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Skin colour and vitamin D: An update

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Abstract

Homo sapiens evolved in East Africa and had dark skin, hair, and eyes, in order to protect against deleterious consequences of intensive UV radiation at equatorial latitudes. Intensive skin pigmentation was thought to bear the risk of inefficient vitamin D_3 synthesis in the skin. This initiated the hypothesis that within the past 75 000 years, in which humans migrated to higher latitudes in Asia and Europe, the need for vitamin D_3 synthesis served as an evolutionary driver for skin lightening. In this review, we summarize the recent archeogenomic reconstruction of population admixture in Europe and demonstrate that skin lightening happened as late as 5000 years ago through immigration of lighter pigmented populations from western Anatolia and the Russian steppe but not primarily *via* evolutionary pressure for vitamin D_3 synthesis. We show that variations in genes encoding for proteins being responsible for the transport, metabolism and signalling of vitamin D provide alternative mechanisms of adaptation to a life in northern latitudes without suffering from consequences of vitamin D deficiency. This includes hypotheses explaining differences in the vitamin D status and response index of European populations.

KEYWORDS

evolution, genetic variations, melanin synthesis, pigmentation, skin, vitamin D, vitamin D receptor, vitamin D response index, vitamin D status

1 | INTRODUCTION

Most anthropomorphic properties of humans, such as skin, hair and eye colour,[1] are based on the genotype of individuals, that is on the function and expression of their genes. Nowadays, these traits vary a lot between human populations, but they are the result of the rather recent evolution of anatomically modern humans (*homo sapiens*). Skin, hair and eyes were dark, when some 50-75 000 years ago *homo sapiens* left its origin in equatorial East Africa and migrated first to Asia and Oceania and later to Europe and the Americas.[2,3] In particular in northern Europe and Siberia, human skin and hair turned lighter and blue eyes occurred leading throughout Europe to a North-South gradient in pigmentation.[4] This leads to the question, whether in new geographic environments, such as regions of rather high latitude, there were evolutionary drivers for these changes in pigmentation intensity.

Vitamin D_3 is a prehormone that is essential for proper bone formation and a functional immune system.[5] The main way of providing the human body with vitamin D_3 is its synthesis in UV-B-exposed skin.[6] At higher latitudes, UV-B exposure is significantly lower and

Abbreviations: $1,25(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; $25(OH)D_3$, 25-hydroxyvitamin D_3; CARD9, caspase recruitment domain family member 9; CD14, CD14 molecule; CYP, cytochrome P450; DHCR7, 7-dehydrocholesterol reductase; GC, GC vitamin D binding protein; GWAS, genome-wide association studies; KITLG, KIT ligand; OCA2, OCA2 melanosomal transmembrane protein; PBMC, peripheral blood mononuclear cell; RXR, retinoid X receptor; SLC, solute carrier family; SNP, single nucleotide polymorphism; VDR, vitamin D receptor.

displays prominent seasonal changes.[7] Accordingly, in winter there is no endogenous production of vitamin D_3 possible so that it needs to be taken up by diet or pills, whereupon the molecule can act as a dietary vitamin. The fact that there are only few food sources naturally rich in vitamin D_3 makes its endogenous production essential. This led to the hypothesis that the need for a more efficient synthesis of vitamin D_3 may have acted as an evolutionary driver for skin lightening, in order to avoid deleterious consequences vitamin D deficiency, such as musculoskeletal diseases and immunosuppression.[8,9] Interestingly, a recent large twin study estimated that half of the genetic variance in the vitamin D status, that is the 25-hydroxyvitamin D_3 ($25(OH)D_3$) serum levels, may be explained by skin colour and sun exposure behaviour.[10] A more detailed study with nearly 80 000 European-descent unrelated participants indicated that genes related to vitamin D endocrinology but not to skin colour are contributing to the vitamin D status.[11] On the basis of some 400 000 participants, the number of involved genomic regions increased to more than 100 but still skin colour was not found as a major trait.[12]

In this review, we challenge the hypothesis of skin lightening due to vitamin D by summarizing recent archeogenomic data on changes of skin, hair and eye colour in European populations within the past 10 000 years. Moreover, we discuss changes in the allele frequency of single nucleotide polymorphisms (SNPs) in genes related to vitamin D metabolism and function by comparing present European populations with Africans and East Asians. In this context, we present our own hypotheses explaining differences in the vitamin D status and response index of individuals.

2 | MELANIN AND MODULATION OF ITS SYNTHESIS

Since the beginning of life on Earth some 3.9 billion years ago[13] species had to protect themselves against the harmful consequences of excessive UV radiation being part of the solar spectrum.[14] Basically, all sun-exposed species synthesize molecules that efficiently absorb UV radiation, in order to protect sensitive macromolecules, such as DNA and proteins, from mutagenesis and destruction. In humans and many other species, melanin is used as the main UV-absorbing pigment, since it has a very high refractive index[15] as well as a very broad absorption spectrum ranging from gamma rays via UV and visible to infrared. Melanin is produced via the oxidation and polymerization of the aromatic amino acid tyrosine.[16] This process happens in melanosomes, which are specialized organelles within melanocytes that can be transferred to other cells, such as keratinocytes and hair follicles, in order to pigment them[17] (Figure 1, left). The process of melanogenesis can be induced by UV radiation, such as sun tanning of human skin.[18] The most common form of melanin, eumelanin, is brown to black, while the cysteine derivative pheomelanin is yellow to red.[19] Accordingly, skin and hair colour depend on the absolute amount of eumelanin and the addition of pheomelanin, such as in red hair. The ratio between eumelanin and pheomelanin depends on the activity of the enzyme tyrosinase and the availability of cysteine.

