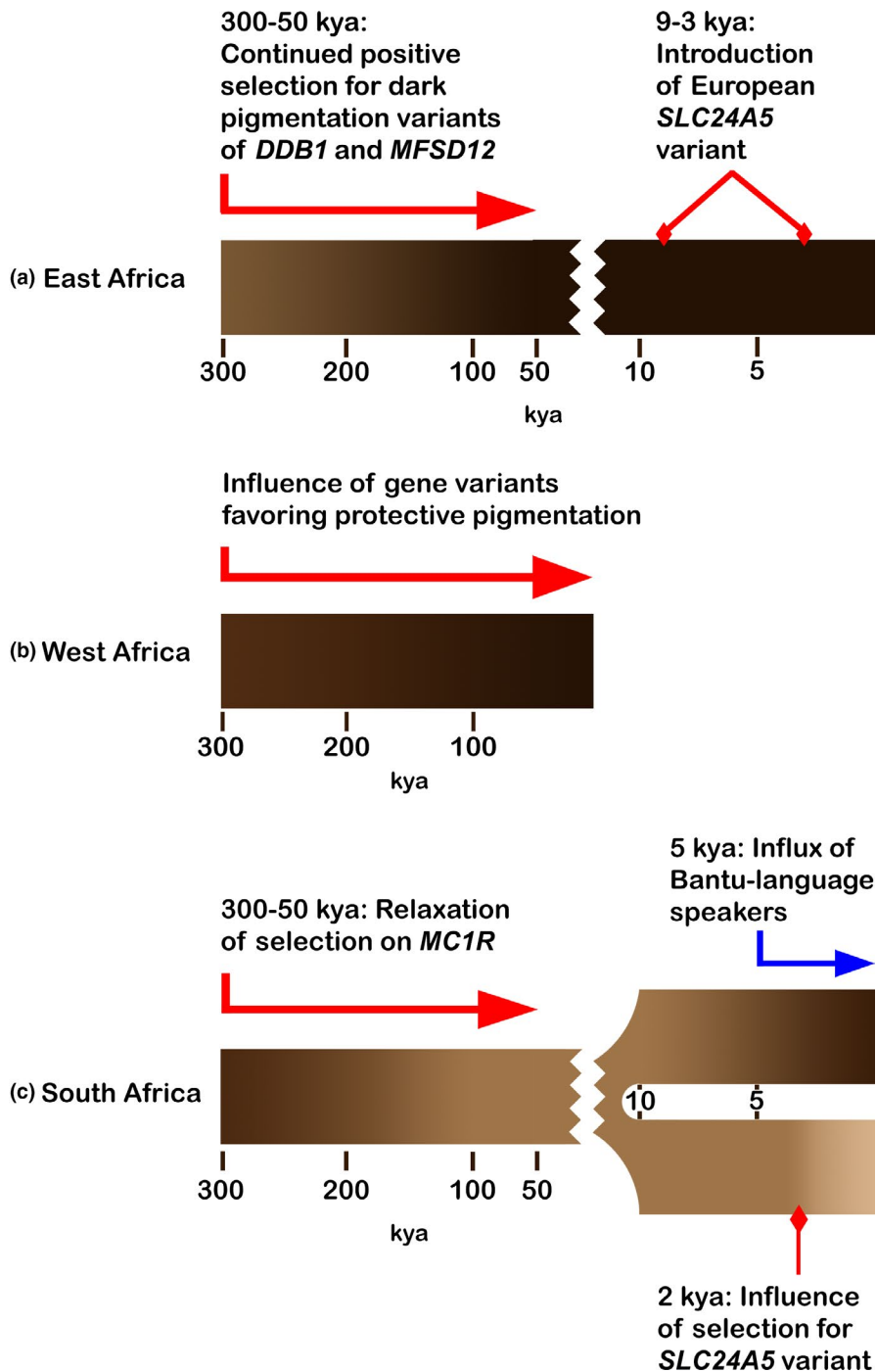


FIGURE 2 Generalized timeline of main events in the evolution of skin pigmentation in Africa, by region. After originating around 0.3 mya, *H. sapiens* evolved in Africa only until about 80 kya when some dispersals from northeastern Africa into the Afro-Arabian Peninsula occur. (a) In East Africa, continued purifying selection on *MC1R* variants is accompanied by positive selection on variants of *DDB1* and *MFSD12* leads to darker pigmentation. The introduction of the classic depigmentation *SLC24A5* variant around 9 kya via the Afro-Arabian Peninsula sees its rapid dispersal southward. (b) In West Africa, purifying selection on *MC1R* variants continues, accompanied by positive selection on variants of *DDB1* and *MFSD12* producing darker pigmentation. (c) In South Africa, among Khoe-san hunter-gatherers, relaxation of selection on *MC1R* is accompanied by positive selection on the *SLC24A5* introduced from northeastern Africa. The dispersal of darkly pigmented Bantu-language speaking agriculturalists from western and central Africa from 5 ka onward and their admixture with Khoe-san hunter-gatherers leads to the evolution of complexly mixed pigmentation genotypes and a wide range of moderately pigmented phenotypes

Henn et al., 2018; Hublin et al., 2017; Stringer, 2016; White et al., 2003). The skeletal traits which define *H. sapiens* emerged in Africa over the course of about 100,000 years, from 0.3 to 0.2 mya (Galway-Witham & Stringer, 2018). By 0.2 mya, diverse forms of anatomically modern humans lived in Africa, mostly in dispersed regional and environmental enclaves, and pursued technologically and artistically complex but locally distinctive cultures (Scerri et al., 2018). The genetic history of modern people in Africa thus reflects deep roots, and complex patterns of isolation and reticulation. Some of the reasons for this can be readily appreciated when the vastness, ecological diversity, and remarkable latitudinal extent

of Africa are considered. Other reasons are demographic. Until the advent of agriculture and animal husbandry in Africa about 5 kya, most populations of hunter-gatherers were relatively small, scattered, and probably experienced repeated bottlenecks and periods of expansion due to sometimes dramatic environmental perturbations (Ambrose, 1998; Hsieh et al., 2016; Powell et al., 2009).

