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THEORY AND SYNTHESIS

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Basis for the gain and subsequent dilution of epidermal pigmentation during human evolution: The barrier and metabolic conservation hypotheses revisited

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Abstract

The evolution of human skin pigmentation must address both the initial evolution of intense epidermal pigmentation in hominins, and its subsequent dilution in modern humans. While many authorities believe that epidermal pigmentation evolved to protect against either ultraviolet B (UV-B) irradiation-induced mutagenesis or folic acid photolysis, we hypothesize that pigmentation augmented the epidermal barriers by shifting the UV-B dose–response curve from toxic to beneficial. Whereas *erythemogenic* UV-B doses produce apoptosis and cell death, *suberythemogenic* doses benefit permeability and antimicrobial function. Heavily melanized melanocytes acidify the outer epidermis and emit paracrine signals that augment barrier competence. Modern humans, residing in the cooler, wetter climes of south-central Europe and Asia, initially retained substantial pigmentation. While their outdoor lifestyles still permitted sufficient cutaneous vitamin D3 (VD3) synthesis, their marginal nutritional status, coupled with cold-induced caloric needs, selected for moderate pigment reductions that diverted limited nutritional resources towards more urgent priorities (=metabolic conservation). The further pigment-dilution that evolved as humans reached north-central Europe (i.e., northern France, Germany), likely facilitated cutaneous VD3 synthesis, while also supporting ongoing, nutritional requirements. But at still higher European latitudes where little UV-B breaches the atmosphere (i.e., present-day UK, Scandinavia, Baltic States), pigment dilution alone could not suffice. There, other nonpigment-related mutations evolved to facilitate VD3 production; for example, in the epidermal protein, filaggrin, resulting in reduced levels of its distal metabolite, *trans*-urocanic acid, a potent UV-B chromophore. Thus, changes in human pigmentation reflect a complex interplay between latitude, climate, diet, lifestyle, and shifting metabolic priorities.

KEYWORDS
barrier function, filaggrin, melanocytes, metabolic conservation, pH, pigmentation, urocanic acid, UV-B, vitamin D

SYNOPSIS

Consideration of the evolution of human skin pigmentation must address two distinct questions; namely (1) what drove the initial evolution of widespread and intense epidermal pigmentation in early hominins; and (2) what led to the much later, progressive dilution of pigmentation in northern-dwelling modern humans? Presently, most authorities hold that epidermal pigmentation evolved in ancestral humans to protect against either ultraviolet B irradiation (UV-B)-induced mutagenesis or to prevent photolysis of circulating folic acid. Because epidermal pigmentation confers important functional advantages for human skin, we provide new evidence here in support of our previously articulated hypothesis that dark pigmentation evolved in the xeric, UV-B-saturated (toxic) environment of sub-Saharan Africa not only to augment the epidermal permeability barrier; that is, to optimize water conservation, but also to enhance cutaneous antimicrobial defense. Central to this hypothesis, the evolution of deep epidermal pigmentation in ancestral hominins would have shifted the dose–

TABLE 1 Degrees of epidermal pigmentation, according to Fitzpatrick scale[a]

Skin pigment type	Phenotypic characteristics	UV-B sensitivity
I	Pale white skin; blue eyes; freckles; redhead → blonde hair	Always burns; never tans
II	White skin; blue/green/hazel eyes; blonde to light brown hair	Commonly burns; minimal tanning
III	Lightly pigmented skin; any eye color, including brown; brown hair	Occasionally burns; uniform tanning
IV	Moderately brown skin, eyes and hair	Sometimes burns, easily tans
V	Dark brown skin, eyes and hair	Very rarely burns, always tans
VI	Very dark brown (darkest) skin, eyes and hair	Never burns

[a]From "The validity and practicality of sun-reactive skin types I-VI," by T. B. Fitzpatrick, 1988, Archives of Dermatology, 124, p. 869.

response curve to UV-B from toxic to beneficial for epidermal functions. Whereas *erythemogenic* UV-B; that is, doses that induce sunburn, compromises epidermal permeability and antimicrobial functions by producing apoptosis and cell death, *suberythemogenic* UV-B; that is, doses below the sunburn threshold, instead benefit both the permeability barrier and antimicrobial defense. Our recent work has shown that it is not only the greater capacity of heavily melanized melanocytes to acidify the outer epidermis that accounts for the superior function of darkly pigmented epidermis, but melanocytes in darkly pigmented skin generate still-unidentified, paracrine signals that stimulate epidermal differentiation, lipid synthesis, and secretion, thereby further augmenting epidermal function.

Recent genetic studies show that modern humans, who first successfully migrated from Africa into Europe <45,000 years ago (kya), retained substantial pigmentation until the advent of the agricultural era (<9 kya). Yet, habitation of the cooler, wetter climes of central/southern Europe and Asia required increased caloric expenditures that would have further challenged the already marginal nutritional status of these hunter-gatherers. The modest pigment reduction in this population allowed the diversion of precious protein resources from melanin synthesis towards more urgent metabolic requirements. Thus, dietary insecurity, coupled with the increased energy requirements of habitation in a colder climate, likely exerted evolutionary pressure to extinguish the substantial metabolic expenditures required for pigment production. Regardless of the depth of skin pigmentation, the outdoor lifestyle of hunter-gatherers and subsequent early agriculturists at these intermediate latitudes would have allowed sufficient cutaneous vitamin D3 (VD3) synthesis during summer months to provide for year-round VD3 requirements. Yet, VD3 may have provided an impetus for the further pigment dilution that occurred as humans reached north-central Europe (i.e., present-day northern France and Germany) behind retreating glaciers, a latitude where annual UV-B doses might not otherwise suffice, even with outdoor lifestyles. But at latitudes still further to the north (i.e., present-day Scandinavia, United Kingdom, and Baltic states), little UV-B penetrates the atmosphere, even during summer months, favoring further extreme pigment dilution, as well as other, nonpigment-related, loss-of-function mutations that facilitated additional intracutaneous VD3 production. One such mutation, that is prevalent in these populations, occurred in the epidermal structural protein, filaggrin. Loss of filaggrin results in decreased generation of its proteolytic, deiminated product, *trans*-urocanic acid, the most potent UV-B chromophore in skin. Hence, we propose that it was the universal imperative for metabolic conservation that was the initial "driver" of pigment loss as modern humans migrated northward out of Africa; later, metabolic conservation, coupled with VD3 requirements, favored the evolution of the very pale skin pigmentation of Europeans residing in the far North.

1 | EVOLUTION OF PIGMENTATION IN ANCESTRAL HUMANS—AN UPDATE

Darkly melanized skin is recognized as one of the key evolutionary adaptations of ancestral hominins arising in their sub-Saharan African cradle. Because melanin protects against the harmful effects of ultraviolet irradiation (Kollias, Sayre, Zeise, & Chedekel, 1991; Pathak & Fitzpatrick, 1974; Yamaguchi, Brenner, & Hearing, 2007), the development of deep epidermal pigmentation in newly hairless hominins almost certainly represented an adaptive response to UV-B irradiation (Jablonski & Chaplin, 2013). Although all theorists agree that intense melanization of skin arose in response to the extreme insolation of their habitat, they differ in their assessment of the principal evolutionary benefit that accrued. Presently, three hypotheses have their advocates: (1) protection from UV-induced skin mutagenesis; (2) protection from UV-induced folic acid deficiency; and (3) water conservation through pigmentation-induced enhancement of the cutaneous permeability barrier, a hypothesis that we recently advanced (Elias, Menon, Wetzel, & Williams, 2009, 2010). Note: because of its widespread usage and clinical utility, in this review we retain the widely accepted Fitzpatrick classification of human skin pigmentation (Table 1) (Fitzpatrick, 1988), rather than the reflectance spectrophotometric assays that are widely deployed by anthropologists.

