Exploring Skin Pigmentation Adaptation: A Systematic Review on the Vitamin D Adaptation Hypothesis

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PRACTICE **POINTS**

- Sufficient UV radiation exposure is required to synthesize vitamin D, but excess exposure increases skin cancer risk.
- Genes associated with vitamin D production and melanin synthesis form an interconnected network that explains skin tone polymorphisms and their influence on healthy sun behaviors.
- Adaptations in genetics of skin pigmentation and vitamin D metabolism due to anthropologic patterns of migration to northern latitudes may help explain predisposition to dermatologic diseases such as skin cancer.

Understanding the genetic adaptations that occurred as humans migrated out of Africa to higher latitudes helps explain on a population-wide level how UV radiation (UVR) exposure will have varying consequences and benefits in patients of different skin pigmentations. It has been hypothesized that the need for efficient vitamin D synthesis was the primary driver for the skin-lightening process that evolutionarily occurred as humans migrated to higher latitudes. This review analyzes the level of support for the hypothesis that skin lightening occurred to enable adequate vitamin D synthesis in populations that migrated to areas with less UVR. Our literature search supported the hypothesis that through natural selection and intricate genetic adaptations, humans who migrated to areas with lower levels of UVR underwent a skin-lightening process to avoid the consequences of vitamin D deficiency. Our review includes an analysis of migration patterns out of Africa and how these affected pigmentation genes that are found in certain ethnic populations can be used to better understand this critical adaptation process when counseling patients on the need for sun protection.

The risk for developing skin cancer can be somewhat attributed to variations in skin pigmentation. Historically, lighter skin pigmentation has been observed in populations living in higher latitudes and darker pigmentation in populations near the equator. Although skin pigmentation is a conglomeration of genetic and environmental factors, anthropologic studies have demonstrated an association of human skin lightening with historic human migratory patterns.[1] It is postulated that migration to latitudes with less UVB light penetration has resulted in a compensatory natural selection of lighter skin types. Furthermore, the driving force behind this migration-associated skin lightening has remained unclear.[1]

The need for folate metabolism, vitamin D synthesis, and barrier protection, as well as cultural practices, has been postulated as driving factors for skin pigmentation variation. Synthesis of vitamin D is a UV radiation (UVR)–dependent process and has remained a prominent theoretical driver for the basis of evolutionary skin lightening. Vitamin D can be acquired both exogenously or endogenously via dietary supplementation or sunlight; however, historically it has been obtained

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through UVB exposure primarily. Once UVB is absorbed by the skin, it catalyzes conversion of 7-dehydrocholesterol to previtamin D_3, which is converted to vitamin D in the kidneys.[2,3] It is suggested that lighter skin tones have an advantage over darker skin tones in synthesizing vitamin D at higher latitudes where there is less UVB, thus leading to the adaptation process.[1] In this systematic review, we analyzed the evolutionary vitamin D adaptation hypothesis and assessed the validity of evidence supporting this theory in the literature.

Methods

A search of PubMed, Embase, and the Cochrane Reviews database was conducted using the terms *evolution*, *vitamin D*, and *skin* to generate articles published from 2010 to 2022 that evaluated the influence of UVR-dependent production of vitamin D on skin pigmentation through historical migration patterns (Figure). Studies were excluded during an initial screening of abstracts followed by full-text assessment if they only had abstracts and if articles were inaccessible for review or in the form of case reports and commentaries.