In the specific context of human skin pigmentation evolution in Africa, the diversity of UVR regimes in the African continent, including the highly seasonal pattern of UVB in the far south, is one of many factors that must be appreciated (Coussens et al., 2015; Jablonski & Chaplin, 2014a). These patterns are reflected in the complex mosaic

of genes that contribute to skin pigmentation across Africa today (Crawford et al., 2017; Feng et al., 2021; Lin et al., 2018; Martin et al., 2017; Rocha, 2020). The strong and relatively seasonally invariant UVR regimes of East Africa, including the Horn of Africa and the East African coast, have continued to drive selection for increasingly dark skin pigmentation in these regions (Chaplin, 2004; Feng et al., 2021; Jablonski & Chaplin, 2000, 2014a). This trend has also been influenced by the wearing of relatively little clothing during daylight hours and while active, up to and including historical times, because of extreme environmental heat. A trend toward increasing pigmentation darkening also appears to have occurred in West Africa, but the combination of genetic variants contributing to this is less clear (Crawford et al., 2017; McEvoy et al., 2006). The nature of the genes and genetic epistasis contributing to the enhancement of dark constitutive pigmentation and tanning abilities in equatorial African people (and elsewhere) is still poorly understood, but it is likely that insights will come from functional genomic studies and those focused on the study of recently admixed populations in order to determine causal effects (Beleza, Johnson, et al., 2013; Lona-Durazo et al., 2019; Rocha, 2020).

The other major phenomena that have influenced the evolution of skin pigmentation in Africa were recent human dispersals, but not those associated with European colonialism. The first of these was the dispersal of people from Eurasia via the Afro-Arabian Peninsula into eastern and southern Africa. These people carried derived variants of *SLC24A5* (solute carrier family 24 [sodium/potassium/calcium exchanger], member 5) associated with depigmented skin (Martin et al., 2017). These variants spread relatively quickly southward, beginning around 5,000 yr (Crawford et al., 2017), and were favored under positive selection in the far southern latitudes of Africa among Khoe-san hunter-gatherers and pastoralists, especially in the last 2,000 yr (Lin et al., 2018; Martin et al., 2017). The evidence for positive selection for *SLC24A5* variants that conferred some skin lightening in the indigenous Khoe-san peoples inhabiting the lower and more seasonal UVR conditions of southern Africa is significant. It complements evidence that non-synonymous mutations in the *MC1R* locus exist in the Khoe-san (John et al., 2003) and that other variant forms of *MC1R* may have arisen in southern African under relaxed selection. It also illustrates that a new genetic variant can achieve high frequency in human populations after being introduced if it affects a trait that positively impacts fitness. This result is also important because it puts paid to arguments that the relatively light skin pigmentation of the Khoe-san was due to genetic admixture with Europeans early in colonial history.

The second major dispersal event within Africa that has affected the distribution of skin pigmentation phenotypes and the continuing evolution of skin pigmentation by population admixture is the expansion of Bantu-language speakers from western Africa into central, eastern, and southern Africa, beginning about 5.6 kya (Li et al., 2014; Patin et al., 2017). The timing and nature of dispersals of Bantu-speaking peoples have been characterized using genome-wide microsatellite markers and are now understood to have, in general, proceeded from west to east, and then south (Li et al., 2014).

Linguistic, archeological, and genetic evidence for the movement of Bantu-speaking agriculturalists attests that this was one of the largest and most genetically impactful dispersals in human history because of its effects on preexisting populations of rainforest- and desert-dwelling hunter-gatherers in western, central, and southern Africa (Patin et al., 2017). With respect to skin pigmentation, the ingress of very darkly pigmented people into southern Africa in recent millennia appears to have adversely affected vitamin D status and health, especially in modern, mostly urban populations in southernmost Africa (Coussens et al., 2015). A hypothetical skin pigmentation timeline for the major regions of Africa is presented in Figure 2.

3.2 | Coastal south and southeast Asia, Melanesia, and Australia

The timing and routes of the dispersal of *H. sapiens* into Eurasia, and the population sizes of dispersing populations, have been studied intensively by geneticists and genomicists in the last 20 years and are now reasonably well understood (Henn et al., 2012, 2016; Nielsen et al., 2017; Pagani et al., 2016; Reyes-Centeno et al., 2014). The number, timing, and exact routes of these dispersals are still debated, but genetic and paleontological evidence indicates that the first groups of *H. sapiens* dispersed out of Africa beginning about 70 kya, following a primarily coastal route from the Afro-Arabian Peninsula into south and southeast Asia, thence into Melanesia and, eventually, into Australia (Groucutt et al., 2015; James et al., 2019; Malaspina et al., 2016; Pagani et al., 2016; Posth et al., 2016; Reyes-Centeno, 2016; Reyes-Centeno et al., 2014). Divergence of populations ancestral to modern Papuans and Aboriginal Australian from Eurasians is estimated from genomic evidence to have occurred 72–51 kya, after which time admixture of ancient Denisovans with an ancestral Papuan-Australian population occurred (Malaspina et al., 2016).

Populations dispersing and living along the coasts of southern and southeastern Asia in the Late Pleistocene experienced strong and seasonally relatively invariant UVR levels, favoring maintenance of dark pigmentation, probably involving selection on ancestral gene variants *MFSD12* and *DDB1* (Feng et al., 2021) and variant forms of *SLC24A5* and *OCA2* (Jinam et al., 2017; Stokowski et al., 2007). The contribution of Denisovan genes to these populations is recognized (Gittelman et al., 2016; Jinam et al., 2017) but the genetic contribution of Denisovans to skin pigmentation is not yet clearly established. In considering the evolution of skin pigmentation in these populations, the effects of population size, diet, and habitual raiment must be considered, even if the strength of these influences cannot be quantified easily. The populations dispersing along these coasts were hunter-gatherers and probably of small population size. Some of these, notably several so-called “Negrito” populations, manifest genetic evidence of severe population bottlenecks as well as recent admixture (Jinam et al., 2017). Based on ethnographic accounts of living Andamanese, these people ate traditional diets of fish, wild boar, shellfish, turtle, and turtle eggs, along with foraged tubers and

fruits (Headland, 1989; Sahani, 2010). They also wore few, if any, body coverings. This lifestyle conduced to a high level of vitamin D sufficiency, thereby rendering unlikely the development of any level of vitamin D insufficiency as long as a traditional diet was being consumed. This may have released a selective constraint on further pigment darkening.