About 2 million years ago, when hominins lost most of their body hair,[20] in order to improve *via* more efficient heat dissipation their physical performance,[21] their initial pale skin developed an intensive pigmentation, in order to protect from sunburn and UV-induced cancer.[22,23] Variations in the pigmentation intensity of skin, eyes and hair can be explained by SNPs in gene encoding for key proteins in melanogenesis.[16] For the European populations, the most relevant SNPs are those related to the genes *SLC24A5* (solute carrier family 24 member 5), *SLC45A2* and *OCA2* (OCA2 melanosomal transmembrane protein)[3,24] encoding for proteins functioning as a potassium-dependent sodium/calcium exchanger, ion transporter and pH regulator in melanosomes[16] (Figure 1, left). Since ion concentrations and pH values within melanosomes are critical for tyrosinase activity and efficient melanogenesis, loss of function at derived alleles, such as at SNP rs1426654 causing an alanine to threonine exchange at position 111 of the SLC24A5 protein (Ala111Thr) and at SNP rs16891982 leading to a leucine to phenylalanine exchange at position 374 (Leu374Phe) of the SLC45A2 protein, significantly reduce skin pigmentation. Moreover, SNP rs12913832 is located on a transcription factor binding site within an enhancer residing in an intron of the *HERC2* gene but affecting the expression of the *OCA2* gene. The homozygous G/G-derived allele of this SNP is associated with blue irises in Europeans.[25] Another critical gene is *KITLG* (KIT ligand), which encodes for a ligand produced in keratinocytes that stimulates the tyrosine kinase KIT-inducing melanogenesis. The derived allele of SNP rs12821256 controlling the expression of the *KITLG* gene significantly reduces hair pigmentation and leads to blond hair[26] (Figure 1, left).

In summary, a few variations in genes involved in melanogenesis explain well the differences in skin, hair and eye pigmentation, in particular in European populations.

3 | SYNTHESIS OF VITAMIN D_3 AND ITS METABOLITES

The secosteroid vitamin D_3 is synthesized in human skin when the direct precursor of cholesterol, 7-dehydrocholesterol, is exposed to UV-B[27] (Figure 1, right). Although this reaction is non-enzymatic, the 7-dehydrocholesterol level, and by this amount of producible vitamin D_3, is critically dependent on the activity of the enzyme 7-dehydrocholesterol reductase (DHCR7).[27] Individuals with less active DHCR7 have a higher amount of substrate in their skin, that is they can produce vitamin D_3 more efficiently even at less intense UV-B exposure. Moreover, vitamin D synthesis takes place predominantly in keratinocytes of the upper epidermis layer *stratum spinosum*[28] (Figure 1, centre), where highest concentrations of 7-dehydrocholesterol are found.[29] In contrast, 70-80% of total melanin is found in the basal epidermis layer irrespectively of the skin phototype,[23] ensuring photodamage protection to the most cancer-susceptible skin layer.[28] Thus, a dark pigmentation of the skin, which is mainly due