1.1 | Mutagenesis hypothesis

UV irradiation is carcinogenic and pigmentation protects against UV-induced skin cancers [rev in (Lin & Fisher, 2007; Miyamura et al., 2007; Yamaguchi et al., 2007)] (Table 2). The observation that darkly pigmented individuals are at much lower risk for the development of skin cancers provides the principal support for the hypothesis that epidermal pigmentation evolved to protect against the development of skin cancers. Nonetheless, the present authors, as well as many evolutionary biologists have concerns about the skin cancer (genotoxic) hypothesis, primarily because the peak incidence of the most common,

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TABLE 2 Basis for epidermal pigmentation in hominins: Current hypotheses

Hypotheses	Evidence for	Evidence against
Genotoxic (to prevent UV-B-induced skin cancers)	1. Melanin is a moderately effective UV-B filter	1. Potentially fatal NMSC occurs long after peak reproductive age
	2. Melanin forms protective supranuclear cups	2. Short life expectancy of *H. erectus*
	3. Early onset of fatal NMSC in African albinos	
	4. Value of "aged grandmothers"	
Nutrient Photolysis (folic acid degradation)	1. Folate deficiency correlates with latitude	1. Low overall incidence of serious congenital anomalies in folate-deficient populations
	2. Congenital anomalies with folic acid deficiency	2. Little UV-B reaches dermal blood vessels
	3. UV-B $>$ UV-A degrades folic acid in vitro	3. Ample folate available from dietary sources
		4. No in vivo evidence for UV-induced folic acid deficiency
Barrier hypothesis	1. Superior permeability + antimicrobial barriers in darkly pigmented individuals	1. Retention of dark pigmentation in humans who re-entered tropical forests
	2. Climatic stress on permeability barrier	2. Little or no difference in basal barrier function between pigmentation types
	3. Eccrine sweating → ↑ water loss → need for highly competent barrier	

NMSC, nonmelanoma skin cancer.

potentially lethal skin cancer, squamous cell carcinoma, occurs above the age of 70 (Franceschi, Levi, Randimbison, & La Vecchia, 1996; Ridky, 2007), well past both the reproductive years (Blum, 1961; Goding, 2007; Robins, 1991) and life expectancy of ancestral hominins (Kennedy, 2003; Sievert, 2015; Trinkaus, 1995). Pertinently, fair-skinned humans residing near the Equator in Queensland, Australia exhibit much earlier onsets of skin cancer (Olsen, Thompson, Green, Neale, & Whiteman, 2015), without evidence of a reduction in reproductive success. While the deadliest of skin cancers, melanoma, can occur during childhood and reproductive years, its overall incidence ($<$2% of all skin cancers) (Jemal, Devesa, Hartge, & Tucker, 2001; Le et al., 2016) is likely too uncommon to have exerted an evolutionary influence. While modeling studies may still be needed to determine the threshold prevalence rate of melanoma that could begin to impact natural selection, it is fundamentally illogical to posit that pigmentation arose to prevent the development of melanoma—without the evolution of interfollicular melanocytes, melanoma would not occur.

Some workers continue to promote the genotoxic hypothesis, based upon the "grandmother effect;" i.e., the concept that long-term survival due to a reduced incidence of skin cancer could have provided an invaluable repository of knowledgeable, female elders, as well as a pool of physically-able kindred, who could assist with child care (Diamond, 2005; Hawkes & Coxworth, 2013; Osborne & Hames, 2014). Yet, the timetable of menopause occurs at least one decade prior to the peak incidence of squamous cell carcinomas; hence, one would have to propose that pigmentation evolved in service to a "great-grandmother effect," despite a lack of evidence of longevity in this era. Often cited in favor of this hypothesis are observations of the utility of the elderly in some current hunter-gatherer cultures, such as the Hazdas of Northern Tanzania (Finkel, 2009; Villar, Celdran, & Triado, 2012). Yet, the utility of elders is not a cultural absolute, even in recent hunter-gatherer cultures. For example, when no longer able to hunt or reproduce, "elderly" Inuits, who resided in resource-limited northern habitats, became expendable; i.e., they no longer were venerated, and senicide was widely practiced by quite literally nudging the elderly to the periphery of igloos, until they succumbed to hypothermia (Malaurie, 1982; Nansen, 1894).

In support of the UV-skin cancer hypothesis, a recent review notes the high mortality rates from skin cancer in African albinos in their third and fourth decades (Greaves, 2014), in line with earlier observations (Yakubu & Mabogunje, 1993), but strongly refuted in a follow-up commentary (Jablonski & Chaplin, 2014). Yet, it may not be appropriate to extrapolate backwards from contemporary albinos to newly-hairless *Homo erectus* residing in sub-Saharan Africa, 1 to 2 million years ago (mya), in light of the following considerations: First, it can be assumed that the peak reproductive age of these *H. erectus* occurred substantially earlier than occurs in modern humans (≈age 19) (Sievert, 2015). Though modern females in their 30s and 40s remain capable of reproduction, their peak periods of fecundity have long passed. Second, it likely is not appropriate to equate modern African albino skin to the lightly pigmented skin of newly-hairless *H. erectus*, because the skin of the latter would have displayed some interfollicular and follicular melanocytes (Montagna, 1972; Perkins, 1975). Third, a full repository of melanocytes, which are incapable of generating melanin pigment, is present in albino epidermis. These melanin-deficient melanocytes, rather than lessen pigmentation, may be responsible for the increased risk of epidermal cancer in albinos, because skin cancers are very uncommon in vitiligo skin (Teulings et al., 2013), an acquired condition in which melanocytes are completely absent. Thus, the amelanotic melanocytes in albino skin (and likely also the effete melanocytes of lightly pigmented skin) may generate potentially toxic substances (e.g., melanin precursors) that could promote skin cancer in conjunction with UVB exposure. Fourth and finally, albinos in Africa today are socially-ostracized (Lund, 2005). Hence, it is entirely feasible that psychosocial abnormalities could dampen host innate and adaptive immunity, and/or even compromise normal, sun-avoiding behavior (Wright, Norval, & Hertle, 2015). Together, these considerations suggest that albinism among contemporary Africans is an imperfect model for understanding the evolution of pigmentation. Nonetheless, it certainly is true that epidermal pigmentation protects against the mutagenic effects of UV light on nucleic acids (Miyamura et al., 2007; Yamaguchi et al., 2007; Young & Sheehan, 2001), a function that is illustrated eloquently by the distribution of melanin granules as supranuclear caps that shield the nuclear DNA of epidermal keratinocytes from penetrating UV rays (Gibbs et al., 2000; Kobayashi et al., 1993).

The protective benefits of epidermal pigmentation against UV-B-induced cytotoxicity (i.e., "sunburn") was likely more critical than melanin's antineoplastic effects. Acute UVB-induced damage to epidermal DNA induces premature cell death (apoptosis) (Slominski, Tobin, Shibahara, & Wortsman, 2004; Young & Sheehan, 2001). Accordingly, it is widely believed that the evolution of pigmentation could have protected hominins from the debilitating effects of sunburn, thereby assisting early humans' departure from equatorial forests to open, solar-saturated savannas (Robins, 1991). But it is more likely that protection against epidermal cytotoxicity acted in concert with the positive benefits of melanin/melanocytes in enhancing the permeability barrier that selected for wide-spread epidermal pigmentation (see below).

1.2 | Folic acid hypothesis

Because the essential nutrient, folic acid, and its metabolites are susceptible to photodegradation *in vitro*, it has been proposed that epidermal pigmentation evolved to protect against UV-induced folic acid deficiency (Branda & Eaton, 1978; Chaplin, 2004; Jablonski, 1999; Jablonski & Chaplin, 2000, 2013) (Table 2). The fact that administration of folic acid supplements to pregnant women reduces the incidence of spinal tube defects in contemporary populations has provided the primary impetus for the folic acid hypothesis (Chaplin & Jablonski, 2009; Northrup & Volcik, 2000; Scholl & Johnson, 2000; Stover, 2014). Yet, it seems unlikely that folic acid deficiency (even if it could be induced in humans by solar irradiation) provided a reproductive cost sufficient to drive the evolution of skin pigmentation. The overall frequency of neural tube defects, attributable to folic acid deficiency, most of which are insufficiently severe to compromise reproductive success, is low (1:2,000–5,000 births) (Northrup & Volcik, 2000).

Folic acid absorbs UV light most strongly in the UVB range, with a lesser peak in the UVA spectrum (Mitchell, 1944; Williams & Jacobson, 2010). However, unlike UVA, which penetrates deeply into the dermis, where the cutaneous vasculature resides, very little UV-B can reach the circulating pool of folate (Honigsmann, 2002; Parrish, Jaenicke, & Anderson, 1982). To circumvent this concern, proponents of the folic acid hypothesis propose that hematologic UVA chromophores, such as uroporphyrins (Moan, Nielsen, & Juzeniene, 2012) and oxyhemoglobin (Chaplin, 2004; Jablonski & Chaplin, 2013), could augment UVA-induced photolysis of folic acid. But it should also be noted that albumen, which is by far the most abundant protein in plasma, protects folic acid from photodegradation (Vorobey, Steindal, Off, Vorobey, & Moan, 2006).

In further support of the folic acid hypothesis, several population studies have described an inverse relationship between circulating folate levels and ambient UV exposure (Jablonski, 1999; Lapunzina, 1996). Yet, little or no depletion of circulating folic acid occurs when humans receive frequent, high, therapeutic doses of either UV-B or UV-A irradiation (Cicarma et al., 2010; Fukuwatari, Fujita, & Shibata, 2009; Gambichler, Bader, Sauermann, Altmeyer, & Hoffmann, 2001; Juzeniene, Stokke, Thune, & Moan, 2010). The preponderance of clinical studies instead shows that such frequently-administered, supraphysiologic doses of UV irradiation, when deployed to treat various inflammatory dermatoses, do not substantially reduce circulating folate levels. Moreover, we know of no evidence that congenital anomalies, whether associated with folic acid deficiency or not, occur more frequently in either avid sunbathers or tanning bed habitués. Furthermore, it is difficult to separate the potential impact of a deficiency of this single nutrient from that of other essential nutrients in contemporary malnourished populations, since folic acid deficiency is uncommon in isolation from other nutritional deficiencies (review in Stover, 2014). Finally, because folic acid is a widely available nutrient, found in vegetables, fruits and animal sources, particularly liver (Stover, 2014), it seems likely that dietary sources of folic acid could compensate for most, if not all putative, UV-induced losses of folic acid. Together, these observations cast serious doubt upon the notion of solar-induced folic acid deficiency.