Knowledge of the skin pigmentation phenotypes and pigmentation genes of Melanesians and Australian Aboriginals is limited, but the available data indicate that skin pigmentation is very dark, with Bougainvilleans exhibiting the darkest levels of pigmentation measured by reflectometry among people living today (Jablonski & Chaplin, 2000; Norton et al., 2006). Similar, extremely dark pigmentation reportedly existed among Aboriginal Tasmanians (Diamond, 2005). Melanesian populations notably lack evidence for purifying selection at the *MC1R* locus (Norton et al., 2015) and, thus, their extremely dark pigmentation must be accounted for by enhanced eumelanin production and tanning abilities controlled by other genes, possibly *MFSD12* and *DDB1*, and others. Under these conditions, dark skin pigmentation evolved to what appears to be a threshold level, past which no further darkening appears to be possible (Chaplin, 2004). It is noteworthy that the people who exhibit some of the darkest skin pigmentation observed are not only exposed to extremely high environmental UVR, but, traditionally, wear few clothes and eat diets rich in fish. These are also mostly coastal and island populations that have also been relatively isolated throughout most of history because of lack of accessibility over land. Thus, they were not subject to high levels of admixture from mainland groups. These populations are exemplars of one of the

extremes of skin pigmentation evolution, occurring as the result of people being isolated in geographic dead-ends, while simultaneously experiencing little admixture and positive selection. In these cases, diets replete in vitamin D may have worked to further promote the evolution of increasingly dark, protective eumelanin pigmentation up to a threshold level. This hypothesis invites further study of genes affecting skin pigmentation, vitamin D metabolism, and the eumelanin threshold effect. A hypothetical skin pigmentation timeline for coastal South and Southeast Asia, Melanesia, and Australia is presented in Figure 3.

3.3 | Hinterland Eurasia and the Americas

The evolution of skin pigmentation in Eurasia, especially in Europe, has been the focus of considerable attention (Norton, 2019; Quillen et al., 2019), especially with the advent of archeogenomics and the functional genomic interpretation of skin pigmentation genes in ancient Eurasian populations. New and comprehensive reviews of Eurasian skin pigmentation genomics in relation to historical genomics should be consulted for details, especially with regard to the movements of peoples and genes in historic times and their likely effects on skin pigmentation (Allentoft et al., 2015; Hanel & Carlberg, 2020a; Ju & Mathieson, 2020; Røyrvik et al., 2018). Here, I reiterate salient points of those reviews and other works and supplement them sparingly with some additional insights.

Inferences about the likely evolutionary factors affecting human skin pigmentation among people living at high latitudes in Eurasia

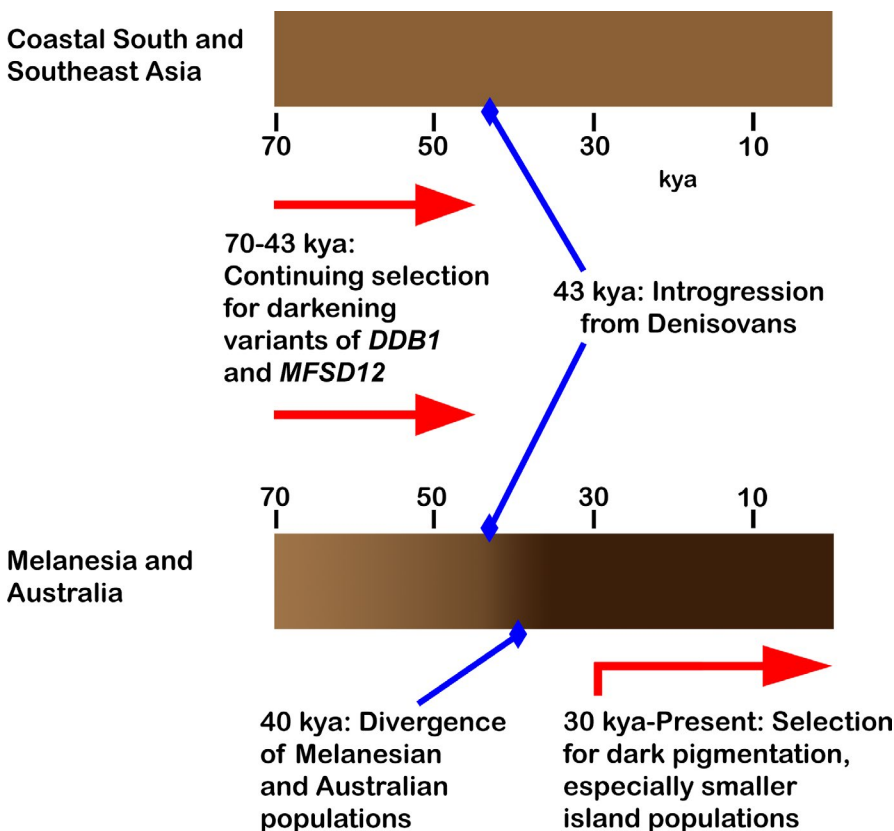


FIGURE 3 Generalized timeline of main events in the evolution of skin pigmentation in Coastal South and Southeast Asia, Melanesia, and Australia. (a) Beginning around 70 kya, small populations of coastal dispersers make their way along the coasts of southern and southeastern Asia. Introgression from Denisovans occurs about 43 kya, possibly involving introduction of variants favoring darker pigmentation. (b) In Melanesia and Australia, following the divergence from mainland coastal groups, continued positive selection on variants of *DDB1*, *MFSD12*, and other loci promotes in the absence of purifying selection on *MC1R* produces dark and very dark skin pigmentation phenotypes