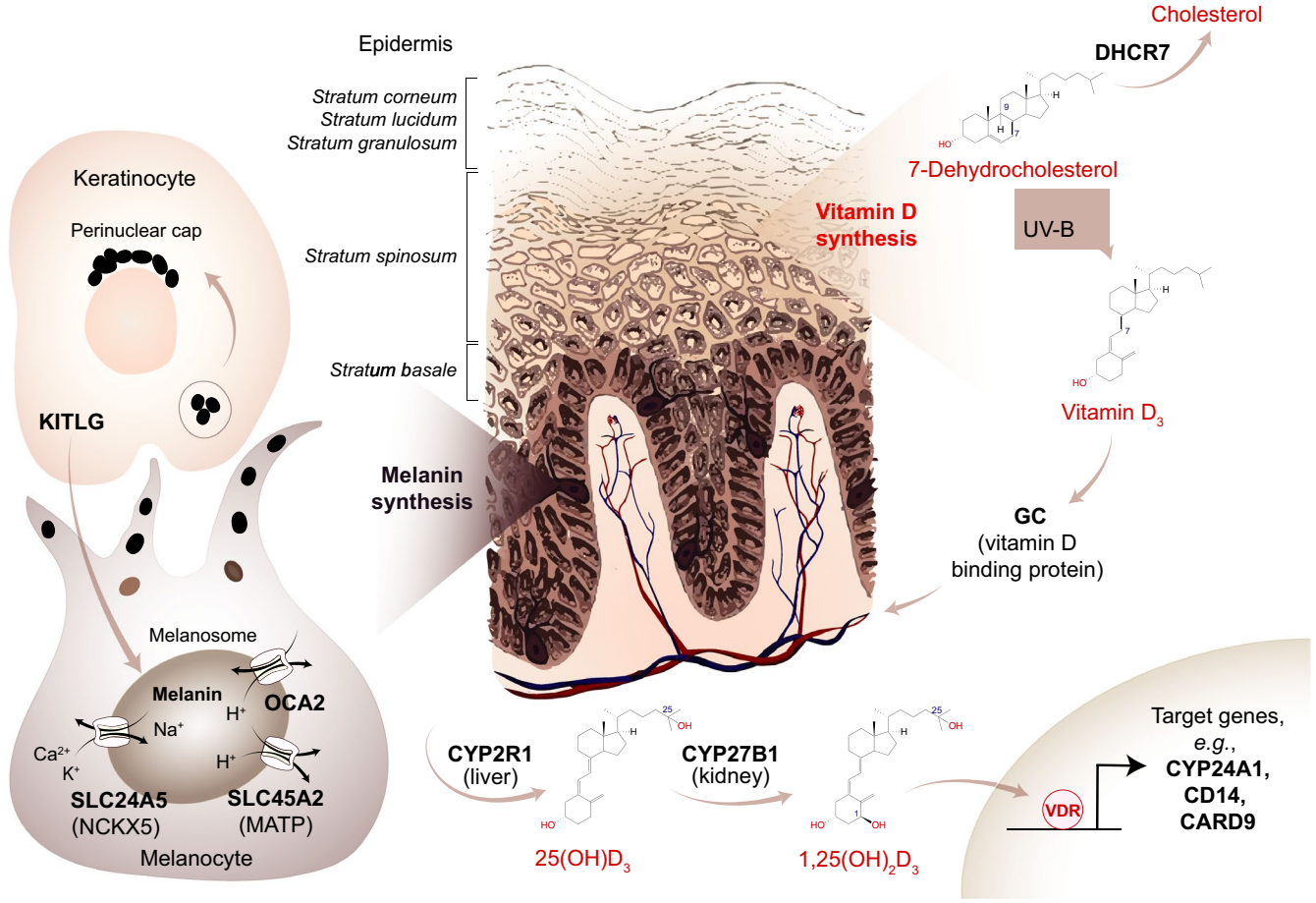

FIGURE 1 Biology of skin pigmentation and vitamin D synthesis. Melanocytes residing in the basal layer of the epidermis provide keratinocytes and hair follicles (not shown) with melanosomes (left). In keratinocytes, melanosomes are taken up by phagocytosis and reorganized in the supranuclear area to form melanin caps. In the process of melanogenesis, melanin is produced in melanosomes under the control of the proteins KITLG, SLC24A5 and SLC45A2. Vitamin D_3 is produced when the cholesterol precursor 7-dehydrocholesterol is exposed to UV-B radiation (right). This non-enzymatic reaction produces previtamin D_3 (not shown) that rapidly isomerizes to vitamin D_3. In serum, vitamin D_3 and its metabolites are transported bound to the GC protein. In the liver, the enzyme CYP2R1 converts vitamin D_3 into $25(OH)D_3$ and in the kidneys (and other cell types) CYP27B1 produces $1,25(OH)_2D_3$, which is the high-affinity ligand to the transcription factor VDR. Examples of VDR target genes are indicated

to eumelanin-laden melanosomes in keratinocytes of lower layers, seems not to inhibit significantly vitamin D_3 synthesis taking place in the upper layers.[6,30,31] Accordingly, dark skinned hunter-gatherer populations of Africa that live traditionally and expose most of their skin to intensive sun, such as the Tanzanian Hadza, have a rather high vitamin D status with average $25(OH)D_3$ serum levels in the order of 110 nmol/L.[32]

Like other dietary fats, vitamin D_3 obtained from diet or supplements is assembled in intestinal enterocytes into chylomicrons and passed through the lymphatic system to the bloodstream, where the vitamin is unloaded to the serum glycoprotein GC (GC vitamin D binding protein).[33] Similarly, vitamin D_3 obtained from endogenous synthesis is released from keratinocytes into the bloodstream and is as well transported *via* the GC protein. In the liver, vitamin D_3 is converted to $25(OH)D_3$, primarily by the enzyme CYP2R1[34] (cytochrome P450 family 2 subfamily R member 1). Due to a half-life of some 3 weeks, $25(OH)D_3$ is the most stable and abundant vitamin D metabolite and often used as a biomarker for the vitamin D status of a person.[35] Kidneys and a few other cell types, such as immune cells and keratinocytes, express the enzyme CYP27B1 mediating further hydroxylation of $25(OH)D_3$ into 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$).[36] The GC protein is responsible for the transport of all vitamin D metabolites but shows higher affinity for $25(OH)D_3$ than for $1,25(OH)_2D_3$. Accordingly, in serum vitamin D metabolites are mainly protein-bound and only a very small fraction circulates as "free" molecules.[36] $1,25(OH)_2D_3$ binds with high affinity ($K_D = 0.1$ nM) to the transcription factor vitamin D receptor (VDR).[37] Thus, vitamin D regulates *via* $1,25(OH)_2D_3$ and the VDR the expression of hundreds of primary target genes. Examples of important vitamin D target genes are *CYP24A1*, *CD14* (CD14 molecule) and *CARD9* (caspase recruitment domain family member 9)[38] (Figure 1, right).

Vitamin D endocrinology emerged some 550 million years ago in the boneless fish lamprey.[39] Thus, rather than bone metabolism, the prime function of vitamin D was the regulation of energy metabolism.[40] Since the immune system requires substantial amounts

of energy,[41] vitamin D and its receptor obtained *via* the control of immunometabolism a modulatory impact on immunity.[42] Since immune cells are the most rapidly growing cells of the human body, vitamin D extended its functional profile to the control of cellular proliferation, differentiation and apoptosis.[43] When around 400 million years ago bony fish left the calcium-rich ocean, at calcium-poor land they were facing the need to control the homeostasis of this ion being essential for a stable skeleton.[44] Thus, at that time vitamin D endocrinology gained the additional role of regulating calcium homeostasis. In this physiological function, vitamin D obtained key importance,[45] that is in contrast to its other tasks no other regulatory molecules are able to replace it. This explains why the prime phenotype of vitamin D deficiency is bone malformation, such as occurring in rickets.[46] Nevertheless, the rather ubiquitous expression of the *VDR* gene in more than half of the 400 human tissues and cell types indicates that vitamin D has a wider physiological role than the regulation of calcium homeostasis.[47]

Taken together, vitamin D and its metabolites are important biomolecules, the sufficient synthesis of which is critical for a number of physiological functions of the human body.