Nonetheless, it remains possible that folic acid deficiency could exert broader effects on reproductive success (Scholl & Johnson, 2000). For example, experimental induction of folic acid deficiency in rats induces oligospermia, although folic acid supplements affect neither sperm counts nor motility in humans (Landau, Singer, Klein, & Segenreich, 1978; Raigani et al., 2014). In summary, although folic acid deficiency might exert significant effects on cell division, thereby impairing reproductive fitness, the absence of direct evidence that excessive UV exposure in vivo induces folic acid deficiency renders this hypothesis moot.

1.3 | Skin barrier hypothesis

1.3.1 | Introduction

Hominin evolution took place in the arena of sub-Saharan Africa, a region bathed in toxic doses of UVB, and during an era of extreme aridity further impacted by a series of mega-droughts (Blome Cohen, Tryon, Brooks, & Russell, 2012; Bobe, Behrensmeyer, & Chapman, 2002; Cerling et al., 2011; DeMenocal, 2004; Lahr & Foley, 1998). Intense UV-B, coupled with extreme heat and aridity, can place enormous stress on the skin's capacity to prevent the outward escape of body fluids; i.e., its epidermal permeability barrier (Figure 1) (Table 2). In fact, the primary overarching function of the skin, without which life in a terrestrial environment would not be possible, is to restrict excessive transcutaneous water loss (Elias & Choi, 2005; Elias Feingold, & Fluhr, 2003; Feingold, 2009; Feingold & Elias, 2013). That provision of a physical barrier against the excessive escape of internal fluids is the skin's paramount function is evidenced by the immediate, devastating consequences of an acute loss of this critical function following extensive thermal burns: untreated individuals die within hours from circulatory shock due to the unrestricted, transcutaneous fluid losses. Accordingly, the skin barrier hypothesis holds that epidermal pigmentation evolved to enhance the skin's permeability barrier (Elias et al., 2009, 2010; Elias & Williams, 2013). The barrier to water loss resides in the outermost layer of the epidermis, the stratum corneum, and is mediated by the extracellular deposition of lipid-enriched, hydrophobic membranes that surround protein-laden corneocytes. In this manner, a redundant system of water-repellent lipids seals the fluid-rich interior from exposure to the desiccating atmosphere.

For any given level of barrier competence, net rates of transcutaneous water loss reflect the partial vapor pressure of water at the stratum corneum-environmental interface. Because net rates of evaporation are dependent upon both ambient temperature and humidity, heat and low external humidity accelerate water loss, placing further stress on the permeability barrier. Prior or concurrent evolutionary changes in the skin of *H. erectus*, including the loss of their ancestral, pigmented pelage, would have not only removed an effective UV filter, but also resulted in a loss of the humidified microenvironment that normally resides beneath a cover of fur. Thus, loss of body hair would have further stressed the permeability barrier in this UV-B-saturated, desiccating milieu.

Perhaps the most critical, barrier-driven driver of pigmentation would have been another, prior or co-evolutionary adaptation, i.e., the wide-spread dispersion of eccrine glands across the skin surface. By greatly facilitating thermoregulation, eccrine sweating doubtless represented a critical adaption to the high temperatures of open savannas (Jablonski, 2006). Most authorities agree that body hair was lost to both prevent overheating and increase the efficiency of sweating. Yet, while eccrine sweating provides an effective means of heat dissipation that allows sustained physical exertion during the heat of day, the water lost in service to thermoregulation (eccrine sweating can release up to 15 l of water/d) would have further imperiled internal fluid homeostasis. Hence, eccrine sweating would have imposed further selective pressure to evolve an ever-more competent permeability barrier.

To allow for episodic, massive expenditures of body water through sweating, the skin needed to drastically reduce its rates of *constitutive* water loss across the skin, thereby compensating for high rates of *facultative* loss of water from eccrine sweating. Without the co-evolution of an ever-more competent epidermal permeability barrier, hairlessness and eccrine sweating would have comprised a "recipe for disaster" in open savannas, effectively tethering hairless, pale-skinned hominins to the immediate vicinity of water sources (Elias & Williams, 2013). Hence, we proposed that under the adverse circumstances that prevailed in sub-Saharan Africa at this stage of hominin evolution, "perfection" of the permeability barrier, aided in part by epidermal pigmentation, would have provided an important evolutionary advantage (Elias et al., 2009, 2010). Seen in this context, the three major evolutionary adaptions of human skin—loss of body hair, eccrine sweating,

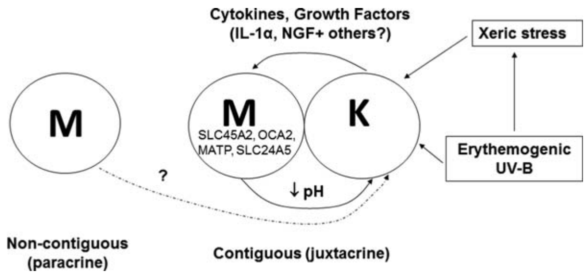

FIGURE 1 Cross-talk between keratinocytes and melanocytes—potential influence of stress to the barrier in stimulating the evolution of epidermal pigmentation (modified from "Evidence that stress to the epidermal barrier influenced the development of pigmentation in humans," by P. M. Elias et al., 2009, Pigment Cell & Melanoma Research, 22, p. 420)

and development of widespread pigmentation, whether they evolved sequentially or in concert, *can now be viewed as inextricably linked to each other through permeability barrier requirements; and, therefore, to the existential imperative for water conservation*.

1.3.2 | Summary of prior studies

To understand how melanization of the epidermis contributes to barrier function, it is critical to consider the differences in melanin content and distribution between darkly and lightly pigmented skin (Boissy, 2003; Pathak, 1995). Melanin granules in darkly pigmented skin are both larger and more numerous, and persist well into the outermost layers of the epidermis (Figure 2). In contrast, the smaller and less densely melanized granules of lightly pigmented skin are largely digested before reaching the outer epidermis. There, all cellular organelles suddenly disappear, as epidermal cells transition from the outermost, nucleated cell layers into the cornified cell compartment.

In light of the critical importance of permeability barrier competence for survival, it does not seem inappropriate to propose that certain components of the skin, including its pigmentary system, though appearing at first glance to be servicing other functions, could also play an additional, important role in optimizing permeability barrier function. Indeed, both pigmented human and murine epidermis display not only a more competent permeability barrier (Gunathilake et al., 2009; Man et al., 2014; Reed, Ghadially, & Elias, 1995), but also enhanced antimicrobial defense (Gasque & Jaffar-Bandjee, 2015; Mackintosh, 2001; Man et al., 2014; Rodriguez-Martin et al., 2011), as well as superior mechanical strength (Gunathilake et al., 2009; Reed et al., 1995) in comparison to lightly pigmented skin (Figure 3). In support of our prior hypothesis that epidermal pigmentation likely evolved to support these critical functions (Elias et al., 2009, 2010), we review below new information about how epidermal pigmentation optimizes cutaneous functions.

1.3.3 | Skin barrier hypothesis—An update

Erythemogenic doses of UV-B; i.e., those doses that induce toxic sunburn responses, are well-known to both damage the epidermal permeability barrier in a dose-dependent fashion (Haratake et al., 1997; Holleran et al., 1997), and to suppress adaptive immunity (Schwarz,