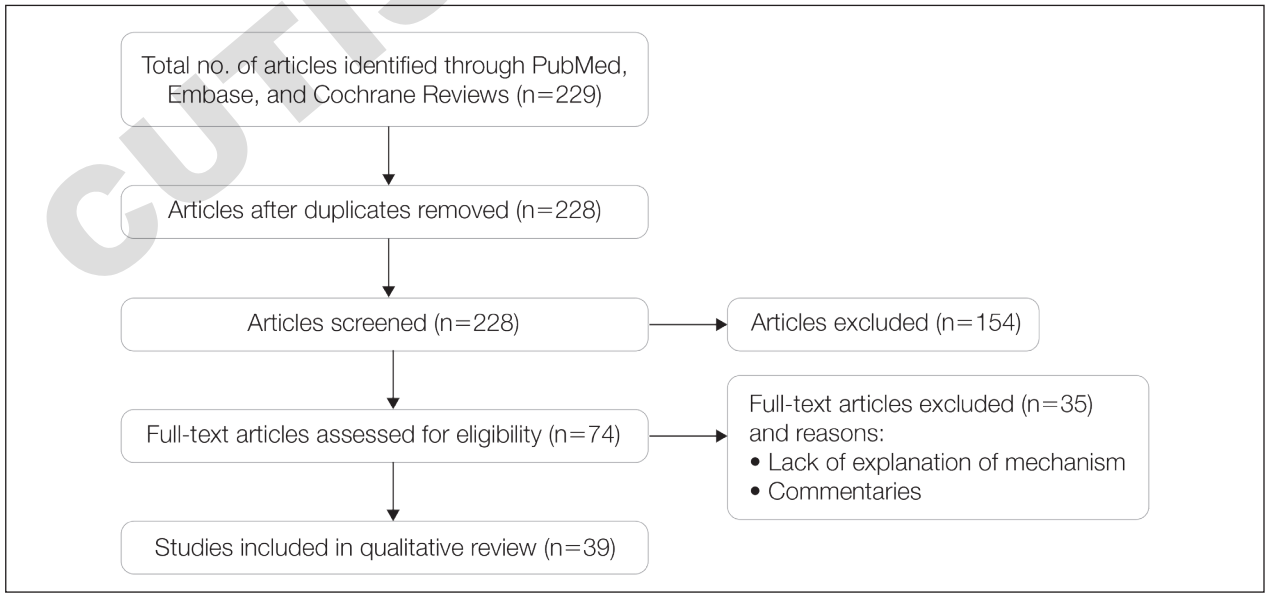
The following data were extracted from each included study: reference citation, affiliated institutions of authors, author specialties, journal name, year of publication, study period, type of article, type of study, mechanism of adaptation, data concluding or supporting vitamin D as the driver, and data concluding or suggesting against vitamin D as the driver. Data concluding or supporting vitamin D as the driver were recorded from statistically significant results, study conclusions, and direct quotations. Data concluding or suggesting against vitamin D as the driver also were recorded from significant results, study conclusions, and direct quotes. The mechanism of adaptation was based on vitamin D synthesis modulation, melanin upregulation, genetic selections, genetic drift, mating patterns, increased vitamin D sensitivity, interbreeding, and diet.

Studies included in the analysis were placed into 1 of 3 categories: supporting, neutral, and against. Strength of Recommendation Taxonomy (SORT) criteria were used to classify the level of evidence of each article.[4] Each article's level of evidence was then graded (Table 1). The SORT grading levels were based on quality and evidence type: level 1 signified good-quality, patient-oriented evidence; level 2 signified limited-quality, patient-oriented evidence; and level 3 signified other evidence.[4]

Results

Article Selection—A total of 229 articles were identified for screening, and 39 studies met inclusion criteria.[1-3,5-40] Systematic and retrospective reviews were the most common types of studies. Genomic analysis/sequencing/genome-wide association studies (GWAS) were the most common methods of analysis. Of these 39 articles, 26 were classified as supporting the evolutionary vitamin D adaptation hypothesis, 10 were classified as neutral, and 3 were classified as against (Table 1).

Of the articles classified as supporting the vitamin D hypothesis, 13 articles were level 1 evidence, 9 were level 2, and 4 were level 3. Key findings supporting the vitamin D hypothesis included genetic natural selection favoring vitamin D synthesis genes at higher latitudes with lower UVR and the skin lightening that occurred to protect against vitamin D deficiency (Table 1). Specific genes supporting these findings included 7-dehydrocholesterol



A search of PubMed, Embase, and the Cochrane Reviews database was conducted to generate research articles published from 2010 to 2022 evaluating the influence of UV radiation–dependent production of vitamin D on skin pigmentation through historical migration patterns.

reductase (*DHCR7*), vitamin D receptor (*VDR*), tyrosinase (*TYR*), tyrosinase-related protein 1 (*TYRP1*), oculocutaneous albinism type 2 melanosomal transmembrane protein (*OCA2*), solute carrier family 45 member 2 (*SLC45A2*), solute carrier family 4 member 5 (*SLC24A5*), Kit ligand (*KITLG*), melanocortin 1 receptor (*MC1R*), and *HECT* and *RLD* domain containing E3 ubiquitin protein ligase 2 (*HERC2*)(Table 2).

Of the articles classified as being against the vitamin D hypothesis, 1 article was level 1 evidence, 1 was level 2, and 1 was level 3. Key findings refuting the vitamin D hypothesis included similar amounts of vitamin D synthesis in contemporary dark- and light-pigmented individuals, vitamin D–rich diets in the late Paleolithic period and in early agriculturalists, and metabolic conservation being the primary driver (Table 1).