4 | HISTORY OF SKIN LIGHTENING IN EUROPEANS

The genetic history of today's European populations is based on continuous migrations over the past 40 000 years. *Homo sapiens* arrived in Europe from Near East some 42 000 years ago.[48,49] Like in their African origin, these humans had dark skin but due to variations of their *OCA2* gene (causing iris depigmentation) many of them had blue eyes[48,50] (Figure 2, left). At that time, still ancestral Neanderthal hominins lived in Europe, whom had arrived from Africa at least some 400 000 years earlier.[50-52] Through interbreeding with modern humans, the Neanderthalers were outnumbered[53] and disappeared a few thousand years after the arrival of the modern humans.[52] In net effect, the genome of today's Europeans contains in average 2.3% Neanderthal DNA.[54] The first European *homo sapiens* lived as hunter-gatherers in ice-free south-western Europe.[55] Following the retreating ice-sheet some 11-12 000 years ago, these hunter-gatherers started to colonize also northern Europe.[48] Interestingly, eastern and Scandinavian hunter-gatherers had light skin,[48] in contrast to Baltic hunter-gatherers who kept their dark skin only until 3800 years ago when farming was introduced in this region by the Bronze Age expansion of people of Russian steppe origin.[56,57] These migrants were associated with the Yamnaya culture and emerged out of a mixture between light-skinned Caucasus and eastern hunter-gatherers.[58,59] In addition, north-eastern speakers of Uralic languages, such as Estonians, Finns and most notably Saami, have a genetic component most similar to modern Siberians who arrived 3500 years ago.[56,60] Thus, Siberians and Yamnayas had a large impact on the phenotype of today's northern Europeans.

Although large genome-wide association studies highlighted skin colour as a highly polygenic trait,[20,61,62] evidence for selection of pigmentation variants in present-day Europeans was found only for a limited number of large-effect variants, the top two of which turned out to be the loci of the genes *SLC24A5* and *SLC45A2*.[24,63] Thus, the light skin colour of today's Europeans is primarily based on non-synonymous SNPs of the genes *SLC24A5* and *SLC45A2*, the geographical origin of which is western Asia and the Near East[48] (Figure 2). Initial estimations based on haplotype diversity of microsatellites in modern humans suggested that derived alleles of these SNPs were common in Europeans already some 11 000 to 19 000 years ago.[64,65] However, recent archeogenomic analysis, that is whole genome sequencing of ancient DNA, allowed a more precise description of the evolution and timing of trait changes within European populations.[48,56,57,65-70]

The SNP rs1426654 within the *SLC24A5* gene has the single largest effect on skin lightening of all gene variants identified to date.[66] It is located within a large (78 kb) haplotype block C11 shared by virtually all carriers of this allele, including ancient Scandinavian, eastern and Caucasus hunter-gatherers,[48] suggesting that this light skin variant derives from a single carrier who lived 22 000-28 000 years ago[48,71] in the Middle East.[72] Similarly, haplotype analysis of the SNP rs16891982 of the *SLC45A2* gene concluded that this skin-lightening mutation occurred only once in the ancestry of Caucasians.[48,73] Migrations across the Caucasus and Eastern Europe would have brought both alleles to Scandinavia, in contrast to southern and central Europe, where they were introduced by farmers from western Anatolia[48] expanding 8500 to 5000 years ago[3] (Figure 2, right). This was the start of the Neolithic revolution in these regions, characterized by a more sedentary lifestyle and the domestication of certain animal and plant species.[3]

The Anatolian farmers had rather short body stature and predominantly brown eyes, which explains the key anthropomorphic traits of today's southern Europeans, in contrast to Yamnayas, who had a high body stature and settled preferentially in northern Europe.[3,74] Moreover, these steppe pastoralists brought the horse, the wheel and Indo-European languages.[66,74-76] Interestingly, ancient North Eurasian derived populations, such as eastern hunter-gatherers and Yamnayas, carried the blond hair allele rs12821256 of the *KITLG* gene to Europe.[66] Its first evidence was described in an 18 000 years old ancient North Eurasian west of Lake Baikal (Figure 2, right). It is important to note that the four major founding populations of Eurasians, which were farmers of the Fertile Crescent (including western Anatolia), farmers of Iran, hunter-gatherers of central and western Europe as well as of eastern Europe (Figure 2, right), genetically differed from each other probably as much as today's Europeans to East Asians.[77] Thus, the classic light phenotype of Europeans became frequent only within the past 5000 years[3,56,70] and owes its origin to migrants from Near East and western Asia.[48]

Differences in the relative admixture of ancient hunter-gatherers, Anatolian farmers, Yamnaya pastoralists and Siberians explain the variations in skin and hair pigmentation, eye colour, body stature and many other traits of present Europeans.[60,74,78,79] The rapid