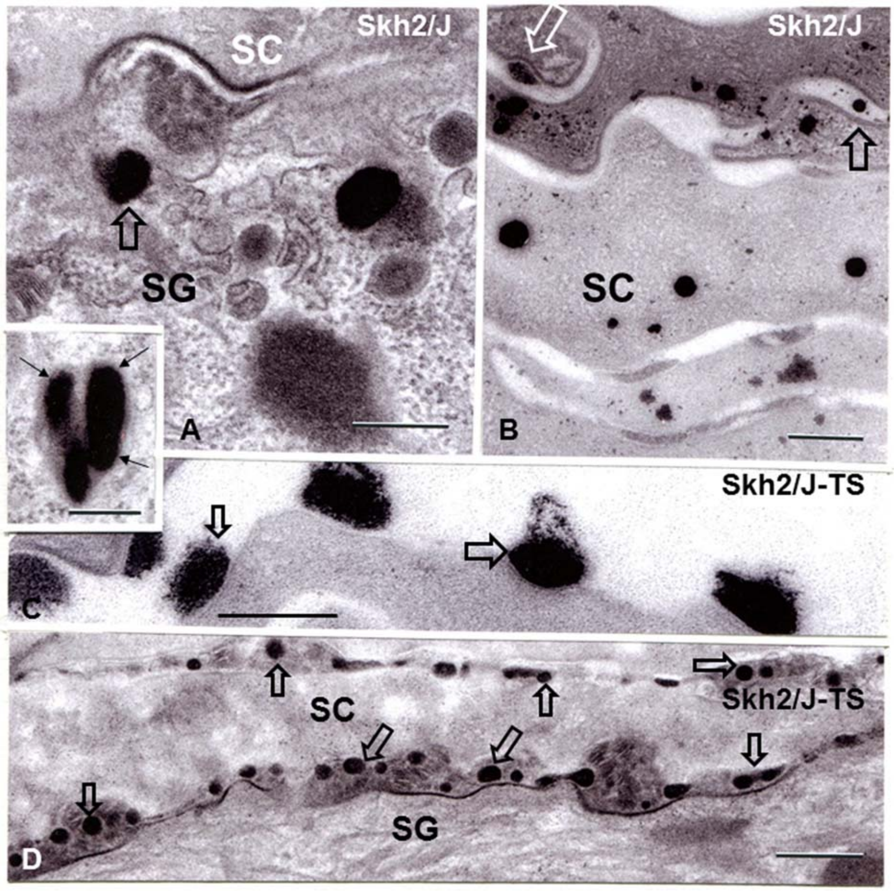

FIGURE 2 Persistence and rapid extrusion of pigment granules after barrier disruption. (A) Under basal conditions, large pigment (Skh2) hairless mice up into the stratum granulosum (SG) and stratum corneum (SC), where they gradually disintegrate within the corneocyte cytosol (A and B). Even under basal conditions, some granules appear to be extruded into the extracellular spaces (B, open arrows). (A, insert) Pigment granules appear enclosed within membrane-bound organelles (likely phagolysosomes) in the outer nucleated cell layers. (C and D) By 20 min after acute barrier disruption by tape stripping (SKH2/J-TS), the preformed pool of pigment granules is extruded into the SG-SC interface, and also within the SC extracellular spaces (open arrows). Mag bars, A–C + insert: 0.25 μm, D: 0.5 μm (Modified from "Basis for enhanced barrier function of pigmented skin," by M.Q. Man et al., 2014, Journal of Investigative Dermatology, 134, p. 2399)

2008). In contrast, recent studies have shown that *sub-erythemogenic* doses of UV-B; i.e., doses below the threshold for sunburn, instead: (1) augment permeability barrier homeostasis (Hong et al., 2008); (2) enhance epidermal innate immunity (i.e., antimicrobial peptide production) (Hong et al., 2008); (3) protect against subsequent UV-B-induced toxicity (Narbutt et al., 2007); and (4) downregulate VD3 receptor

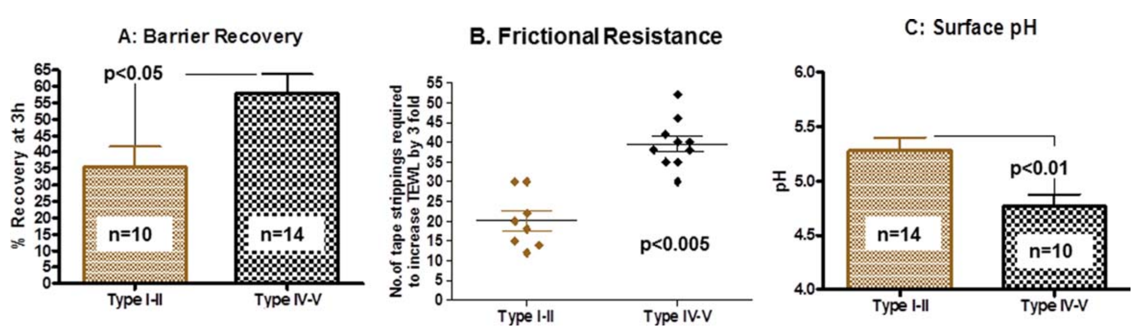

FIGURE 3 Enhanced function of darkly pigmented humans is independent of race, geographic location or occupation: barrier recovery, epidermal fricitional resistance, and forearm surface pH were assessed in a cohort of subjects of diverse racial backgrounds with type I-II and IV-V skin (cf. Table 1) living in the same geographic location (San Francisco, CA) and at the same time of year. Frictional resistance reflects the number of D-squame tape strippings required to increase transepidermal water loss (TEWL) rates threefold. TEWL was assessed both immediately and 3 h barrier disruption and percentage recovery at 3 h was calculated (Modified from "pH-regulated mechanisms account for pigment-type differences in epidermal barrier function," by R. Gunathilake et al., 2009, Journal of Investigative Dermatology, 129, p. 1719)

protein expression, reducing the likelihood of VD3 toxicity (Hong et al., 2008; Lesiak et al., 2011; Narbutt et al., 2007). Indeed, permeability barrier homeostasis and epidermal antimicrobial defense (innate immunity) are not disparate functions, but interdependent and co-regulated processes that fall under the broad umbrella of cutaneous protection (Aberg et al., 2008; Elias 2007; Elias & Wakefield, 2014; Rodriguez-Martin et al., 2011). Because the threshold dose of UV-B that can elicit a toxic, sunburn response is dependent upon the degree of epidermal pigmentation, *the most important advantage of deep epidermal melanization in newly hairless hominins would have been to shift the dose–response curve of an equivalent dose of UV-B from the deleterious (toxic) to the beneficial*. Thus, the evolution of widespread epidermal pigmentation not only prevented intense equatorial sun exposure from compromising these critical functions, it also turned a potential "negative" into a "positive" (Elias & Williams, 2013)!

A key concept in understanding how pigmentation influences permeability barrier homeostasis relates to pH. In contrast to the neutral pH of other tissues, human stratum corneum displays a highly acidic surface pH (4.5–5.5). Acidification of the outer epidermis is required not only for antimicrobial defense, but also for optimal permeability barrier function and normal skin turnover (desquamation) (Elias, 2015; Hachem et al., 2005, 2010; Hatano et al., 2013). Central to the skin barrier hypothesis is our prior observation that the stratum corneum of darkly pigmented human skin is substantially more acidic than that of lightly pigmented skin (1/2 unit lower surface pH), amounting to an approximately fivefold increase in proton concentrations (Gunathilake et al., 2009) (Figure 3). The critical role of an acidic pH is demonstrated by the fact that experimental acidification of the stratum corneum of lightly pigmented human subjects "resets" permeability barrier competence and stratum corneum mechanical integrity to levels encountered in darkly pigmented individuals (Gunathilake et al., 2009; Hachem et al., 2010).

The impact of pigmentation on pH can be attributed in part to the donation of acidic melanosomes to keratinocytes in darkly pigmented skin (Gunathilake et al., 2009). Moreover, once engulfed by keratinocytes, these single, dark melanin granules become sequestered within phagolysomes, organelles with a highly acidic content (Canton, Khezri, Glogauer, & Grinstein, 2014; Nyberg, Johansson, Rundquist, & Camner, 1989), followed by their persistence well into the stratum corneum (Figure. 3). There, keratinocytes eventually release some of their granule contents into extracellular domains, further acidifying the outer epidermis (Man et al., 2014). In contrast, the smaller "crumbly" melanin granules from lightly pigmented melanocytes, which are also transferred and engulfed within phagolysomes, decompose well before keratinocytes reach the stratum corneum (Boissy, 2003). The physiologic importance of this cellular mechanism is evidenced by the amplification of melanin granule extrusion in parallel with enhanced stratum corneum acidification immediately after the permeability barrier of darkly pigmented skin is either acutely perturbed or challenged by exogenous alkalization (Man et al., 2014) (Figure 2).

But melanin granule-mediated proton donation alone does not completely account for the enhanced function of darkly pigmented skin. Still uncharacterized, melanocyte-derived, paracrine factors stimulate both epidermal differentiation (i.e., the maturation of epidermal cells to form corneocytes), as well as the production of lipids destined for the extracellular membranes that mediate the permeability barrier (Man et al., 2014), processes that likely further enhance function in darkly pigmented skin by mechanisms unrelated to melanin granule persistence alone (Figure 1). Therefore, the melanocytes that reside in darkly pigmented epidermis profoundly enhance epidermal function by both pH- and non-pH-related, paracrine mechanisms.

1.3.4 | Arguments raised against the skin barrier hypothesis

There is considerable disagreement in the literature concerning differences in barrier function in fair-skinned Caucasians versus African-Americans [see reviews by (Rawlings, 2006; Wesley & Maibach, 2003)]. Measurement of the rates of water evaporation from the skin surface under nonsweating conditions, called transepidermal water loss (TEWL), represents the standard assessment of permeability barrier competence (Fluhr, Feingold, & Elias, 2006). Some previous studies have shown increased rates of basal TEWL in African-Americans among various modern human populations. Yet, these studies were based upon ethnic/racial groupings, rather than upon assessment of the depth of skin pigmentation. As noted above, not only is there considerable overlap in the intensity of melanin pigmentation among these "racial" groups (Wilson, Berardesca, & Maibach, 1988), recent population genetic data demonstrate substantial intermixing of modern populations, leading many anthropologists to conclude that racial definitions are no longer biologically valid (Schwartz, 2001; Sussman, 2014; Wilson et al., 2001). Finally, even in those studies that reported slightly increased rates of basal TEWL in African-American populations—the observed differences were not sufficiently robust to be of functional relevance (i.e., 1.1- to 1.3-fold increase) (Kompaore, Marty, Dupont, 1993; Wilson et al., 1988).