Of the articles classified as neutral to the hypothesis, 7 articles were level 1 evidence and 3 were level 2. Key findings of these articles included genetic selection favoring vitamin D synthesis only for populations at extremely northern latitudes, skin lightening that was sustained in northern latitudes from the neighboring human ancestor the chimpanzee, and evidence for long-term evolutionary pressures and short-term plastic adaptations in vitamin D genes (Table 1).

Comment

The importance of appropriate vitamin D levels is hypothesized as a potent driver in skin lightening because the vitamin is essential for many biochemical processes within the human body. Proper calcification of bones requires activated vitamin D to prevent rickets in childhood. Pelvic deformation in women with rickets can obstruct childbirth in primitive medical environments.[15] This direct reproductive impairment suggests a strong selective pressure for skin lightening in populations that migrated northward to enhance vitamin D synthesis.

Of the 39 articles that we reviewed, the majority (n=26 [66.7%]) supported the hypothesis that vitamin D synthesis was the main driver behind skin lightening, whereas 3 (7.7%) did not support the hypothesis and 10 (25.6%) were neutral. Other leading theories explaining skin lightening included the idea that enhanced melanogenesis protected against folate degradation; genetic selection for light-skin alleles due to genetic drift; skin lightening being the result of sexual selection; and a combination of factors, including dietary choices, clothing preferences, and skin permeability barriers.

Articles With Supporting Evidence for the Vitamin D Theory—As *Homo sapiens* migrated out of Africa, migration patterns demonstrated the correlation between distance from the equator and skin pigmentation from natural selection. Individuals with darker skin pigment required higher levels of UVR to synthesize vitamin D. According to Beleza et al,[1] as humans migrated to areas of higher latitudes with lower levels of UVR, natural selection favored the development of lighter skin to maximize vitamin D production. Vitamin D is linked to calcium metabolism, and its deficiency can lead to bone malformations and poor immune function.[35] Several genes affecting melanogenesis and skin pigment have been found to have geospatial patterns that map to different geographic locations of various populations, indicating how human migration patterns out of Africa created this natural selection for skin lightening. The gene *KITLG*—associated with lighter skin pigmentation—has been found in high frequencies in both European and East Asian populations and is proposed to have increased in frequency after the migration out of Africa. However, the genes *TYRP1*, *SLC24A5*, and *SLC45A2* were found at high frequencies only in European populations, and this selection occurred 11,000 to 19,000 years ago during the Last Glacial Maximum (15,000–20,000 years ago), demonstrating the selection for European over East Asian characteristics. During this period, seasonal changes increased the risk for vitamin D deficiency and provided an urgency for selection to a lighter skin pigment.[1]

The migration of *H sapiens* to northern latitudes prompted the selection of alleles that would increase vitamin D synthesis to counteract the reduced UV exposure. Genetic analysis studies have found key associations between genes encoding for the metabolism of vitamin D and pigmentation. Among this complex network are the essential downstream enzymes in the melanocortin receptor 1 pathway, including *TYR* and *TYRP1*. Forty-six of 960 single-nucleotide polymorphisms located in 29 different genes involved in skin pigmentation that were analyzed in a cohort of 2970 individuals were significantly associated with serum vitamin D levels ($P<.05$). The exocyst complex component 2 (*EXOC2*), *TYR*, and *TYRP1* gene variants were shown to have the greatest influence on vitamin D status.[9] These data reveal how pigment genotypes are predictive of vitamin D levels and the epistatic potential among many genes in this complex network.

Gene variation plays an important role in vitamin D status when comparing genetic polymorphisms in populations in northern latitudes to African populations. Vitamin D_3 precursor availability is decreased by *7-DHCR* catalyzing the precursors substrate to cholesterol. In a study using GWAS, it was found that"variations in *DHCR7* may aid vitamin D production by conserving cutaneous *7-DHC* levels. A high prevalence of *DHCR7* variants were found in European and Northeast Asian populations but not in African populations, suggesting that selection occurred for these *DHCR7* mutations in populations who migrated to more northern latitudes.[5] Multilocus networks have been established between the *VDR* promotor and skin color genes (Table 2) that exhibit a strong in-Africa vs out-of-Africa frequency pattern. It also has been shown that genetic variation (suggesting a long-term evolutionary inclination) and epigenetic modification (indicative of short-term exposure) of *VDR* lends support to the vitamin D hypothesis. As latitude decreases, prevalence of VDR FokI (F allele), BsmI