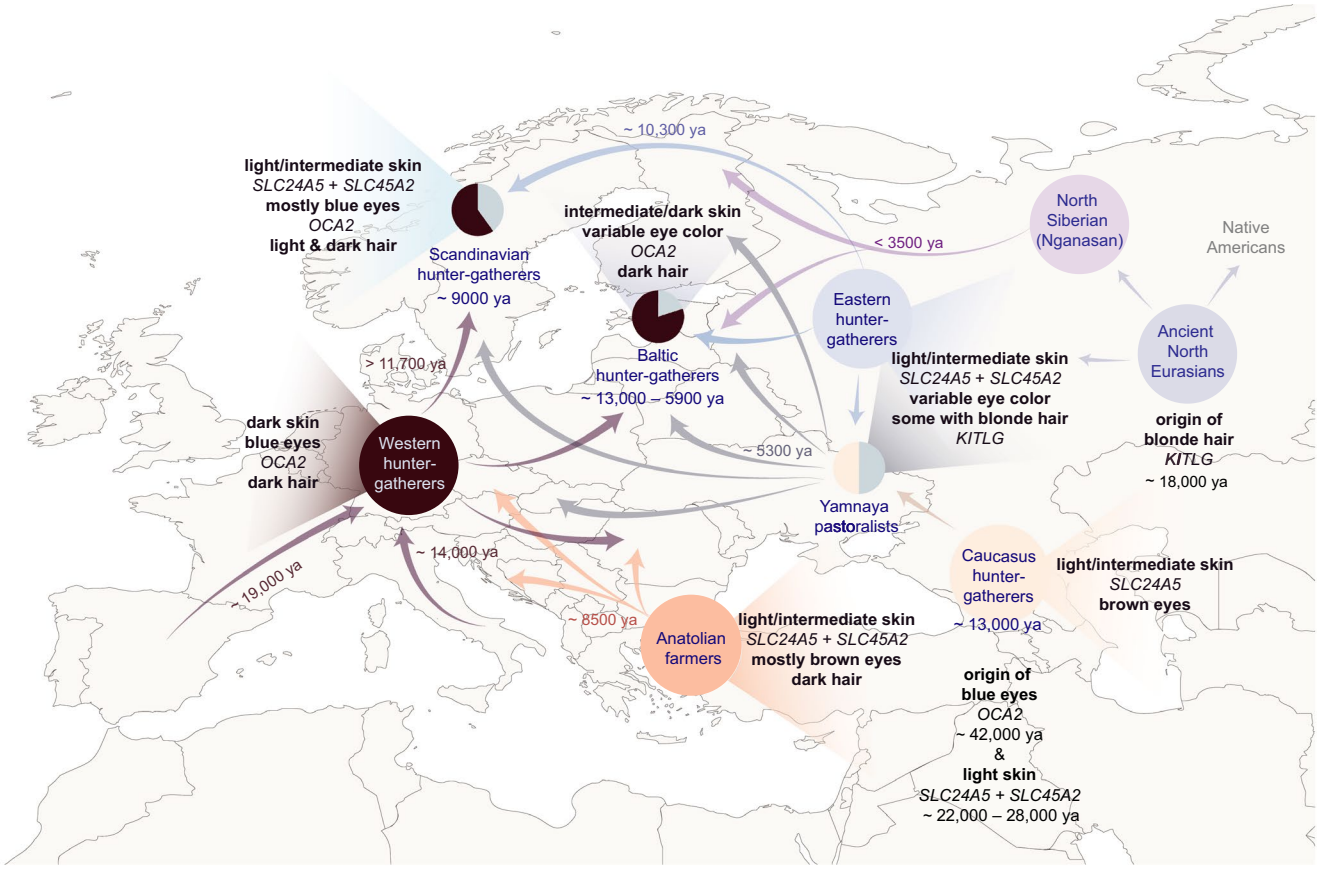

FIGURE 2 History of human pigmentation in Europe. Archeogenomic data were downloaded from the Reich Lab webpage (https://reich.hms.harvard.edu, version 37.2, released February 22, 2019) and complemented with recent data,[55,56,58,67-69,108] in order to create the map of migration and admixture of populations in Europe since the arrival of *homo sapiens* some 40 000 years ago. Phenotype information was retrieved from supplementary files of the according publications or additionally assessed following the instructions of HirisPlex-S (https://hirisplex.erasmusmc.nl), which is a forensic DNA phenotyping tool based on an array of different marker SNPs providing additional support to the SNPs of the genes *SLC24A5*, *SLC45A2* and *OCA2*. The map was plotted using the R package rnaturalearth (https://CRAN.R-project.org/package=rnaturalearth) and sf (https://CRAN.R-project.org/package=sf). Ya, years ago

increase in population size due to the Neolithic revolution,[64,80] such as the use of milk products as food source for adults and the rise of agriculture,[81] as well as the massive spread of Yamnaya pastoralists likely caused the rapid selective sweep in European populations towards light skin and hair. Interestingly, there had been an increase in the frequencies of the alleles of the genes *SLC45A2* and *SLC24A5* for light skin even after the admixture event indicating that selection for depigmentation variants was ongoing until rather recent times.[24,48,82] Phenotype predictions of ancient individuals have been recently based not only on the genes *SLC24A5*, *SLC45A2* and *OCA2* but on a whole array of marker pigmentation SNPs used in forensics[56,67,68,70,83] suggesting that light skin was for many thousand years not essential for survival at higher latitudes of Europe.[84] In addition, there is no mechanistical link between vitamin D and the expression of the main light skin alleles, such as primary vitamin D target genes carrying VDR binding sites in their regulatory regions.[85]

In summary, there is no convincing evidence of a direct evolutionary effect of vitamin D on skin lightening of Europeans.

5 | GENETIC VARIANTS ASSOCIATED WITH VITAMIN D METABOLISM AND SIGNALLING

A genome-wide association study (GWAS) based on nearly 80,000 European-descent subjects indicated that SNPs in the genes *DHCR7*, *GC*, *CYP2R1* and *CYP24A1*, which are related to vitamin D metabolism and transport, may explain some of the genetics behind their vitamin D status.[11] For example, the derived allele of the SNP rs12785878 results in reduced expression of the *DHCR7* gene causing increased concentrations of 7-dehydrocholesterol in the skin and more efficient synthesis of vitamin D_3.[86] The SNP is located within an enhancer residing in an exon of the *NADSYN1* gene some 8 kb upstream of the transcription start site of the *DHCR7* gene. Compared to African and Asian populations, today's Europeans have a 2.4- to 3.1-fold higher frequency of the derived allele of rs12785878 (Figure 3), that is they can better manage with low UV-B exposure and still synthesize sufficient vitamin D_3. The derived allele occurred already with ancient European