have been mooted in the literature for nearly a century (Loomis, 1967; Murray, 1934). Emphasis on loss of pigmentation in order to promote cutaneous vitamin D photosynthesis at high latitudes has been emphasized, but so too has the importance of consumption of vitamin D-rich foods in regions where cutaneous biosynthesis is insufficient to fulfill year-round needs for the vitamin (Chaplin & Jablonski, 2013; Jablonski & Chaplin, 2000, 2010). Elucidation of the genetic basis for depigmentation began with the landmark study in which a zebrafish model was used to demonstrate the action of the *SLC24A5* variant common to northwestern European people (Lamason et al., 2005). The absence of the same variant in East Asian peoples living at similar latitudes (Lamason et al., 2005; Norton et al., 2007) inaugurated an intensive search for the genes responsible for depigmentation in East Asians. Subsequent historical genomic studies of modern and ancient populations have shown that depigmentation in Europeans, especially among far northern-dwelling peoples, occurred in a step-wise fashion, beginning with a shared variant of the Kit ligand (*KITLG*) gene in the common ancestor of western European and east Asian people (Hanel & Carlberg, 2020a; Lao et al., 2007; Sulem et al., 2007). Extreme depigmentation in northwestern Europeans involved multiple skin pigmentation genes and appears to have been further promoted by the introduction of agriculture (Brace et al., 2019). At the highest European latitudes, including Scotland, genetic variants contributing to mostly depigmented or lightly pigmented skin comprise one component of the biocultural compromise necessary for survival and reproductive success under low and markedly seasonal UVB at extreme high latitudes (Chaplin & Jablonski, 2013). Modifications of genes affecting the production and metabolism of vitamin D constitute another part of this compromise, in some cases offsetting extreme depigmentation in high-latitude Eurasian populations (Hanel & Carlberg, 2020a). The last component of the high-latitude biocultural compromise is a vitamin D-rich diet, focused on oily fish and, depending on the location, also including marine mammals and wild or domesticated reindeer (Chaplin & Jablonski, 2013; de Barros Damgaard et al., 2018; Ross et al., 2006). The fragility of the biocultural compromise at high latitudes in Eurasia is illustrated by the high prevalence of chronic lifestyle diseases, including cardiovascular disease and metabolic syndrome, in populations that mostly or completely abandon vitamin D-rich diets (Chaplin & Jablonski, 2013; Ross et al., 2006).

The evolutionary trend toward depigmented skin in high-latitude Eurasian populations involved numerous genes affecting skin pigmentation and vitamin D metabolism and did not result in uniform adaptive strategies across the great expanse of northern Eurasia favoring extreme depigmentation (Hanel & Carlberg, 2020a, 2020b). Rather, what we observe is that skin pigmentation has evolved as part of a larger genetic and cultural package favoring enhanced availability and economical utilization of dietary and cutaneously synthesized vitamin D. Because habitation of far-northern latitudes in Eurasia was predicated on the development of material culture, including sewn clothing, which afforded protection against extreme cold and wind, the surface area of skin available for cutaneous vitamin D production was reduced, thereby intensifying the selective

pressure for depigmentation. A further consideration is that increased thickening of the stratum corneum in response to repeated outdoor conditions and UVR (Oh et al., 2004) would also have served to attenuate any possible cutaneous vitamin D production under these conditions (Young et al., 2020).

In far northwestern Europe, the extreme physical isolation of people in northernmost Britain at the end of the Pleistocene and early Holocene favored maximal skin depigmentation and a near absence of eumelanin in the skin. This was made possible by positive selection for the classic depigmentation variant of *SLC24A5*, and by relaxation of selection pressure on the *MC1R* locus, resulting in high levels of polymorphism at the locus (Harding et al., 2000; Latreille et al., 2009; Rees, 2000). Under these circumstances, cutaneous production of vitamin D could be maximized during the few months when photocatalytic UVB wavelengths were present in the sunlight (Chaplin & Jablonski, 2013; Jablonski & Chaplin, 2000, 2010). During the millennia in prehistoric and early historic times when people did not travel widely or migrate to other climes, this highly depigmented skin phenotype worked well. Because their UVR regimes were markedly different from those of people in the tropics, they experienced only short periods of UVB during the height of the summer and sunburns would have been rare (Chaplin & Jablonski, 2013; Jablonski & Chaplin, 2010). Outdoor lifestyles meant that people adapted to gradually changing durations and intensities of UVR—mostly UVA—exposure throughout the year, to which their skin adapted primarily by thickening of the stratum corneum; the fact that they could develop only negligible protection from melanin production did not matter because the challenge from UVB was not severe or prolonged (Bech-Thomsen & Wulf, 1995; Hennessy, Oh, Rees, et al., 2005; Sheehan et al., 1998). Under these conditions, mostly depigmented skin was not a liability because it did not detract from health and well-being and did not affect reproductive success. This situation changed markedly when people from northwestern and northern Europe began to travel and migrate to sunnier places in colonial times, and experience high episodic or sustained loads of UVR (Jablonski, 2012). Historical migrations of people from northern Europe to far southern Europe, Africa, Australia, and tropical latitudes of the Americas in the last 200 years, along with the increased popularity of holiday travel, caused dramatic shifts in the nature of UVR exposure, and increased prevalence of all skin cancers (Latreille et al., 2009; Rees, 2003; Sturm et al., 2003).

The evolution of skin lightening in northeastern Asia occurred under similar, but not identical, conditions of generally low and seasonal UVB as those of northwestern Europe (Chaplin & Jablonski, 2013; Jablonski & Chaplin, 2000). Among the most interesting facts to emerge in the study of the evolution of human skin pigmentation evolution is that different suites of genes have influenced depigmentation in northern Europeans and East Asians. Recent research on the function of the upstream region of *KITLG* shared by the common ancestor of all Eurasians shows that the region was under stronger selective pressure in East Asians, possibly because it conferred depigmentation along with greater resistance to cold (Yang et al., 2018). This appears to have complemented selection on an

OCA2 (oculocutaneous albinism, type 2) variant absent in Europeans (Yang et al., 2016) and a variant of *MFS12* (Adhikari et al., 2019) to create a comparable level of depigmentation conducive to cutaneous vitamin D production. Thus, depigmentation in the ancestors of modern western Europeans and East Asians provides an excellent example of convergent evolution (Norton et al., 2007; Yang et al., 2016). Natural selection has acted upon on different genes and gene variants in response to comparable environmental forces to produce comparable physiological solutions to a problem affecting health and reproductive success.

East Asians and western Europeans share visibly similar “light” skin, but their responses to UVR are different. The skin of East Asians has a higher density of melanosomes and produces more eumelanin and pheomelanin in response to UVR exposure than does the skin of western Europeans (Hennessy, Oh, Diffey, et al., 2005; Hennessy, Oh, Rees, et al., 2005). Thus, most East Asian people can tan, whereas many Europeans, especially northern Europeans, can tan only slightly or not at all. The development and persistence of tanning abilities are conferred by many genes operating on melanin production, distribution, and breakdown in the skin (Del Bino et al., 2018) and tanning abilities, like depigmentation, have evolved multiple times independently in human history under conditions of seasonally strong UVR (Martínez-Cadenas et al., 2013; Quillen, 2015; Quillen et al., 2019). The moderate tanning abilities among some Scandinavians and northern Europeans appear to have been conferred by recent genetic admixture across northern Eurasia (Hanel & Carlberg, 2020a), but other factors, including altered epistatic interactions among pigmentation genes, may have also contributed.