TABLE 1. Articles on Vitamin D As the Primary Driver for Skin Lightening in Humans

Stance	No. of articles	Level of evidence (no. of articles)	Summary of key findings (level of evidence[a])
Supporting	26	Level 1 (13)[1,5-16]; level 2 (9)[2,17-24]; level 3 (4)[25-28]	As humans moved away from the equator, decreases in levels of skin pigmentation occurred to accommodate for decreasing levels of UVR, resulting from upregulation of genes for vitamin D biosynthesis[5,17] (level 1 and 2)
			Human skin color is adapted and optimized for a regional sun UV intensity[25] (level 3)
			DHCR7 plays a role in conserving cutaneous 7-DHC concentrations for improved vitamin D production, and high prevalence of 7-DHC variants were found in European and Northeast Asian populations but not in African populations[5] (level 1)
			Multilocus networks have been established between the VDR promotor and skin color genes (*TYR*, *TYRP1*, *OCA2*, *SLC45A2*, *SLC24A5*, *KITLG*, and *MC1R*) that exhibit a strong in-Africa vs out-of-Africa frequency pattern[1] (level 1)
			As latitude decreases, prevalence of VDR FokI (F allele), BsmI (B allele), ApaI (A allele), and TaqI (T allele) also decreases in a linear manner, linking latitude to VDR polymorphisms[6] (level 1)
			HERC2 (AA) genotype has a high rate of vitamin D loss occurring in those with the darkest pigmentation, as *HERC2* (GG) genotypes had increased vitamin D_3 photosynthesis in individuals with the lightest pigmentation[6] (level 1)
Neutral	10	Level 1 (7)[3,29-34]; level 2 (3)[35-37]	At extremely high northern latitudes with low levels of UVR, the genetic selection for genes favoring vitamin D metabolism plays a more important role, but even at the highest latitudes, stored vitamin D was sufficient to meet physiologic needs during the months when UVR was lowest[29] (level 1)
			It has been assumed that skin pigment lightened as humans migrated to higher latitudes with lower sunlight; however, this has been challenged by the idea that the human's most closely related ancestor, the chimpanzee, had pale skin beneath its hair. The loss of hair led to exposed pale skin, and genetic selections for melanogenesis played a more important role for protection. Pale skin was the ancestral state sustained as humans migrated to higher latitudes[35] (level 2)
			VDR-TaqI and VDR-BsmI genotype occurrence through postconceptional wk 7 to wk 8 and VDR-EcoRV in wk 6 were related to solar radiation; because this is a critical period when late embryo skeletal ossification begins, VDR genotypes may exhibit both long-term evolutionary pressures and shorter-term plastic adaptations[36] (level 2)
Against	3	Level 1 (1)[38]; level 2 (1)[39]; level 3 (1)[40]	Dark- and light-pigmented individuals generate similar amounts of vitamin D[39] (level 2)
			Vitamin D–rich diets in the late Paleolithic period and in early agriculturalists supplemented year-round vitamin D requirements[39] (level 2)
			Cold climates increase BMRs, which favor metabolic conservation through selection for pigment-diluting polymorphisms[39] (level 2)
			Even small amounts of UVB exposure to a small surface area of the skin during the summer months can generate substantial stores of vitamin D, even in darkly pigmented populations[38] (level 1)
			Darkly pigmented individuals have a lower incidence of osteoporosis compared to lightly pigmented individuals, regardless of latitude[38] (level 1)

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TABLE. (continued)

Stance	No. of articles	Level of evidence (no. of articles)	Summary of key findings (level of evidence[a])
Against (continued)			Fossil records show prevalence of rickets after the Industrial Revolution only[38] (level 1)
			The vitamin D hypothesis does not explain why skin pigment lightened in body sites that were unexposed to light or why hair became lightly pigmented, as hair does not play a role in vitamin D synthesis[38] (level 1)

Abbreviations: BMR, basal metabolic rate; *CYP2R1*, vitamin D 25-hydroxylase; *7-DHC*, 7-dehydrocholesterol; *DHCR7*, 7-dehydrocholesterol reductase; *EXOC2*, exocyst complex component 2; *HERC2*, HECT and RLD domain containing E3 ubiquitin protein ligase 2; *IRF4*, interferon regulatory factor 4; *KITLG*, KIT tyrosine kinase receptor ligand; *MC1R*, melanocortin 1 receptor; *OCA2*, oculocutaneous albinism type 2 melanosomal transmembrane protein; *SLC45A2*, solute carrier family 45 member 2; *TYR*, tyrosinase; *TYRP1*, tyrosinase-related protein 1; UVR, UV radiation; VDR, vitamin D receptor.