Our studies, which were based upon differences in skin pigment type, using the widely used Fitzpatrick identification (Fitzpatrick, 1988) (Table 1) rather than upon race, demonstrated comparable basal rates of TEWL in lightly and darkly pigmented skin (Gunathilake et al., 2009; Reed et al., 1995). But basal TEWL is no more reliable an indicator of true functional capacity than is an electrocardiogram (EKG) obtained at rest. A much more sensitive method to assess barrier competence is to examine the kinetics of barrier repair following acute external perturbations (Elias & Feingold, 2006b; Feingold, 2009). Just as a treadmill examination can unmask abnormalities in cardiac function that are not apparent in EKGs taken at rest, so too, the kinetics of repair following acute perturbations of the skin barrier comprise a much more accurate indicator of the skin's functional competence (Elias & Feingold, 2006a). Using this approach, the kinetics of barrier recovery markedly accelerate in darkly pigmented skin in comparison to paler skin, indicating the superior overall functional capacity of the permeability barrier in pigmented skin (Gunathilake et al., 2009; Reed et al., 1995) (Figure 3).

While it is true that some body sites; e.g., lips and palms/soles, remain lightly pigmented in darkly pigmented individuals, these areas support other specialized functions of these skin sites. The lips, a mucosal epithelium, are adapted to optimize hydration/lubrication

TABLE 3 Basis for latitude-dependent pigment lightening: Viable hypotheses

Hypotheses	Evidence for	Evidence against
Vitamin D	1. Pigment impedes access of UV-B to epidermal layers where VD3 is synthesized	1. Poor correlation of extent of pigmentation with latitude
	2. Partial loss of pigmentation at northern latitudes	2. Agriculturalists led outdoor lives; had domesticated livestock; and continued to hunt and fish
	3. Insufficient dietary VD3 in cereal-based diets	3. Paucity of evidence of rickets in pre-Industrial Age fossils
		4. Equivalent increase in serum VD3 in dark versus light skin after comparable UV-B doses
		5. ↓Osteoporosis in persons with darkly pigmented skin
Metabolic Conservation	1. Reduced demand for optimal barrier with clothing and ↑ambient humidity	1. Distinction between metabolic conservation and "relaxation" not always clear
	2. Melanin is a large protein polymer, leading to nutrient drain in darkly pigmented persons	
	3. Natural selection for mutations that ↓pigmentation at northern latitudes	
	4. Increased energy requirements to support high basal metabolic rates at northern latitudes	

rather than permeability barrier capacity, which in any case, becomes a lesser priority in such fully-hydrated microenvironments (Elias Menon, Grayson, Brown, & Rehfeld, 1987). Similarly, the palms and soles, which must resist mechanical injury, augment their frictional resistance through other, nonpigment-based mechanisms. Finally, while the permeability barrier of the palms and soles, like the lips, is less competent than elsewhere on the skin surface (Lampe et al., 1983), these sites comprise a relatively minor portion of the body surface (<2%). Hence, their reduced barrier capacity is irrelevant to the global requirement of the organism for a competent permeability barrier.

Because alterations in permeability barrier requirements are not known to upregulate melanin synthesis; and further, because relocation to an arid environment does not result in immediate tanning (the immediate tanning response represents the dispersion of preformed melanin, while true tanning entails increased melanin synthesis), it has been suggested that the evolution of pigmentation is unrelated to barrier function (Jablonski & Chaplin, 2013). Yet, this apparent anomaly likely reflects differences in biological responses to *acute* or episodic environmental threats versus evolutionary adaptations in response to *sustained* environmental stressors that operate over more prolonged periods. Indeed, the epidermis continually fine-tunes its permeability barrier competence in response to acute modulations in the external environment, including reductions in external humidity (Denda et al., 1998). Under such conditions, we have shown that the epidermis enhances its permeability barrier competence by upregulating the epidermal production, secretion and post-secretory processing of barrier lipids within minutes-to-hours after exposure to such acute, environmental stressors, resulting in rapid barrier optimization [review in (Feingold, 2009; Feingold & Elias, 2013)]. In contrast, an acute repair strategy that relies upon increased melanin production would necessarily be very slow, and accomplished only over several days-to-weeks, rather than minutes-to-hours. To impact the barrier, melanin first needs to be synthesized in melanocytes residing in the basal epidermal cell layer, and subsequently transferred to keratinocytes, which then would need to complete their vertical, outward transit towards the stratum corneum before they could impact permeability barrier homeostasis through pH-related mechanisms. It requires ≈2 weeks for a newly formed epidermal cell to reach the cornified cell compartment, and another ≈2 weeks for these cells to be shed from the skin surface (Simonart, Heenen, & Lejeune, 2010). Thus, while enhanced epidermal melanization likely does not comprise a viable strategy to mitigate against acute stress to the barrier, it nonetheless could have evolved to provide the long-term benefits of enhanced barrier competence.

Finally, the evolution of human skin pigmentation should be viewed within the broader context of functional adaptations of existing structures to new purposes. Melanocytes clearly have physiologic roles that are not limited to their ability to prevent UV-induced toxicity. Melanocytes and melanin are present in numerous, primitive eukaryotic organisms, where they impact a host of functions unrelated to protection from UV light (Blois, 1968; Jacquin, Lenouvel, Haussy, Ducatez, & Gasparini, 2011; Plonka et al., 2009). For example, while the role of pigment in the central nervous system remains unknown, melanocytes secrete potent neuroendrocrine mediators, independent of melanin production (Takeda, Takahashi, & Shibahara, 2007). Given this pleiotropy, it seems not unreasonable to propose a role for melanocytes in skin, beyond a role in pigment production to absorb ultraviolet light.

2 | PIGMENT DILUTION IN MODERN HUMANS

Currently, there are three extant explanations for pigment dilution in modern humans (Table 3). Most widely held is the hypothesis that pigment lightening occurred in modern humans to support *intracutaneous synthesis of vitamin D3* (VD3), necessitated by geographic reductions in UVB (Branda & Eaton, 1978; Loomis, 1967; Murray, 1934; Norton

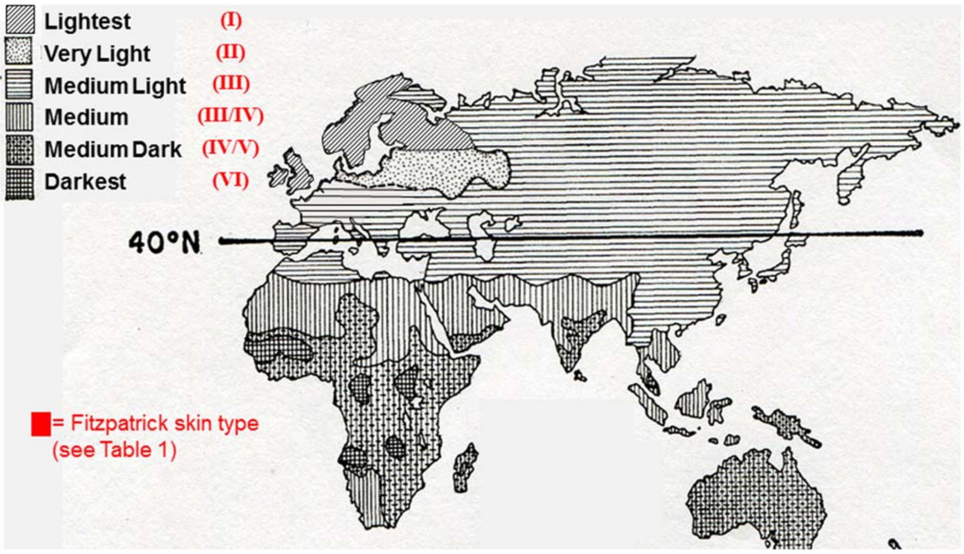

FIGURE 4 The Loomis diagram (1967) of the latitude-dependent distribution of human skin pigmentation revisited. Pigment dilution does not strictly correlate with latitude: e.g., moderately pigmented skin persists at all northern latitudes, except northern Europe

et al., 2006; Reichrath, 2007; Relethford, 1997). While vitamin D (VD3) can be obtained from both dietary sources and de novo synthesis in the skin, cutaneous VD3 generation remains the most important source of this nutrient at all but the most Northern latitudes, even when abundant sources of dietary VD3 are available (Chen et al., 2007; Vieth, 2003; Webb & Holick, 1988). Moreover, VD3 sufficiency could have influenced natural selection, because its active metabolite, 1,25-dihydroxyvitamin D3 (calcitriol), is required not only for bone and mineral metabolism (Bikle, 2010; Holick, 2011), but also for cognitive development, and for the regulation of innate immune responses that protect against viral and mycoplasma infections (Bartley, 2010; Bryson, Nash, & Norval, 2014; Holick, 2008; Yuen & Jablonski, 2010).