Following the amelioration of climatic conditions at the end of the Pleistocene, the development of extensive steppe grasslands across much of hinterland Eurasia created a theater for rapid human population growth associated with animal husbandry, and relatively rapid, bidirectional east–west movements of people (Allentoft et al., 2015; Damgaard et al., 2018). The results of genomic, linguistic, and archeological studies show a gradual transition from Bronze Age pastoralists of West Eurasian ancestry toward horse-mounted warrior peoples of increased East Asian ancestry (Damgaard et al., 2018). The rise and expansion of agriculture from Anatolia and Iran saw incursions of agriculturalists into southern and central Europe, increasingly displacing earlier hunter-gatherer populations (Skoglund & Mathieson, 2018). The evolution of skin pigmentation genes and phenotypes of the region reflects these dramatic movements, and the influence of relatively few genes of major effect transmitted over long distances by admixture (Ju & Mathieson, 2020). Of these, the effect of the classic depigmentation variant of *SLC24A5* is greatest, with recent evidence showing that this variant reached western Europe by admixture from Anatolian agriculturalists followed by continued positive selection (Ju & Mathieson, 2020). Recent genomic evidence indicates that some of the hunter-gatherer populations of Mesolithic western Europe and Britain had moved along the coast from the Iberian Peninsula into northern France, and thence up the Atlantic coast, making use of marine food resources as they went (Brace et al., 2019). In

this context, the much-discussed dark or “dark to black” skin reconstructed for “Cheddar Man,” a Mesolithic inhabitant of Cheddar Gorge in Somerset, England (Brace et al., 2019), becomes more clearly understandable and less sensational. Traditional hunter-gatherer diets centered around coastal marine sources, hunted terrestrial game, and foraged plant foods are rich in vitamin D and make it possible for people to continue to live healthy reproductive lives while maintaining “dark” and highly tannable skin. Skin depigmentation in northwestern Europe occurred gradually, over many millennia, with the introduction of the classic *SLC24A5* variant being the last and most dramatic step in the process after the introduction of agriculture.

3.3.1 | Beringia and the Americas

Discussion of the evolution of human skin pigmentation among indigenous populations of the Americas follows naturally from that of northern and northeast Asians because northern Asia was the area of origin for the earliest peoples entering Beringia and North America via coastal and overland routes (Goebel et al., 2008; Moreno-Mayar et al., 2018; Nielsen et al., 2017). Considerable research and debate over the number, nature, timing, and routing of these dispersals over the last century have resulted in general consensus that the first humans to disperse into the Americas traveled via a coastal route beginning around 15 kya, having genetically diverged from ancient north Asians beginning around 36 kya with gene flow continuing until about 25 kya (Moreno-Mayar et al., 2018; Nielsen et al., 2017). Details of the population movements are beyond the scope of this paper, but a key feature of this dispersal event was that it involved a prolonged “Beringian standstill” lasting about 15,000 years (Moreno-Mayar et al., 2018), during which an isolated population lived under conditions of limited and highly seasonal sunlight, including virtually no UVB (Hlusko et al., 2018). In the absence of UVB and cutaneous biosynthesis of vitamin D, the consumption of vitamin D-rich foods was necessary for survival and reproductive success. Because normal human development *in utero* and in early postnatal months depends on maternal vitamin D stores, the evolution of efficient transmission of vitamin D in breastmilk was critical for infant survival. This need appears to have been met by positive selection on the human-specific *EDAR* (Ectodysplasin A receptor) variant V370A associated with mammary ductal branching, which appears to have amplified the transfer of vitamin D to infants via mothers’ milk (Hlusko et al., 2018). Evidence for the rapid spread and positive selection of this variant back into northern Asia and Scandinavia (Mathieson et al., 2015) suggests that it conferred an evolutionary advantage to people inhabiting regions in which the potential for cutaneous production of vitamin D from UVB was severely limited and the vitamin could be derived only from dietary sources. This example illustrates the importance of understanding the evolution of skin pigmentation in the broader context of human evolution and dispersals, and recognizing the nature of life events most likely to be influenced by natural selection.

Skin pigmentation among Inuit people is often discussed, but has been inadequately measured or genetically characterized. Ancestral Inuit traversed the Bering Land Bridge in the mid-Holocene, dispersing into Americas from northern Siberia about 10,000 years after first coastal dispersal about 15 kya (Nielsen et al., 2017; Skoglund & Mathieson, 2018). Their constitutive pigmentation is light to moderate, but they have remarkable tanning abilities, as illustrated by the “tan lines” evident on traditional hunters when their animal skin parkas are removed (Jablonski, 2012). This is another case of biocultural compromise involving skin pigmentation, dietary vitamin D, and regulation of vitamin D availability at critical points in the lifespan. Inuit and their ancestral populations were, traditionally, hunter-gatherers who, depending on location, subsisted primarily on marine mammals, oily fish, and caribou. Living near or above the Arctic Circle, they experienced markedly seasonal patterns of daylight and UVR exposure, and negligible UVB; they did, however, experience seasonally strong direct and reflected UVA (Chaplin & Jablonski, 2013; Jablonski, 2012; Jablonski & Chaplin, 2000, 2010). Modest cutaneous production of vitamin D occurs in some populations, but the physiological significance of this is unclear (Andersen et al., 2012). In the presence of a traditional diet replete in vitamin D, and a physiological mechanism to ensure ample vitamin D to rapidly developing neonates (Hlusko et al., 2018), there was little selective pressure for further depigmentation; if anything, there may have been selective pressure to enhance facultative pigmentation. The fragility of the biocultural compromise here is witnessed by the high levels of vitamin D deficiency and high prevalence of rickets and metabolic syndrome in people no longer eating traditional diets year round (Andersen et al., 2013; El Hayek et al., 2010).