[a]Grading levels were based on quality and evidence type: level 1: good-quality, patient-oriented evidence; level 2: limited-quality, patient-oriented evidence; level 3: other evidence.[4]

(B allele), ApaI (A allele), and TaqI (T allele) also decreases in a linear manner, linking latitude to *VDR* polymorphisms. Plasma vitamin D levels and photoperiod of conception—UV exposure during the periconceptional period—also were extrapolative of *VDR* methylation in a study involving 80 participants, where these 2 factors accounted for 17% of variance in methylation.[6]

Other noteworthy genes included *HERC2*, which has implications in the expression of *OCA2* (melanocyte-specific transporter protein), and *IRF4*, which encodes for an important enzyme in folate-dependent melanin production. In an Australian cross-sectional study that analyzed vitamin D and pigmentation gene polymorphisms in conjunction with plasma vitamin D levels, the most notable rate of vitamin D loss occurred in individuals with the darkest pigmentation *HERC2* (AA) genotype.[31] In contrast, the lightest pigmentation *HERC2* (GG) genotypes had increased vitamin D_3 photosynthesis. Interestingly, the lightest interferon regulatory factor 4 *(IRF4)* TT genotype and the darkest *HERC2* AA genotype, rendering the greatest folate loss and largest synthesis of vitamin D_3, were not seen in combination in any of the participants.[30] In addition to *HERC2*, derived alleles from pigment-associated genes *SLC24A5*A* and *SLC45A2*G* demonstrated greater frequencies in Europeans (>90%) compared to Africans and East Asians, where the allelic frequencies were either rare or absent.[1] This evidence delineates not only the complexity but also the strong relationship between skin pigmentation, latitude, and vitamin D status. The GWAS also have supported this concept. In comparing European populations to African populations, there was a 4-fold increase in the frequencies of "derived alleles of the vitamin D transport protein (*GC*, rs3755967), the 25(OH)D_3 synthesizing enzyme (*CYP2R1*, rs10741657), VDR (rs2228570 (commonly known as *FokI* polymorphism), rs1544410 (*Bsm1*), and rs731236 (*Taq1*) and the VDR target genes *CYP24A1* (rs17216707), *CD14* (rs2569190), and *CARD9* (rs4077515)."[32]

Articles With Evidence Against the Vitamin D Theory—This review analyzed the level of support for the theory that vitamin D was the main driver for skin lightening. Although most articles supported this theory, there were articles that listed other plausible counterarguments. Jablonski and Chaplin[3] suggested that humans living in higher latitudes compensated for increased demand of vitamin D by placing cultural importance on a diet of vitamin D–rich foods and thus would not have experienced decreased vitamin D levels, which we hypothesize were the driver for skin lightening. Elias et al[39] argued that initial pigment dilution may have instead served to improve metabolic conservation, as the authors found no evidence of rickets—the sequelae of vitamin D deficiency—in pre–industrial age human fossils. Elias and Williams[38] proposed that differences in skin pigment are due to a more intact skin permeability barrier as "a requirement for life in a desiccating terrestrial environment," which is seen in darker skin tones compared to lighter skin tones and thus can survive better in warmer climates with less risk of infections or dehydration.

Articles With Neutral Evidence for the Vitamin D Theory—Greaves[41] argued against the idea that skin evolved to become lighter to protect against vitamin D deficiency. They proposed that the chimpanzee, which is the human's most closely related species, had light skin covered by hair, and the loss of this hair led to exposed pale skin that created a need for increased melanin production for protection from UVR. Greaves[41] stated that the *MC1R* gene (associated with darker pigmentation) was selected for in African populations, and those with pale skin retained their original pigment as they migrated to higher latitudes. Further research has demonstrated that the genetic natural selection for skin pigment is a complex process that involves multiple gene variants found throughout cultures across the globe.