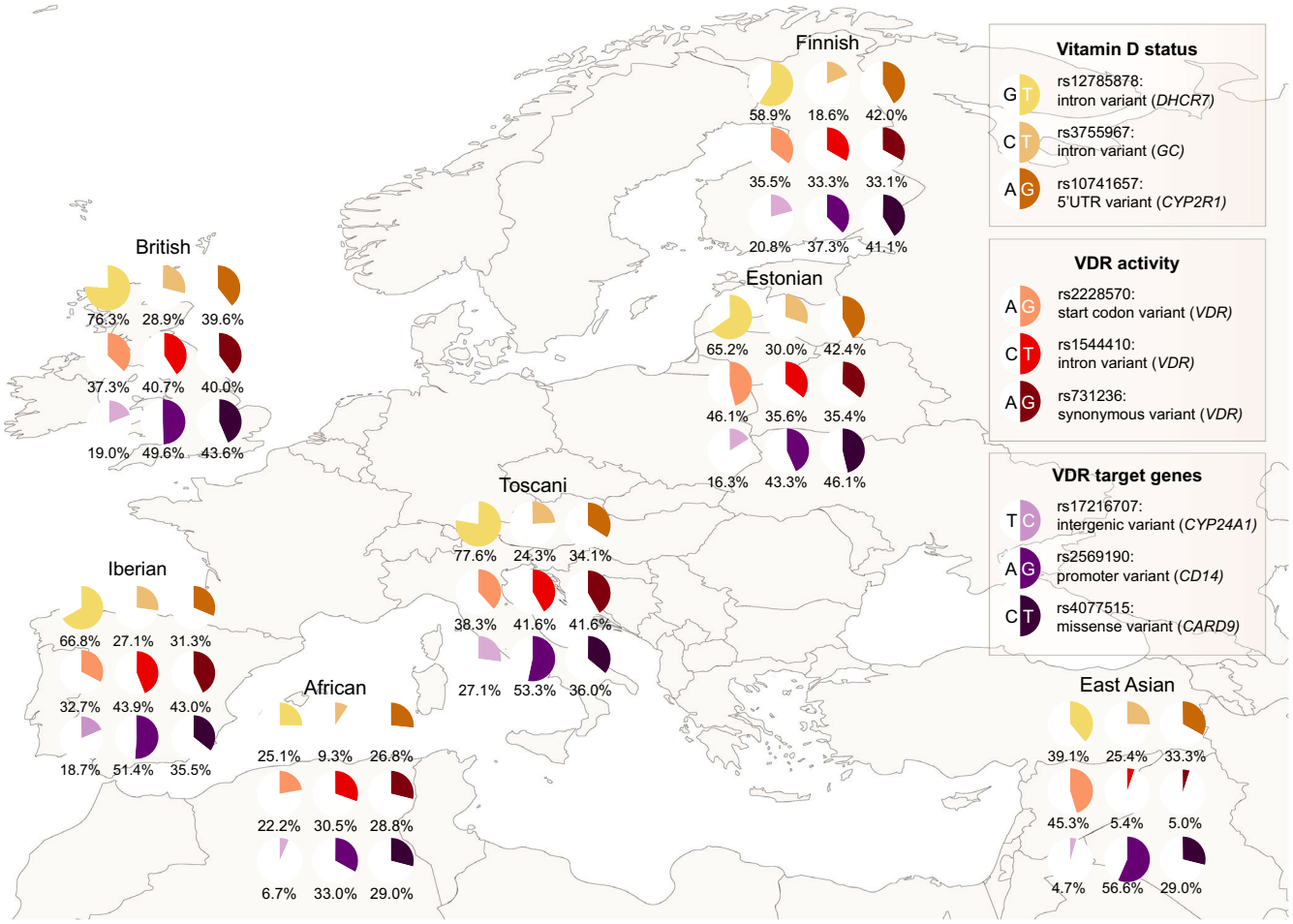

FIGURE 3 SNPs affecting the vitamin D system. Five modern European populations were compared with average African and East Asian populations for the frequency of derived alleles (in colour) of SNPs related to the synthesis, transport, metabolism, receptor function and target gene efficiency of vitamin D. The nine SNPs affect the seven indicated genes, which were selected due to their impact of determining the 25(OH)D_3 serum level as well as for vitamin D signalling. Population genomics data for African/African American (n = 21 042), East Asian (n = 1567), Finnish (n = 5244) and Estonian (n = 2297) populations were retrieved from the genome aggregation database gnom.AD (https://gnomad.broadinstitute.org). Data for the British population (n = 1927) are based on the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort and were together with Toscani (n = 107) and Iberian (n = 107) population retrieved from the 1000 Genomes Project (https://www.internationalgenome.org).[107] UTR, untranslated region

hunter-gatherers[63] (Figure 2, left). Interestingly, *DHCR7* is a risk gene for autoimmune diseases, type 1 diabetes[87] and multiple sclerosis,[88] which are both highly associated with vitamin D deficiency. Thus, evolution rather used the adaption of *DHCR7* expression than that of skin-lightening genes as a mechanism of avoiding vitamin D deficiency and its medical consequences.[89]

Like the minor allele of the *DHCR7* SNP rs12785878, also the frequencies of the 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) increased up to 4-fold in European populations compared with the reference from Africa and even up to 8.6-fold in relation to data from Asian populations (Figure 3). In addition, also variants in the genes *CYP11A1* and *CYP27A1*, which are encoding for enzymes involved in vitamin D metabolism, as well as the genes *RXRA* and *RXRG*, encoding for VDR partner proteins retinoid X receptors α and γ, had been shown to be enriched in European populations.[90] The mechanistic details how the minor alleles of these gene variants affect vitamin D metabolism and signalling are not fully understood, but in net effect the European populations seem to be more sensitive in their response to vitamin D. For example, the translation start site polymorphism of the *VDR* gene (rs2228570, *FokI*) results in a three amino acid shorter protein mediating higher transcriptional activity to its target genes.[91] Moreover, increased circulating levels of the fibroblast growth factor 23 proteins are associated with the minor allele of SNP rs17216707 close to the *CYP24A1* gene,[92] a beneficial elevated pro-inflammatory response in the contextof sepsis is linked to the derived allele of SNP rs2569190 of the *CD14* gene[93] and the minor allele of SNP rs4077515 of the *CARD9* gene leads to a lower likelihood of progressive liver disease.[94] Thus, all thirteen example SNPs underwent positive selection within the European population.