The evolution of skin pigmentation in the Americas has been studied relatively little, with the exception of a few pioneering studies in the last decade (Adhikari et al., 2019; Quillen et al., 2012). The peopling of the Americas from people of northern and northeastern Asian ancestry at the end of the Pleistocene and during the Holocene meant that indigenous populations carried novel mixtures of skin pigmentation genes, which reflect histories of extreme natural selection and population bottlenecks. Study of the evolution of skin pigmentation in the pre-Columbian Americas has been made difficult by the facts that many indigenous populations have not been studied comprehensively for both their skin pigmentation phenotypes and genetics, and because most of the populations that have been studied exhibit evidence of considerable admixture from colonial European and enslaved sub-Saharan African populations (Quillen et al., 2019). In this context, studies in which the effects of genetic admixture have been “dissected” to reveal novel skin pigmentation genes have been of key importance (Bonilla et al., 2005; Quillen et al., 2012). Because of the northern and northeastern Asian origin of New World populations, the variants of *OCA2* and *MFSN1* found in Asian populations are also present among indigenous Americans (Adhikari et al., 2019; Yang et al., 2016). In addition, other genes not previously implicated in skin pigmentation, including *EGFR* (epidermal growth factor receptor) and *OPRM1* (opioid receptor, mu-1), have emerged as important contributors to skin pigmentation among

indigenous Americans (Quillen et al., 2012, 2019). One of the most biologically significant facts about the evolution of skin pigmentation in the Americas is that it has involved selection for genes that confer enhanced tanning (facultative pigmentation) rather than darker constitutive pigmentation. Most indigenous Americans, including those that inhabit areas of high and relatively nonseasonal UVR, exhibit “moderate” skin reflectance values for unexposed skin, but strong tanning abilities (Jablonski & Chaplin, 2000; Quillen et al., 2019). The genetic basis of these abilities is almost completely unknown and warrants considerable study (Quillen et al., 2019). Looking in general at the evolution of skin pigmentation in the Americas, it is important to view the range of factors that have contributed to the phenomenon: population bottlenecks limiting the pool of potential variant pigmentation genes, a relatively short history of human habitation, and the fact that the Late Pleistocene populations dispersing into the Americas brought with them many means to buffer themselves and their skin against the exigencies of the environment and seasonal changes in food availability through sewn clothing, constructed shelters, and food storage technologies (Jablonski, 2012).

3.3.2 | Indian subcontinent

The evolution of skin pigmentation on the Indian subcontinent can only be understood in light of the complex demographic and social histories of the region. Because of this complexity and the practical difficulties of studying living populations on the subcontinent and obtaining biological samples therefrom, studies of skin pigmentation diversity and evolution are still in their infancy. The history of dispersals and genetic admixture within the subcontinent is complex and still poorly understood (Dennell & Petraglia, 2012; Majumder & Basu, 2014; Moorjani et al., 2013). Genetic evidence attests that the southern coast of the subcontinent received *H. sapiens* populations early in the history of dispersal along the coast of the Afro-Arabian Peninsula (Majumder & Basu, 2014). Since then, populations dispersing into the subcontinent have followed mostly hinterland routes, from central and western Asia, primarily via a northwestern corridor (Damgaard et al., 2018; Majumder & Basu, 2014), southward. Tracing the fate and routes of these populations has been difficult. The subcontinent contains people hailing from four distinct language groups who live in mostly non-overlapping regions and who reached their current locations at different times in late prehistory and early history (Majumder & Basu, 2014). Some populations belong to groups designated as tribal, while most belong to caste societies. One of the most distinctive aspects of population structure in the subcontinent is the pattern of endogamy within groups, including within the hierarchically arranged Hindu castes (Majumder & Basu, 2014). Because of the complex pattern of dispersal and the prevalence of within-group marriage, the subcontinent is more accurately described as a genetic mosaic and, not surprisingly, social factors and population structure have played a stronger role than natural selection in shaping skin color diversity across the region (Iliescu et al., 2018; Stokowski et al., 2007). Two striking findings have emerged from studies of skin