TABLE 2. Summary of Vitamin D Contributory Genes

Enzyme/ligand	Enzyme/ligand function
DHCR7	Decreases vitamin D_3 precursor availability by catalyzing the precursors substrate to cholesterol[33]
VDR	Nuclear hormone receptor for 1,25(OH)2D3 ligand that functions as a transcription factor; activation leads to increased plasma calcium levels and inhibition of parathyroid hormone synthesis[7]
TYR	Responsible for the first step of melanin synthesis; converts tyrosine to dopaquinone[2]
TYRP1	Stabilizes TYR protein and modifies its activity, indirectly promoting melanin synthesis[2]
OCA2	Integral membrane protein that transports tyrosine (melanin precursor)[7]
SLC45A2	Participates in molecular transport in melanocytes[1]
KITLG	Ligand for *KIT* receptor; activation leads to RAS activation, promoting melanogenesis, proliferation, and migration[38]
MC1R	Cell membrane enzyme activated by melanocyte-stimulating hormone that causes downstream signaling, which leads to eumelanin production[2]
HERC2	Large ubiquitin protein ligase enzyme that participates in melanin synthesis and increases expression of P protein[30]
CYP2R1	Converts vitamin D to its active form calcitriol[14]
EXOC2	Part of the exocyst complex responsible for docking of exocytic vesicles[9]
IRF4	Unknown mechanism; has shown implications in folate-dependent melanin production[30]

Abbreviations: *CYP2R1*, vitamin D 25-hydroxylase; *DHCR7*, 7-dehydrocholesterol reductase; *EXOC2*, exocyst complex component 2; *HERC2*, HECT and RLD domain containing E3 ubiquitin protein ligase 2; *IRF4*, interferon regulatory factor 4; *KITLG*, *KIT* tyrosine kinase receptor ligand; *MC1R*, melanocortin 1 receptor; *OCA2*, oculocutaneous albinism type 2 melanosomal transmembrane protein; *SLC45A2*, solute carrier family 45 member 2; *TYR*, tyrosinase; *TYRP1*, tyrosinase-related protein 1; *VDR*, vitamin D receptor.

Conclusion

Skin pigmentation has continuously evolved alongside humans. Genetic selection for lighter skin coincides with a favorable selection for genes involved in vitamin D synthesis as humans migrated to northern latitudes, which enabled humans to produce adequate levels of exogenous vitamin D in low-UVR areas and in turn promoted survival. Early humans without access to supplementation or foods rich in vitamin D acquired vitamin D primarily through sunlight. In comparison to modern society, where vitamin D supplementation is accessible and human lifespans are prolonged, lighter skin tone is now a risk factor for malignant cancers of the skin rather than being a protective adaptation. Current sun behavior recommendations conclude that the body's need for vitamin D is satisfied by UV exposure to the arms, legs, hands, and/or face for only 5 to 30 minutes between 10 AM and 4 PM daily without sunscreen.[42-44] Approximately 600 IU of vitamin D supplementation daily is recommended in a typical adult younger than 70 years to avoid deficiency. In adults 70 years and older who are not receiving adequate sunlight exposure, 800 IU of daily vitamin D supplementation is recommended.[45]

The hypothesis that skin lightening primarily was driven by the need for vitamin D can only be partially supported by our review. Studies have shown that there is a corresponding complex network of genes that determines skin pigmentation as well as vitamin D synthesis and conservation. However, there is sufficient evidence that skin lightening is multifactorial in nature, and vitamin D alone may not be the sole driver. The information in this review can be used by health care providers to educate patients on sun protection, given the lesser threat of severe vitamin D deficiency in developed communities today that have access to adequate nutrition and supplementation.

Skin lightening and its coinciding evolutionary drivers are a rather neglected area of research. Due to heterogeneous cohorts and conservative data analysis, GWAS studies run the risk of type II error, yielding a limitation in our data analysis.[9] Furthermore, the data regarding specific time frames in evolutionary skin lightening as well as the intensity of gene polymorphisms are limited.[1] Further studies are needed to determine the interconnectedness of the current skin-lightening theories to identify other important factors that may play a role in the process. Determining the key event can help us better understand skin-adaptation mechanisms and create a framework for understanding the vital process involved in adaptation, survival, and disease manifestation in different patient populations.