Chaplin and Jablonski (2009) invoked Hill's criteria to support an indisputable link between latitude-dependent reductions in pigmentation and enhanced cutaneous VD3 production. Hill proposed that correlative evidence, if sufficient, can establish a firm causal link, *in the absence of an alternative hypothesis* (Hill, 1965). However, there are several, significant problems with the VD3 hypothesis, which we will review in the next section [see also (Elias & Williams, 2013; Neer, 1975; Robins, 1991)]. Moreover, there are currently at least two alternate explanations for pigment dilution in modern humans that should be considered as well (Table 3).

2.1 | Arguments against the VD3 hypothesis

At the heart of the VD3-pigment hypothesis is the supposition that melanin in darkly pigmented skin interferes with epidermal vitamin D3 (VD3) production, by reducing the amount of incident UV-B irradiation that can reach those loci in the nucleated layers of the epidermis where vitamin D is synthesized (Kollias et al., 1991; Miyamura et al., 2007; Pathak, 1995; Pathak & Fitzpatrick, 1974). Despite the fact that melanin is a modestly effective UV-B chromophore (with an SPF between 1 and 2), several studies have demonstrated a robust capacity for even deeply melanized skin to generate VD3 (Bogh, Schmedes, Philipsen, Thieden, & Wulf, 2010; Brazerol, McPhee, Mimouni, Specker, & Tsang, 1988; Holick, MacLaughlin, & Doppelt, 1981; Lo, Paris, & Holick, 1986; Rockell, Skeaff, Williams, & Green, 2008; Sallander, Wester, Bengtsson, & Wiegleb Edstrom, 2013; Young, 2010). Moreover, with the exception of northernmost latitudes, summertime sun exposures can suffice for VD3 requirements year round in all skin types (Bogh, Schmedes, Philipsen, Thieden, & Wulf, 2011). Hence, the central thesis that epidermal melanin substantially interferes with VD3 synthesis is debatable. Moreover, the retention of substantial pigmentation in recent Mesolithic humans (Olalde et al., 2014) did not result in vitamin D deficiency among hunter-gatherer and early agricultural populations living in regions with annual sunlight comparable to south-central Europe and Asia. Indeed, there is a paucity of fossil evidence of rickets in either Neanderthals (Mayr & Campbell, 1971) or among Eurasians prior to the Industrial Revolution (Cook, 2015; Holt, 2015; Robins, 1991). Accordingly, a critical (re)examination of the Loomis diagram demonstrates that moderate skin pigmentation (i.e., Fitzpatrick Skin Types III and IV) persisted over a broad range of Eurasian latitudes. Lighter skin types (Fitzpatrick I and II) become prevalent (Figure 4) only in those Europeans who migrated northward much more recently behind retreating glaciers (<11 kya) (Allentoft et al., 2015).

The recent revelation that epidermal pigmentation remained quite dark in central European Mesolithic humans (Beleza et al., 2013; Olalde et al., 2014; Wilde et al., 2014), led to a modification of the VD3 hypothesis, based upon the putative dietary inadequacies of cereal-based diets in later, agrarian societies (Khan & Khan, 2010). (The cereal diet modification of the vitamin D hypothesis asserts that early agriculturalists were at risk for a VD3 deficiency due to a paucity of this vitamin in cereal crops). According to this view, a shift in diet from the animal-based diet of hunter-gatherers (animal) to agricultural sources risked VD3 deficiency in these more Northern climes, in turn driving the relatively recent evolution of pigment dilution. It also has been

TABLE 4 Metabolic conservation: "Drivers" of natural selection

Latitudes	Pigment Type (c.f., Table 1)	Pigment-Based Mutations	Non-Pigment-Based Mutations	'Drivers' of ↓Pigmentation		Metabolic Benefits
Far Northern Europe	I	MC1R (loss-of-function)	↓Filaggrin ↓7-DHCR		Extreme cold	↑↑Calorigenesis (↑BMR) ↑↑VD3 synthesis Protein nutrient diversion
North-Central Europe	II	MC1R (reduced function)	↓7-DHCR			↑Calorigenesis ↑VD3 synthesis Protein nutrient diversion
South-Central Europe, Asia	III/IV	↓SLC24A5 ↓SLC45A2	--		Cold	↑Calorigenesis (seasonal) Protein nutrient diversion
Sub-Saharan Africa	V/VI		--	Dietary stress (+ childbirth/ lactation in females)	Hairlessness	--

7-DHCR = 7-dehydrocholesterol reductase; BMR = basal metabolic rate; MC1R = melanocortin 1 receptor.

suggested that modern humans made a "tragic mistake" in shifting from a hunter-gatherer to an agricultural diet for political reasons (Diamond, 1987).

But were these agriculturalists really at risk for VD3 deficiency? First, it should be noted that the advent of agriculture likely was not a matter of choice (or of climate change, as suggested by some European paleoanthropologists), but rather a result of the inexorable propensity of modern humans to extirpate megafauna from their immediate environments (Blois, Williams, Fitzpatrick, Jackson, & Ferrier, 2013; Kolbert, 2014). Moreover, as agriculturalists expanded from Mesopotamia into south-central Europe around 9 kya, they brought with them domesticated animals, which doubtless provided some dietary VD3 [e.g., egg yolks and calf livers store substantial vitamin D (Little & Blumler, 2015)]. More importantly, they still toiled predominantly outdoors, where they would have received substantial UV-B exposure during much of the year; hence, they were not at risk for VD3 deficiency, despite having retained dark skin pigmentation.

The complexity of human VD3 metabolism, which is still in an early stage of discovery, also resists any simplistic notion that the progressive lightening of human skin was driven solely by VD3 requirements. For example, several polymorphisms have been described both in VD3 transport proteins (Ahn et al., 2010; Hochberg & Templeton, 2010; Powe et al., 2013; Ramagopalan et al., 2010; Wang et al., 2010), and in distal pathways of VD3 metabolism that equalize the net bioavailability of 1,25-dihydroxyvitamin D3 in darkly- and lightly pigmented populations in Americans (Berg et al., 2015; Powe et al., 2013; Rockell et al., 2008; Wang et al., 2010). Hence, dark skin pigmentation provides little or no impediment to net systemic VD3 status (Holick, 2013; Holick et al., 1981; Webb & Holick, 1988). These studies clarify two heretofore puzzling, and apparently paradoxical observations: first, that despite lower circulating levels of the pro-hormone (25-OH-VD3), darkly pigmented individuals display lower overall rates of osteoporosis; and second, that darkly pigmented humans appear to be at increased, rather than decreased risk for vitamin D toxicity (Aloia, 2008). Therefore, it seems safe to conclude that the reported, increased incidence of VD3 deficiency among some contemporary, northern-dwelling, darkly pigmented populations, such as West Indians living in the United Kingdom, can be attributed to cultural (life-style) choices, rather than biological factors [e.g., (Bogh, 2012; van Schoor & Lips, 2011)]. Thus, assessments of vitamin D status in contemporary populations are confounded by differences not only in bioavailability, but also in cultural practices, such as sun-searching behavior and tanning salon visitations.

Extensive pigment dilution began relatively recently in north-central Europe (from Type III/IV to II), with further lightening (to Type I) in those Europeans who migrated to points even further to the North behind retreating glaciers (Allentoft et al., 2015) (Figure 4). With such further reductions in pigmentation, sufficient VD3 is produced at latitudes that correspond to northern France and Germany (comparable to New England) during summer months, sufficient to sustain VD3

TABLE 5 Cutaneous signs of metabolic conservation after episodic (E) versus sustained (S) protein deficiency

Features (E/S)	Affected structure	Characteristics	Basis	Comments
Telogen effluvium (E)	Hair	Sudden, wide-spread shedding of scalp hair	Appearance 4-6 weeks after severe illness	Occurrence reflects re-establishment of normal synchronized hair growth
Hypopigmented bands (E)	Hair	Transverse band of hypopigmented scalp hair (e.g., Figure 5)	Appears weeks after precipitous decline in serum proteins	Reappearance of pigmented hairs after treatment/ resolution of acute illness
Beau's lines (E)	Nail	Transverse, depressed grooves in nail plate	Often, but not always a sign of malnutrition	Reflects impaired cell division in nail matrix
Generalized hypopigmention in neonatal and children's skin (S)	Epidermis	Pale in comparison to adults	(?) Diversion of protein → rapid growth	Moderate; noticeable clinically
Generalized hypopigmention adult female skin (S)	Epidermis	Pale in comparison to males	(?) Diversion of protein → childbirth and/or lactation	Mild; subclinical
Generalized hypopigmentation (kwashiorkor) (E & S)	Epidermis & Hair	Pale skin; reddish hue in darkly pigmented persons	Severe protein malnutrition	Loss of pigment could reflect conservation of protein for more urgent priorities

requirements year-round (Chen et al., 2007; Holick, 2011; Webb & Holick, 1988). Hence, assuming that epidermal pigmentation interferes to some extent with cutaneous vitamin D synthesis, additional pigment dilution could have evolved in north-central Europeans to favor additional VD3 production.