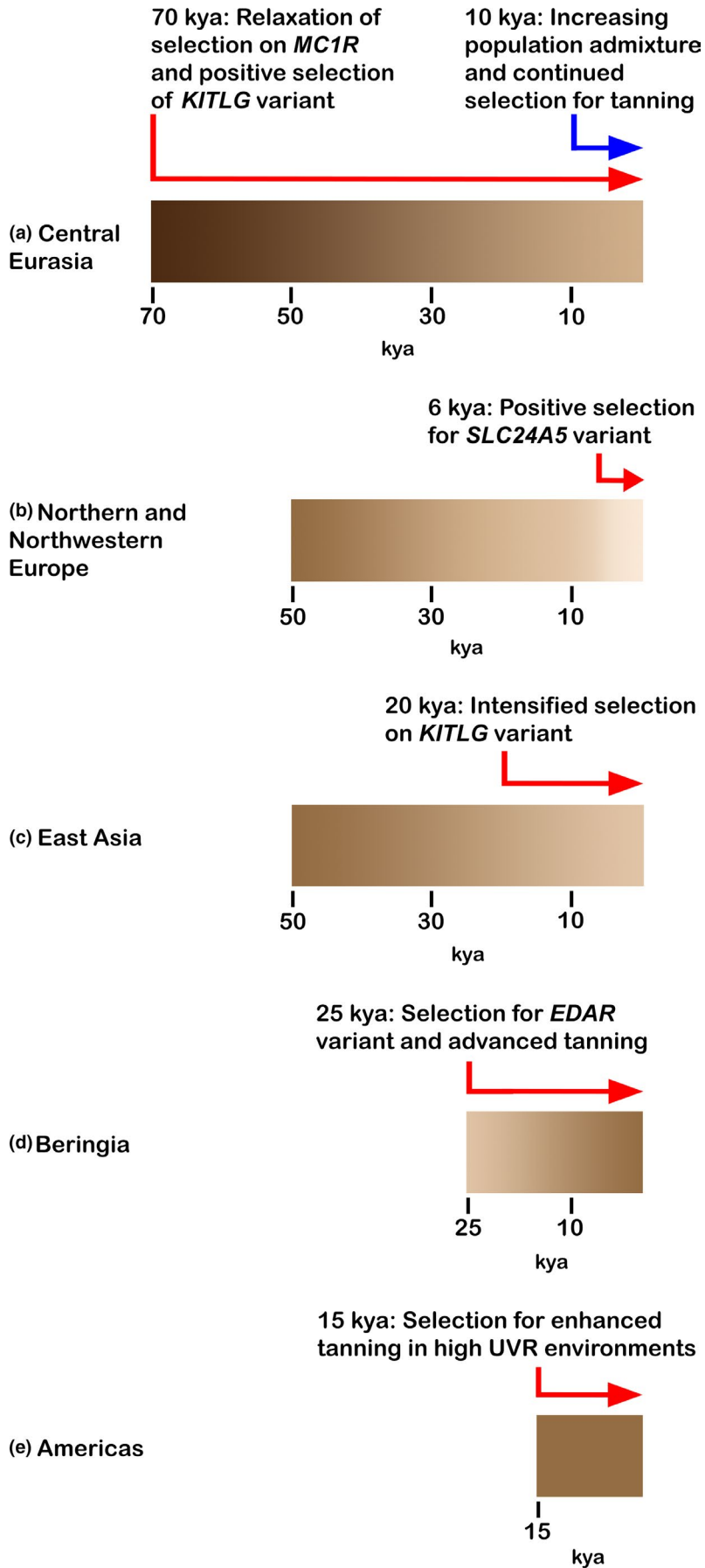


FIGURE 4 Generalized timeline of main events in the evolution of skin pigmentation in hinterland Eurasia, Beringia, and the Americas. (a) In central Eurasia, beginning around 70 kya, moderately pigmented and tannable phenotypes are favored under continued relaxation of selection on *MC1R* and positive selection of a *KITLG* producing lighter skin. After the introduction of agriculture and animal husbandry around 10 kya, increasing population admixture with diverse skin pigmentation gene assemblages producing moderately pigmented, tannable skin. (b) In northern and northwestern Europe, the introduction of the *SLC24A5* variant from Anatolian agriculturalists around 6 kya is followed by positive selection on the variant; this is favored strongly in relatively isolated populations living under the low and seasonal UVB conditions of northernmost Europe. (c) In East Asia, intensified selection on the *KITLG* variant and other loci produces further depigmentation. (d) In Beringia, hunter-gatherer populations experiencing the “Beringian standstill” from about 25–15 kya undergo selection for the *EDAR* variant favoring enhanced mammary transmission of vitamin D, while maintaining or enhancing their tanning abilities through skin pigmentation genes not yet identified. (e) In the Americas, technologically sophisticated hunter-gatherers disperse southward, carrying genes capable of producing strong tans under high UVB conditions. Dark constitutive pigmentation does not evolve, probably because of the absence of appropriate gene variants and the many cultural buffering mechanisms—including food storage—used by dispersing populations to mitigate the effects of different regimes of UVB and food availability

pigmentation diversity in the subcontinent to date. The first is that while the range of skin pigmentation phenotypes across the breadth and length of the subcontinent is vast (Jablonski & Chaplin, 2000), the pattern is not strongly correlated to strength of UVR (Iliescu et al., 2018). The second is that the classic skin lightening variant of *SLC24A5* is present in high frequencies in most populations but is not expressed (Basu Mallick et al., 2013; Iliescu et al., 2018). Thus, epistasis has affected the expression of the *SLC24A5* in such a way as to prevent the allele's ability to lower eumelanin production (Quillen et al., 2019). The reasons behind this can be traced potentially to the specific and distinct genetic backgrounds, including social selection and sexual selection, that contributed to the unique reproductive structure of the Indian populations, but the relative importance of these phenomena is not clear at present. This result should be seen as a useful cautionary tale for forensic reconstruction of skin pigmentation, viz., specific genotypes are not associated reliably with specific skin color phenotypes (Iliescu et al., 2018; Quillen et al., 2019).

A hypothetical skin pigmentation timeline for the major regions of Eurasia and the Americas is presented in Figure 4.

4 | SEXUAL DIMORPHISM AND SEXUAL SELECTION IN HUMAN SKIN PIGMENTATION

One of the most interesting and still not fully understood aspects of human skin pigmentation evolution is the consistent pattern of sexual dimorphism observed: In most indigenous groups whose skin phenotypes have been quantified using reflectometry, female pigmentation is lighter than male, sometimes to a striking degree (Byard, 1981; Jablonski & Chaplin, 2000; Roberts & Kahlon, 1972). This aspect of human skin pigmentation garnered early attention from natural historians including Charles Darwin and has been the focus of considerable attention since. Darwin believed that differences in human skin color between "races" were caused, not by natural selection, but by sexual selection; in other words, that skin color had been primarily and systematically influenced by deliberate choice of mates (Aoki, 2002; Darwin, 1871). The belief that skin color is an important determinant of human mate choice became fixed in the literature and public imagination in the late 20th century (Aoki, 2002; Diamond, 1991; Robins, 1991; Van den Berghe & Frost, 1986). Further study has revealed, however, that sexual selection is not as dominant and omnipresent force as some have conceived (Jablonski & Chaplin, 2000; Madrigal & Kelly, 2007). Sexual dimorphism in human skin pigmentation is real, but its expression varies greatly, with some populations exhibiting marked levels and others very little (Jablonski & Chaplin, 2000; Norton et al., 2006). The primary cause of the difference between the sexes may be the importance of increased cutaneous vitamin D production potential, and therefore lighter skin, in the skin of reproductively aged women, in order to facilitate absorption and redistribution of dietary calcium to the developing fetus and nursing neonate (Jablonski &

Chaplin, 2000). Satisfactory tests of this hypothesis in populations with varying levels of skin color sexual dimorphism have not yet been undertaken. What seems likely is that sexual selection has probably played a secondary and complementary role in the evolution of skin pigmentation, primarily through manipulating levels of existing sexual dimorphism (Jablonski, 2012; Jablonski & Chaplin, 2000; Quillen et al., 2019). This apparent directional preference for women with lighter skin appears to be particularly strongly marked in Island Melanesia, Japan, and among certain populations in India where cultural preferences for lighter females are strongly culturally reinforced (Iliescu et al., 2018; Jablonski, 2012; Norton et al., 2006). It would be surprising if uniform, global patterns of sexual selection applied because these would rely on uniform preferences (Quillen et al., 2019). Human skin pigmentation is the product of many cultural forces, including culturally determined mating preferences and sexual selection, which have had potent local effects modifying the influence of UVR-determined directional selection (Quillen et al., 2019).