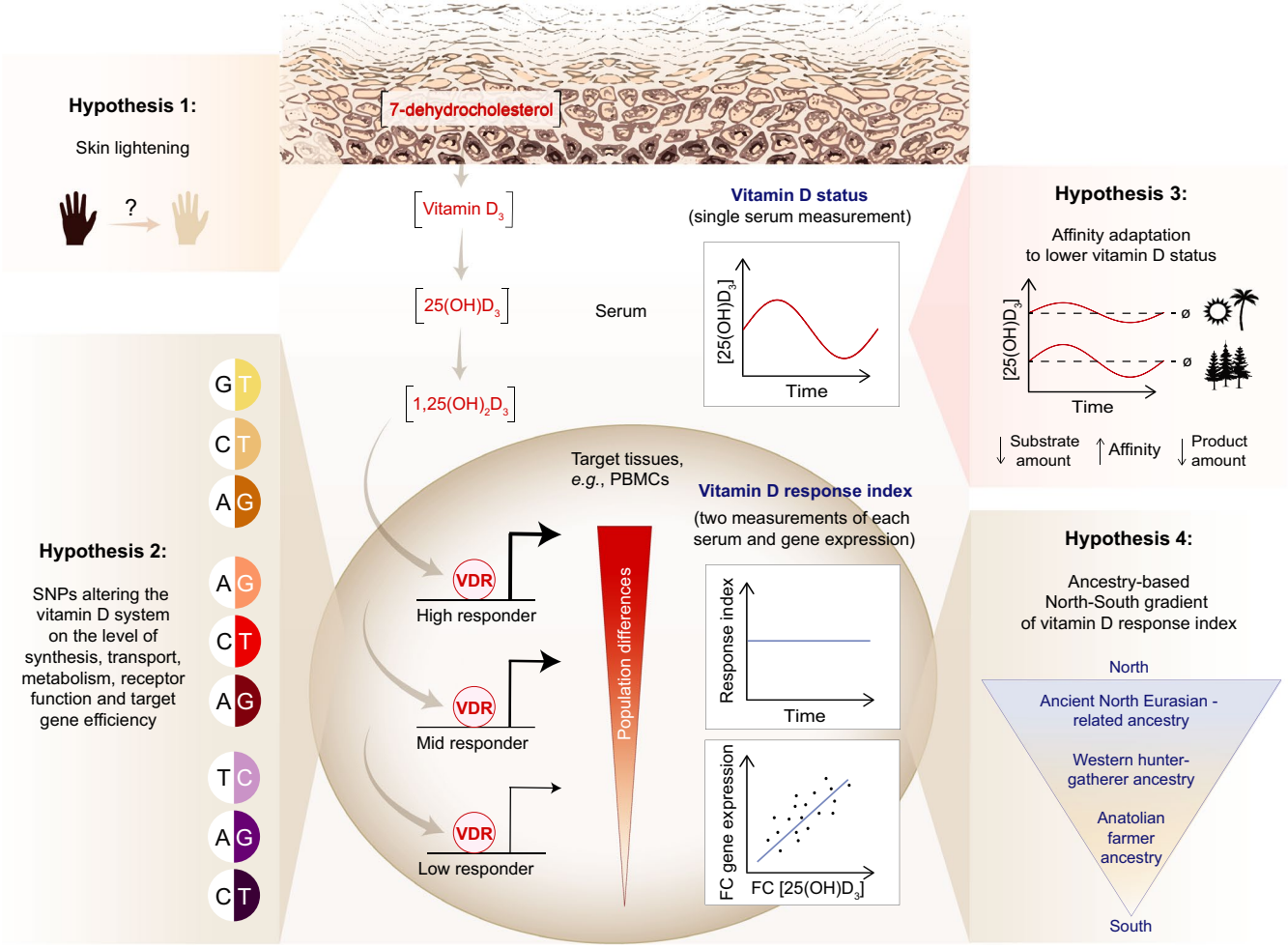

FIGURE 4 Hypotheses explaining vitamin D status and response index. Schematic illustration of the vitamin D status and response index (centre) and hypotheses related to them (left and right). Hypotheses 3 and 4 represent physiological consequences of hypothesis 2. FC, fold change

Taken together, within the past 40 000 years of the presence of *homo sapiens* in Europe populations were selected for genetic variants that allowed to cope *via* different mechanisms with lower levels of circulating 25(OH)D_3.

6 | STATUS AND RESPONSE INDEX OF VITAMIN D

The vitamin D status of an individual is most commonly determined *via* its 25(OH)D_3 serum level. Seasonal changes of sun exposure at latitudes distant from the equator, such as in Europe, lead to variations of the vitamin D status of non-supplemented individuals over the year[7] (Figure 4, centre). The US Institute of Medicine[95] considers a 25(OH)D_3 serum level of 50 nmol/L sufficient, while the US Endocrine Society[96] suggests at least 75 nmol/L, that is there are different recommendations how much daily vitamin D_3 supplementation should be used, in order to reach which vitamin D status. Depending of these threshold levels, some 25%-50% of the world population can be considered as vitamin D deficient.[97] However, it can be questioned, whether a threshold level of the vitamin D status is the best reference for calculating the vitamin D needs of individuals. Based on the vitamin D response index concept[98] persons are distinguished into high, mid and low responders to vitamin D[99,100] (Figure 4, centre). Accordingly, they have a personal need for vitamin D_3 supplementation, which depends on their vitamin D status in relation to their response index. The index describes the molecular response to vitamin D_3 and its metabolites and is measured *via* the change in the expression of a few or all vitamin D target genes in a given tissue, such as peripheral blood mononuclear cells (PBMCs), after a significant change in the vitamin D status[38] (Figure 4, centre). The response index is a variable genetic trait of each individual that is constant over time or may change only slowly, such as during the development of an age-related disease. Importantly, high vitamin D responders benefit even from a low vitamin D status, that is they should tolerate conditions of low or no endogenous vitamin D_3 production during European winters. Accordingly, these persons should be less affected by disorders, such as infections,[101] autoimmune diseases[102] and cancer,[103]

against which vitamin D has a protective function. In contrast, low vitamin D responders need to reach a high vitamin D status, in order to obtain the full benefit from vitamin D.

In summary, analysing the vitamin D response index may be the better parameter for describing vitamin D needs than referring to the vitamin D status.