Yet, the retention of intermediate pigmentation among most Eurasians residing at high latitudes implies that a further dilution of pigmentation was not an imperative for vitamin D homeostasis. Their intermediate pigmentation likely reflects a retention of substantial pigmentation for purposes of insulation (Moran, 1981). Moreover, it is widely accepted that the dark pigmentation of many coastal residents of the far North did not place them at risk for VD3 deficiency, because their marine seafood-containing diet was enriched in antirachitic fats. Yet, a comparable degree of dark pigmentation also persisted in northern Asian and Amerindians living away from the coast, where they would have had less direct access to marine sources of the vitamin. How they avoided VD3 deficiency is uncertain, but any one or more of the following strategies could have been operative: First, they could have traded with their resource-replete coastal neighbors for marine food, such as salt cod (Moran, 1981). In addition, as herders of tundra fauna, they doubtlessly also availed themselves of some VD3-containing foods, such as liver, eggs and red meat (Sweet, 2002). And, though they resided at some distance from the coast, they likely also availed themselves of oily fresh water species, such as eels, as well as salmon as they navigated far inland to spawn. Finally, we should leave open the strong possibility that analyses of the genomes of these sub-coastal residents will soon reveal polymorphisms that enhance the net bioavailability of $1,25(OH)_2$ VD3, analogous to those recently identified in African-Americans. In summary, vitamin D requirements could have provided the initial impetus behind the further reductions in pigmentation that occurred as southern Europeans began to migrate towards northern latitudes. Yet, even if pigmentation interferes to some extent with VD3 synthesis, its effects would have been modest, and overridden by an outdoor lifestyle at all but the most northern of European latitudes.

2.2 | Metabolic conservation as a potential "driver" of pigment lightening

We recently advanced an alternate hypothesis to explain both the initial, moderate pigment reductions that occurred in central and southern Europeans and Asians, and more draconian pigment dilution that occurred in northern Europeans (Figure 4); i.e., the universal, biological imperative for *metabolic conservation* [initially proposed in (Elias & Williams, 2013)] (Table 4). As we employ the term, "metabolic conservation" is not to be confused or equated with "relaxation," a well-accepted concept among evolutionary biologists that envisions a gradual, passive accumulation of mutations due to a decrease or loss of earlier biological requirements. In the context of this review, *metabolic conservation proposes instead that natural selection for reduced pigment production was an imperative that diverted precious resources towards more urgent priorities*. Accordingly, one such potent biological stressor would have been the marginal nutritional status of most northern migrants, favoring selection for reduced-function mutations in genes of the pigment pathway (Elias & Williams, 2013). Accordingly, an increasingly tenuous supply of protein among early modern Europeans, who had largely depleted their environment of megafauna by ≈20 kya (Little and Blumler, 2015), could have threatened late Paleolithic hunter-gatherers with protein deficiency (Formicola & Giannecchini, 1999; Milton, 2000). Indeed, several population studies have demonstrated relatively recent selection for such polymorphisms (Rees & Harding, 2012), most notably affecting alleles encoding the melanocortin 1 receptor (Harding et al., 2000; Makova & Norton, 2005), as well as SLC24A5 and SLC45A2 (Anno, Abe, & Yamamoto, 2008; Basu Mallick et al., 2013; Canfield et al., 2013; Norton et al., 2007; Rana et al., 1999). Together, these mutations account for the modest reductions in pigmentation that occurred not only in Europeans, but also in Asians (Parra, 2007), although the specific mutations differed in these geographically diverse populations.

Substantial metabolic savings accompanied reduced pigmentation (Table 5), because multiple, energy-dependent steps are required both

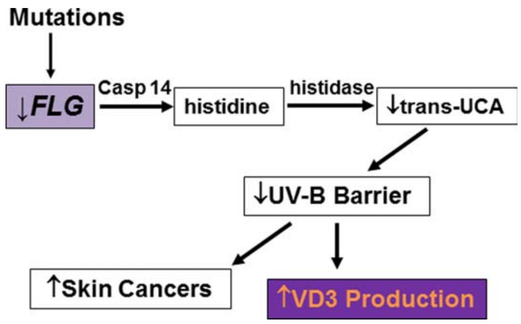

FIGURE 5 Downstream consequences of filaggrin deficiency: how inherited reductions in filaggrin favor intracutaneous vitamin D3 (VD3) production. *Trans*-uracanic acid (*trans*-UCA) is the most potent endogenous UV-B filter in lightly pigmented skin. Casp 14 = Caspase 14

to synthesize melanin and to transfer myriads of melanosomes from melanocytes into keratinocytes [rev. in (Lin & Fisher, 2007; Slominski et al., 2001, 2004)]. In addition to the substantial energetic and material costs of melanin production, these large protein polymers are continually shed during the desquamation of darkly pigmented stratum corneum, constituting a further substantial drain of protein resources. In contrast, the smaller melanin granules of lightly pigmented (Type I/II) skin are degraded long before cornification, allowing their constituent amino acids to be recycled by autophagy (Murase et al., 2013). Thus, lighter shades of skin pigmentation reflect a reduction not only in the extent of pigment synthesis, but also in the distribution and fate of melanin (Boissy, 2003). Finally, it should be noted that pigment reduction could provide a further advantage in that the metabolic precursors of eumelanin can be cytotoxic (Graham, Tiffany, & Vogel, 1978).

Reduced cutaneous pigment production in service to metabolic conservation is observed commonly in both developmental and clinical settings (Table 5). Dilution of epidermal and hair pigmentation is a well-recognized sign of chronic malnutrition in children (kwashiorkor) (Latham, 1991). This pathological hypopigmentation reflects a diminished pool of amino acid substrates for melanogenesis. However, whether it also reflects active shunting of amino acids towards more critical proteins required for the growing child is unknown. The phenotype of protein malnutrition and of the generalized edema due to hypoalbuminemia (albumin is the most abundant protein of plasma) in the growing child; i.e., kwashiorkor, is distinct from that of more general nutrient starvation; i.e., marasmus, which is characterized by emaciation, but not hypopigmentation. Thus, insecurity of dietary protein sources for the most vulnerable segment of the population, children and pregnant women could have exerted evolutionary pressure towards pigmentary dilution.

The link between protein deficiency and hypopigmentaion is not limited to the clinical setting of dietary protein insufficiency, as seen in children with kwashiorkor. Supporting Information Figure 1 illustrates a band of hypopigmented hair that appeared in a young child a few weeks after a severe episode of nephrotic syndrome that was accompanied by massive losses of urinary protein. Note that pigmentation of her hair reappeared after corticosteroid therapy succeeded in normalizing renal function, thereby allowing a resumption of robust pigment production.

Hypopigmentation in service of metabolic conservation is also not limited to pathological situations (Table 5). It is widely recognized that infants normally have significantly lighter pigmentation at birth than they exhibit subsequently as older children and adults (Maibach, 1982; Solomon & Esterly, 1970). The phenomenon of neonatal hypopigmentation is entirely compatible with a superseding imperative to divert precious protein resources in support of the extraordinarily rapid rates of growth that occur during late gestation and the first year of life. Neonatal protein conservation through hypopigmentation should also be seen within the context of the capacity of the growing fetus and infant to acquire the nutrition that it requires, both prenatally [where growth is limited by the maternal metabolic rate (Dunsworth, Warrener, Deacon, Ellison, & Pontzer, 2012)] and in the immediate post period (where it is constrained by the infant's capacity to ingest milk). In the absence of other pathological signs of protein deficiency, such as hypoalbuminemia, it seems likely that the hypopigmentation of neonates reflects a down-regulation of melanin production, with active shunting of precious resources towards other priorities.

It also seems likely that the more subtle, but nonetheless well-documented differences in pigmentation between genders (rev. in Aoki, 2002) represents an adaptation that counterbalances the high protein drain of child-bearing and lactation in females. In support of this notion, pigmentation becomes comparable in children after the neonatal period, but then lightens preferentially as females reach late adolescence (Aoki, 2002; Frost, 2007). Thus, both the lighter pigmentation of adult females, along with their lesser muscle mass and body size, may have a common basis; i.e., diversion of precious resources towards lactation as they reached a reproductive age.

As modern hairless humans moved further northward, by necessity they adopted various forms of clothing for warmth. Yet, as they moved further northwards, cold tolerance must have been challenging during much of the year. Accordingly, several recent studies have demonstrated that contemporary inhabitants of northern latitudes exhibit substantially higher basal metabolic rates (BMRs), particularly during winter months (Froehle, 2008; Leonard et al., 2002; Leonard, Snodgrass, & Sorensen, 2005; Moran, 1981). Thus, the increased metabolic demands of life in colder climes could have provided an impetus that favored metabolic conservation through selection for pigment-diluting polymorphisms. The elevated BMRs in northerners in turn selected for recessive mutations in mitochondrial DNA that uncouple oxidative phosphorylation (Mishmar et al., 2003; Ruiz-Pesini, Mishmar, Brandon, Procaccio, & Wallace, 2004), facilitating increased calorigenesis. However, whether other examples of changes in modern humans, such as the recent, gradual reduction in human tooth size (Brace, Rosenberg, & Hunt, 1987), simply reflect "relaxation" or represent another example of metabolic conservation, perhaps in service to the same nutritional or energy requirements, is not yet known.