5 | CONCLUSIONS

The evolution of human skin pigmentation has never been a simple deterministic process, but it has been influenced potently by environmental UVR and its effects on vitamin availability. Humans evolved under the sun. The early evolution of the genus *Homo* occurred in equatorial Africa under conditions of high UVA and high UVB. Under these conditions, natural selection favored the evolution of enhanced sweating abilities and enhanced permanent eumelanin pigmentation, concomitant with the loss of most body hair. Enhanced eumelanin constitutive pigmentation provided protection against folate degradation and damage to DNA while still permitting cutaneous vitamin D production. Dark skin in early *H. sapiens* was made possible by elimination of variation at the *MC1R* locus and positive selection at the *MFS12*, *DDB1*, and probably other loci. Populations of *H. sapiens* in equatorial Africa underwent further positive selection for very dark, eumelanin-rich pigmentation. Habitation of southern Africa, with its somewhat lower and more seasonal UVR regimes, involved relaxation of purifying selection on *MC1R*. Further depigmentation in southern African hunter-gatherers occurred under the influence of the classic variant of *SLC24A5*, which entered Africa through the Afro-Arabian Peninsula and rapidly spread southward. Dispersal of *H. sapiens* into Eurasia began around 70 kya and involved both rapid coastal and hinterland routes. Dispersing populations were small, and population bottlenecks affected the nature of pigmentation gene variants they carried. Equipped with sophisticated food procurement technologies, but not sewn clothing, agriculture or animal husbandry, people modified their diets and lifestyles according to local resources and conditions. Coastal dispersal routes in South and Southeast Asia and Europe afforded people the opportunity to easily harvest fish and other vitamin D-rich foods, mitigating selective pressure for depigmentation to facilitate cutaneous production of vitamin D. Further darkening of skin pigmentation

occurred, involving intensified selection on *MFS12*, *DDB1*, and probably some variants carried by introgressing Denisovans, in predominantly coastal populations dispersing into equatorial island Southeast Asia, Melanesia, and Australia. Habitation of non-tropical hinterland Eurasia with more highly seasonal UVB regimes saw the evolution of lighter constitutive pigmentation under the influence of positive selection for a variant of *KITLG*, which was then shared by populations dispersing into northern and western Europe, and northeastern Asia. Trends toward loss of constitutive eumelanin pigmentation and variable tanning abilities occurred at different times in these northward diverging populations and involved different suites of pigmentation genes. Prior to the introduction of agriculture and the origin of the classic variant of *SLC24A5*, hinterland Eurasians were moderately pigmented, had some or considerable tanning abilities, probably conferred by varying configurations of pigmentation genes, and pursued outdoor hunter-gatherer lifestyles. The evolution of extremely depigmented skin was a recent novelty in human evolution, occurring in northern and northwestern Europe after the introduction of the *SLC25A5* variant as the result of admixture with agriculturalists. Skin containing little eumelanin and lacking tanning abilities evolved only in relatively isolated populations living under the lowest and most highly seasonal UVB regimes with very limited opportunities for cutaneous vitamin D synthesis. The extremes of human skin pigmentation evolved under extremes of environmental UVB and were mitigated by vitamin D-rich diets. When genetic variants were available that enhanced reproductive success, they underwent rapid positive selection, especially in extreme solar environments, and quickly brought about changes in skin pigmentation phenotypes. Thus, natural selection for dark pigmentation under high UVR conditions and for lighter skin capable of tanning under lower and more seasonal UVR has been the dominant influence, but skin pigmentation has been modified increasingly by population genetic influences on the genetic composition of dispersing populations and by cultural processes, which have mitigated the expression of pigmentation genes and modified the impact of the environment on the human body. In recent millennia, human skin pigmentation has been influenced increasingly by culturally reinforced processes including, in some places, mating practices and sexual selection.

There remains a pressing need for more transdisciplinary research on the evolution of human pigmentation diversity. These need to include functional genomic studies aimed at further elucidating the mechanisms of tanning, as well as studies aimed at understanding the effects of genetic admixture and epistasis, and epigenetic influences on melanin production. We also need to better understand how various combinations of melanin pigments and the physical packaging of melanosomes contribute to the subtly different colors observed in human skin. It has long been appreciated that different forms of melanin in the skin—DHICA-eumelanin, DHI-eumelanin, and pheomelanin—contribute to the chromatic variation in skin color phenotypes (Alaluf et al., 2001, 2002), but much still remains to be clarified about how the different melanin types and, possibly also, the different sizes and physical arrangements of melanosomes impart subtly different colors to skin. Lastly, study of

the contributions of systematic cultural or sexual selection to producing directional evolution of skin pigmentation in recent history also requires further, thoughtful study, but such work must be pursued with careful attention to potential investigator bias, based on individual or cultural preoccupations. The evolution of human skin pigmentation has been a complex and contingent process for hundreds of thousands of years. This should not discourage us, because we now have the tools to understand the many genetic and cultural factors that have contributed to it.

ACKNOWLEDGEMENTS

I am grateful to the editors of the special issue of *Pigment Cell and Melanoma Research* for their invitation to contribute. Shosuke Ito is thanked especially for supervising the review of the manuscript. The ideas in this paper were developed over the course of many years, and I am grateful especially to George Chaplin for lengthy and probing discussions of all of these over the last 25 years. In recent years, I have benefited from clarifying discussions with Roger Bouillon, Tim Caro, Keith Cheng, Brenna Henn, Michael Holick, Mircea Iliescu, Larry Kenney, Beatriz Marcheco-Teruel, Heather Norton, Richard Prum, Ellen Quillen, Mark Shriver, Rick Sturm, Mark Thomas, Sarah Tishkoff, Richard Weller, Tony Wolf, and Antony Young. I thank my research assistant, Tess Wilson, for her continuing excellence and support in maintaining bibliographic materials, producing figures, and providing all-around logistical support for my research.

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How to cite this article: Jablonski NG. The evolution of human skin pigmentation involved the interactions of genetic, environmental, and cultural variables. *Pigment Cell Melanoma Res.* 2021;34:707–729. <https://doi.org/10.1111/pcmr.12976>