REFERENCES

1. Beleza S, Santos AM, McEvoy B, et al. The timing of pigmentation lightening in Europeans. *Mol Biol Evol*. 2013;30:24-35. doi:10.1093/molbev/mss207
2. Carlberg C. Nutrigenomics of vitamin D. Nutrients. 2019;11:676. doi:10.3390/nu11030676
3. Jablonski NG, Chaplin G. The roles of vitamin D and cutaneous vitamin D production in human evolution and health. *Int J Paleopathol.* 2018;23:54-59. doi:10.1016/j.ijpp.2018.01.005
4. Weiss BD. SORT: strength of recommendation taxonomy. *Fam Med.* 2004;36:141-143.
5. Wolf ST, Kenney WL. The vitamin D–folate hypothesis in human vascular health. *Am J Physiol Regul Integr Comp Physiology.* 2019;317:R491-R501. doi:10.1152/ajpregu.00136.2019
6. Lucock M, Jones P, Martin C, et al. Photobiology of vitamins. *Nutr Rev*. 2018;76:512-525. doi:10.1093/nutrit/nuy013
7. Hochberg Z, Hochberg I. Evolutionary perspective in rickets and vitamin D. *Front Endocrinol (Lausanne).* 2019;10:306. doi:10.3389/fendo.2019.00306
8. Rossberg W, Saternus R, Wagenpfeil S, et al. Human pigmentation, cutaneous vitamin D synthesis and evolution: variants of genes (SNPs) involved in skin pigmentation are associated with 25(OH)D serum concentration. *Anticancer Res*. 2016;36:1429-1437.
9. Saternus R, Pilz S, Gräber S, et al. A closer look at evolution: variants (SNPs) of genes involved in skin pigmentation, including *EXOC2*, *TYR, TYRP1*, and *DCT*, are associated with 25(OH)D serum concentration. *Endocrinology.* 2015;156:39-47. doi:10.1210/en.2014-1238
10. López S, García Ó, Yurrebaso I, et al. The interplay between natural selection and susceptibility to melanoma on allele 374F of *SLC45A2* gene in a south European population. *PloS One*. 2014;9:E104367. doi:10.1371/journal.pone.0104367
11. Lucock M, Yates Z, Martin C, et al. Vitamin D, folate, and potential early lifecycle environmental origin of significant adult phenotypes. *Evol Med Public Health*. 2014;2014:69-91. doi:10.1093/emph/eou013
12. Hudjashov G, Villems R, Kivisild T. Global patterns of diversity and selection in human tyrosinase gene. *PloS One*. 2013;8:E74307. doi:10.1371/journal.pone.0074307
13. Khan R, Khan BSR. Diet, disease and pigment variation in humans. *Med Hypotheses*. 2010;75:363-367. doi:10.1016/j.mehy.2010.03.033
14. Kuan V, Martineau AR, Griffiths CJ, et al. DHCR7 mutations linked to higher vitamin D status allowed early human migration to northern latitudes. *BMC Evol Biol*. 2013;13:144. doi:10.1186/1471-2148-13-144
15. Omenn GS. Evolution and public health. *Proc National Acad Sci*. 2010;107(suppl 1):1702-1709. doi:10.1073/pnas.0906198106
16. Yuen AWC, Jablonski NG. Vitamin D: in the evolution of human skin colour. *Med Hypotheses*. 2010;74:39-44. doi:10.1016/j.mehy.2009.08.007
17. Vieth R. Weaker bones and white skin as adaptions to improve anthropological "fitness" for northern environments. *Osteoporosis Int*. 2020;31:617-624. doi:10.1007/s00198-019-05167-4
18. Carlberg C. Vitamin D: a micronutrient regulating genes. *Curr Pharm Des*. 2019;25:1740-1746. doi:10.2174/1381612825666190705193227
19. Haddadeen C, Lai C, Cho SY, et al. Variants of the melanocortin-1 receptor: do they matter clinically? *Exp Dermatol*. 2015;1:5-9. doi:10.1111/exd.12540
20. Yao S, Ambrosone CB. Associations between vitamin D deficiency and risk of aggressive breast cancer in African-American women. *J Steroid Biochem Mol Biol*. 2013;136:337-341. doi:10.1016/j.jsbmb.2012.09.010
21. Jablonski N. The evolution of human skin colouration and its relevance to health in the modern world. *J Royal Coll Physicians Edinb*. 2012;42:58-63. doi:10.4997/jrcpe.2012.114
22. Jablonski NG, Chaplin G. Human skin pigmentation as an adaptation to UV radiation. *Proc National Acad Sci*. 2010;107(suppl 2):8962-8968. doi:10.1073/pnas.0914628107
23. Hochberg Z, Templeton AR. Evolutionary perspective in skin color, vitamin D and its receptor. *Hormones*. 2010;9:307-311. doi:10.14310/horm.2002.1281