At the same time that nutritional insecurities and a cold climate could have favored selection for protein and calorie-sparing mutations, a reduced requirement for an optimally competent permeability barrier also came into play. Not only would these cooler and more humid climates have relaxed the barrier requirements of these northern migrants, but the adoption of clothing would also have created a moist microenvironment just above their skin surface that would have further reduced the need for a highly competent barrier. Hence, reduced production of a less urgently needed, metabolically expensive, and potentially toxic protein; i.e., melanin, would have been biologically appropriate. Finally, it should be noted that a similar hypothesis of energy conversation has been proposed recently to account for the relative immaturity (i.e., altriciality) of human newborns (Dunsworth et al., 2012). Thus, the dilution of human pigmentation does not differ from other examples of metabolic conservation that occurred during evolution—as structures became either functionally obsolete or less necessary, their reduced production by natural selection allowed diversion of precious resources towards more urgent requirements.

2.2.1 | Why further pigment dilution in Europeans of the far north?

For the reasons cited above, we are convinced that vitamin D insufficiency did not drive the intermediate pigmentation that evolved among southern Europeans and Asians. However, the extreme pigment lightening (Types I and II skin phenotypes) that evolved among more northern Europeans could have been driven in part by the need to allow additional UV-B to enter the epidermis for purposes of further VD3 production. In these more extreme, northern climes the quantity of UV-B penetrating the atmosphere is limited to an extent that, in the absence of sufficient dietary sources, hypovitaminosis D could become a potential threat, even in the face of an outdoor lifestyle with ample summertime sun exposure. Likewise, the lighter pigmentation that characterizes females vs. males in northern Europe has been proposed to have facilitated increased VD3 requirements n females (Jablonski & Chaplin, 2000). But it seems more likely that preferential pigment lightening in these females could reflect a selective need for metabolic conservation in females versus males. Nonetheless, it also seems likely that there would have been a selective advantage to dilute pigmentation (from Type III/IV to Type II) to enhance cutaneous VD3 production as modern humans advanced northward from south-central to north-central Europe (present day northern France and Germany) (Figure 4). Assuming a paucity of other sources of VD3 in the predominantly cereal-based diets among these early agriculturalists, a further loss of pigment would have allowed additional cutaneous VD3 generation during summer months. Nonetheless, it has been repeatedly noted that rickets, the most extreme musculoskeletal manifestation of vitamin D deficiency, was essentially unknown until the modern Industrial Revolution (Robins, 2009). In summary, it seems safe to assume that at these latitudes, both metabolic conservation and VD3 requirements could have provided the evolutionary impetus behind the pigment dilution that led to both Type II and the pheomelanin-dominant phenotype of Type I skin (c.f., Table 1).

2.3 | Recent, nonpigment-based mutations that likely sustain cutaneous VD3 status in Northern Europeans

Among those extremely fair-skinned Europeans who settled still further to the North (i.e., present-day United Kingdom, Scandinavia, and northern Baltic states), even a type I pigment phenotype could not sufficiently augment cutaneous VD3 production, because little UV-B penetrates the atmosphere at these high latitudes, even during summer months [rev. in (Holick et al., 1981)]. Moreover, many migrants to the northern Europe, particularly those who resided away from the coast, preferentially consumed a non-seafood-based diet of tundra fauna, such as reindeer, rather than a VD3-enriched diet of marine seafood (Moran, 1981; Shnirelman, 1999). Because pigment dilution and dietary supplementation probably did not suffice to generate sufficient VD3 in these locales, there would have been a compelling need for additional, non-pigment-based evolutionary adaptations that favored enhanced cutaneous vitamin D3 production. One pertinent example is the recent appearance in northerners of loss-of-function mutations in the gene that encodes 7-dehydrocholesterol reductase (7-DHCR) among northern Europeans (Ahn et al., 2010; Witsch-Baumgartner et al., 2008). Because this enzyme converts 7-dehydrocholesterol, the immediate precursor of pre-vitamin D3, into cholesterol, reduced function polymorphisms in 7-DHCR would inevitably increase the intra-epidermal pool of 7-dehydrocholesterol that is available for photoconversion to pre-vitamin D3 (Kuan, Martineau, Griffiths, Hypponen, & Walton, 2013; Witsch-Baumgartner et al., 2008).

Alternatively or additionally, we proposed that *Filaggrin* mutations could have evolved recently (and likely are continuing to evolve) in Europeans of the far North to support additional cutaneous VD3 production (Elias & Williams, 2013; Thyssen, Bikle, & Elias, 2014). Moreover, even in Japanese, the prevalence of *Filaggrin* mutations is significantly higher in the northernmost island, Hokkaido, than in more southern islands of the Japanese archipelago [cited in (Thyssen, Zirwas, & Elias, 2015)]. To briefly review the underlying biologic concept: melanin is not the only UV-B chromophore in skin. Indeed, well over 50% of incident UV-B is filtered out in the stratum corneum, independent of pigmentation (Thomson, 1955), where *trans*-urocanic acid is the major interceptor of incident UV-B irradiation in fair-skinned humans (Brookman, Chacon, & Sinclair, 2002; Kripke, 1984). *Trans*-urocanic acid is derived from the sequential, humidity-dependent proteolysis of the epidermal protein, filaggrin, into one of its constituent amino acids, histidine, followed by the further deimination of histidine into *trans*-urocanic acid within the stratum corneum (Figure 5) (Scott, 1981; Scott, Harding, & Barrett, 1982). Hence, mutations that lead to reductions in filaggrin production would inevitably reduce the *trans*-urocanic acid content of the stratum corneum, allowing additional UV-B to penetrate (Thyssen et al., 2014). Indeed, such *Filaggrin* mutations predominate precisely in those pale-skinned humans of Europe's far North (Irvine, McLean, & Leung, 2011), who would have benefitted directly from additional assistance with cutaneous VD3 production (Elias & Williams, 2013; Thyssen et al., 2014). In contrast, the prevalence of *Filaggrin* mutations is low among genotyped central/southern Europeans, Asians and Africans (Sinclair et al., 2009; Thawer-Esmail et al., 2014; Thyssen et al., 2014; Winge et al., 2011). This strategy appears to have been effective, because the prevalence of *Filaggrin* mutations correlates significantly with circulating 25-hydroxyvitamin D3 levels (25-OH-D3) (Thyssen et al., 2014). Higher blood levels of the pro-hormone 25-OH-D3 are found in northern Europeans than in either southern Europeans or Africans (van Schoor & Lips, 2011); and most pertinently, specifically in those northern Europeans who harbor *Filaggrin* mutations (Thyssen et al., 2015). Taken together, it seems likely that other, non-pigment-based strategies have evolved recently that allowed humans to inhabit extreme northern latitudes successfully without succumbing to widespread VD3 deficiency.

3 | SUMMARY

Most current hypotheses that attempt to explain the development of deep epidermal pigmentation in hominins are problematic. Nonmelanoma skin cancers occur well past peak reproductive years and minimal UV-B penetrates to deeper skin layers, where folic acid circulates. Generating an optimal permeability barrier became an urgent requirement for newly hairless hominins that lost additional water as they became hairless and employed sweat to thermoregulate in open savannas. By shifting the dose–response curve for UV-B from the toxic to the beneficial, epidermal pigmentation provided hominins with a superior permeability barrier, with additional benefits of enhanced antimicrobial defense and a more cohesive (less injury-prone) stratum corneum. Though widely espoused, the view that latitude-dependent pigment dilution evolved to facilitate cutaneous vitamin D3 (VD3) synthesis is also problematic for several reasons, including the fact that UV-B-irradiated, darkly and lightly pigmented skins generate comparable circulating VD3 levels due in part to mutations that increase VD3 bioavailability. Moreover, extracutaneous dietary sources of VD3 supplemented year-round VD3 requirements; in the late Paleolithic, even in early agriculturalists. Finally, rickets has not been found in pre-Industrial Age human fossils. Initial pigment dilution instead likely served the purpose of metabolic conservation—the imperative to redirect scarce protein towards more urgent requirements; e.g., to support nutritionally marginal diets, and/or to enhance calorigenesis in the cold climates of the North. Though vitamin D requirements could have "driven" the further pigment lightening of populations inhabiting north-central European latitudes, inhabitants of the far North evolved additional, nonpigmented related mutations, including loss-of-function *Filaggrin* mutations leading to reduced *trans*-urocanic acid, the major UV-B absorber in stratum corneum, which allowed more efficient cutaneous VD3 production.

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