7 | EVOLUTIONARY VITAMIN D ADAPTION HYPOTHESES

The central point of this review is the question how during the 40,000 year history of *homo sapiens* in Europe they adapted their vitamin D system of synthesis, transport, metabolism, receptor binding and target gene efficiency so that they did not suffer from malfunction due to deficiency. The first answer to this question was the hypothesis of Jablonski[8,9] that the need for efficient vitamin D_3 synthesis acted as evolutionary driver for skin lightening (Figure 4, left). Although this theory has attractive simplicity, the recent data on the history of skin lighting in the European population (Figure 2) demonstrated that European hunter-gatherers of central and western Europe survived for 35 000 years with dark skin and got lighter skin only by interbreeding with external populations from western Anatolia and the Russian Steppe migrating into different European regions. It has been suggested that the introduction of agriculture by these populations, that is dietary change from a hunter-gatherer diet to vitamin D-poor agriculturalist diet, reinforced the selection pressure for light pigmentation.[65,82] Accordingly, the dark skin of some of today's Arctic Native people, such as Inuits, has been traditionally explained for their marine diet rich in vitamin D_3.[8] However, nitrogen and carbon isotope analysis of northern and western Scandinavian hunter-gatherers revealed their had an extreme marine diet as well and yet developed light skin.[48] Thus, archeogenomic data as well as comparisons of today's populations did not provide any indication for an evolutionary pressure for light skin created by the need for vitamin D.

The second hypothesis is based on SNPs of the genes *DHCR7*, *GC* and *CYP2R1* that show association with the vitamin D status of individuals[11] (Figure 4, left). The minor alleles of the SNPs of all three genes accumulated in today's European populations (Figure 3). Importantly, archeogenomic analysis found the derived alleles of the *DHCR7* gene rs12785878, rs7940244 and rs7944926 to be present already in western hunter-gatherers, highlighting rs7944926 as the 7th most significantly selected SNP in ancient Eurasians.[63] Moreover, in contrast to previous beliefs, dark pigmentation seems not to be a prominent inhibitor of vitamin D_3 synthesis, since the latter happens largely in upper layers of the skin that are less pigmented.[6,30] In addition, other SNPs affecting the vitamin D system, such as those discussed in Figure 3, may improve vitamin D's actions, so that individuals can better handle a lower vitamin D status at higher latitudes. Interestingly, based on a recent study with more than 400 000 Europeans[12] in total 143 SNPs were found to be associated with 25(OH)D_3 serum levels. These genetic variants are located in 112 genomic regions carrying genes that are, for example involved in dermal development and integrity, such as *FLG* encoding for the cytoskeletal protein filaggrin.[104] Thus, future studies should provide further mechanistic explanations how these SNPs affect the vitamin D system and when they occurred during the evolution of *homo sapiens* in Europe.

The third hypothesis suggests that populations at higher latitudes managed to live with a lower vitamin D status, because their vitamin D system (enzymes, transporter and receptor) developed a higher affinity for vitamin D_3 and its metabolites, so that it can be activated by a lower vitamin D status (Figure 4, right). This concept has the advantage that individuals would not have to aim for a high vitamin D status. However, although similar affinity adaptions are known from different biological systems, such as sensing glucose or adapting to cold temperature,[105] there is so far no experimental proof for this hypothesis.

Since for high vitamin D responders a rather low vitamin D status is still sufficient to activate all vitamin D target genes,[38] there may have been a selection for high vitamin D responders in northern Europe. Accordingly, hypothesis 4 assumes that Yamnaya ancestry (including ancestry from Siberian hunter-gatherers) had a dominant effect on the phenotype of northern Europeans,[3,106] that is together with other traits Yamnayas also brought high vitamin D sensitivity to Europe, which may have originated predominantly from ancient North Eurasians (Figure 4, right). In a north-south gradient, persons with ancestry from western European hunter-gatherers may show an intermediate responsiveness to vitamin D and those with Anatolian farmers the lowest. The mechanistic basis for the processes behind hypotheses 3 and 4 are likely the SNPs discussed in the context of hypothesis 2. Thus, hypotheses 3 and 4 are closely linked to hypothesis 2 and may be presented as one concept.

Taken together, the concept of increasing frequency of SNPs affecting the vitamin D system may serve as a replacement of the skin-lightening hypothesis.

8 | CONCLUSION

The 1000 Genomes Project[107] indicated that humans of European decent have a number of variants in their genome that have important effects on traits forming their phenotype. The master example of these traits is lactose tolerance, where due to SNPs within an enhancer regulating the *LCT* gene adults are able to digest milk sugar. Furthermore, anthropomorphic traits, such as skin, hair and eye colour, are now well understood on the basis of SNPs affecting the genes *SLC24A5*, *SLC45A2*, *OCA2*, *KITLG* and others. The skin-lightening hypothesis of Jablonski[8] was formulated first 20 years ago and assumed that the need for efficient vitamin D synthesis acted as evolutionary driver for skin lightening in populations living at high latitudes. However, archeogenomic data indicated that Europeans got pale as predominant skin colour just some 5000 years ago

through interbreeding with migrating populations originating from Anatolia and the Russian steppe. The latter populations likely accumulated the light skin alleles *via* genetic drift[24] rather than through an effect of vitamin D.

In this review, we provided alternative explanations for the adaption of the vitamin D system during the migration of *homo sapiens* to geographic regions of low or no endogenous vitamin D_3 production during winter. These concepts are based on SNPs affecting the function of genes involved in vitamin D synthesis, transport, metabolism, receptor binding and target gene efficiency. In conclusion, ancient European populations dealt with their "vitamin D problem" primarily *via* higher sensitivity for vitamin D_3 and its metabolites but less likely by getting lighter skin.

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CONFLICTS OF INTERESTS

The authors have no conflicts of interest.

AUTHOR CONTRIBUTION

A.H. and C.C. conceptualized the project, analysed the data, created the figures, wrote the manuscript and reviewed it.

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