24. Jones P, Lucock M, Veysey M, et al. The vitamin D–folate hypothesis as an evolutionary model for skin pigmentation: an update and integration of current ideas. *Nutrients*. 2018;10:554. doi:10.3390/nu10050554
25. Lindqvist PG, Epstein E, Landin-Olsson M, et al. Women with fair phenotypes seem to confer a survival advantage in a low UV milieu. a nested matched case control study. *PloS One.* 2020;15:E0228582. doi:10.1371/journal.pone.0228582
26. Holick MF. Shedding new light on the role of the sunshine vitamin D for skin health: the lncRNA–skin cancer connection. *Exp Dermatol*. 2014;23:391-392. doi:10.1111/exd.12386
27. Jablonski NG, Chaplin G. Epidermal pigmentation in the human lineage is an adaptation to ultraviolet radiation. *J Hum Evol*. 2013;65:671-675. doi:10.1016/j.jhevol.2013.06.004
28. Jablonski NG, Chaplin G. The evolution of skin pigmentation and hair texture in people of African ancestry. *Dermatol Clin*. 2014;32:113-121. doi:10.1016/j.det.2013.11.003
29. 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. doi:10.1111/pcmr.12976
30. Lucock MD, Jones PR, Veysey M, et al. Biophysical evidence to support and extend the vitamin D-folate hypothesis as a paradigm for the evolution of human skin pigmentation. *Am J Hum Biol*. 2022;34:E23667. doi:10.1002/ajhb.23667
31. Missaggia BO, Reales G, Cybis GB, et al. Adaptation and co-adaptation of skin pigmentation and vitamin D genes in native Americans. *Am J Med Genet C Semin Med Genet*. 2020;184:1060-1077. doi:10.1002/ajmg.c.31873
32. Hanel A, Carlberg C. Skin colour and vitamin D: an update. *Exp Dermatol*. 2020;29:864-875. doi:10.1111/exd.14142
33. Hanel A, Carlberg C. Vitamin D and evolution: pharmacologic implications. *Biochem Pharmacol*. 2020;173:113595. doi:10.1016/j.bcp.2019.07.024
34. Flegr J, Sýkorová K, Fiala V, et al. Increased 25(OH)D3 level in red-headed people: could redheadedness be an adaptation to temperate climate? *Exp Dermatol*. 2020;29:598-609. doi:10.1111/exd.14119
35. James WPT, Johnson RJ, Speakman JR, et al. Nutrition and its role in human evolution. *J Intern Med*. 2019;285:533-549. doi:10.1111/joim.12878
36. Lucock M, Jones P, Martin C, et al. Vitamin D: beyond metabolism. *J Evid Based Complementary Altern Med*. 2015;20:310-322. doi:10.1177/2156587215580491
37. Jarrett P, Scragg R. Evolution, prehistory and vitamin D. *Int J Environ Res Public Health*. 2020;17:646. doi:10.3390/ijerph17020646
38. Elias PM, Williams ML. Re-appraisal of current theories for the development and loss of epidermal pigmentation in hominins and modern humans. *J Hum Evol*. 2013;64:687-692. doi:10.1016/j.jhevol.2013.02.003
39. Elias PM, Williams ML. Basis for the gain and subsequent dilution of epidermal pigmentation during human evolution: the barrier and metabolic conservation hypotheses revisited. *Am J Phys Anthropol*. 2016;161:189-207. doi:10.1002/ajpa.23030
40. Williams JD, Jacobson EL, Kim H, et al. Water soluble vitamins, clinical research and future application. *Subcell Biochem*. 2011;56:181-197. doi:10.1007/978-94-007-2199-9_10
41. Greaves M. Was skin cancer a selective force for black pigmentation in early hominin evolution [published online February 26, 2014]? *Proc Biol Sci*. 2014;281:20132955. doi:10.1098/rspb.2013.2955
42. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266-281. doi:10.1056/nejmra070553
43. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol.* 2017;13:466-479. doi:10.1038/nrendo.2017.31
44. US Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent Skin Cancer.* US Dept of Health and Human Services, Office of the Surgeon General; 2014. Accessed April 29, 2024. https://www.hhs.gov/sites/default/files/call-to-action-prevent-skin-cancer.pdf
45. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al, eds. *Dietary Reference Intakes for Calcium and Vitamin D.* National Academies Press; 2011. https://www.ncbi.nlm.nih.gov/books/NBK56070/