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Short Review

Development of different human skin colors: A review highlighting photobiological and photobiophysical aspects

Asta Juzeniene [a,*], Richard Setlow [b], Alina Porojnicu [c], Arnfinn Hykkerud Steindal [a,c], Johan Moan [a,d]

[a] Department of Radiation Biology, Institute for Cancer Research, Norwegian Radium Hospital, Oslo University Hospital, Montebello N-0310 Oslo, Norway
[b] Biology Department, Brookhaven National Laboratory, Upton, NY 11973, USA
[c] Centre for Theoretical and Computational Chemistry, Department of Chemistry, University of Tromsø, 9037 Tromsø, Norway
[d] Institute of Physics, University of Oslo, Blindern 0316 Oslo, Norway

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ABSTRACT

Skin color has changed during human evolution. These changes may result from adaptations to solar ultraviolet radiation (protection of sweat glands, sunburn, skin cancer, vitamin D deficiency, defence against microorganisms, etc.), and/or sexual selection. Migration to areas with high levels of UV is associated with skin darkening, while migration to areas with low levels has led to skin lightening. However, other factors may have played roles. Temperature and food have probably been secondary determinants: heat exchange with the environment is dependent on ambient temperature, and a high intake of food rich in vitamin D allows a dark skin color to persist even at latitudes of low UV levels, as exemplified by Inuit's living at high latitudes. Future studies of human migration will show if skin lightening is a faster process and has a higher evolutionary impact than skin darkening. Maybe due to that some American Indians have kept a relatively light skin although they live under the equator.

The following hypotheses for skin darkening are reviewed: shielding of sweat glands and blood vessels in the skin, protection against skin cancer and overproduction of vitamin D, camouflage, adaptation to different ambient temperatures, defense against microorganisms, protection against folate photodestruction. Hypotheses for skin lightening are: sexual selection, adaptation to cold climates, enhancement of vitamin D photoproduction, and changing food habits leading to lower intake of vitamin D. The genetical processes behind some of the changes of skin color will be also briefly reviewed.

Contents

* Corresponding author. Tel.: +47 22935113; fax: +47 22934270.
E-mail address: asta.juzeniene@rr-research.no (A. Juzeniene).

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1. Introduction

The ability to change skin color has been of crucial importance for human evolution. Fluence rates of solar radiation and spatial and temporal changes of the spectral composition of this radiation are major determinants for this evolution, which has taken place in periods when humans have migrated or changed diet. A number of hypotheses have been proposed for skin color adaptations. These will be briefly listed and discussed in the present review. Emphasis will be put on photobiological and photobiophysical aspects.

2. The origin of humans and their earliest skin color

When the physical characteristics of the environment change, the individuals who are best adapted to the new conditions have a survival advantage. Over many generations, evolution by natural selection will lead to changes in the genetic and phenotypic composition of the species. In fragmented environments, some members of the species may adapt better to different environmental circumstances than others. This may eventually lead to the formation of new species [1].

During the last 15–10 million years there has been a cooling of the global climate, mostly expressed as a drying close to the equator [2]. Archeological and molecular evidences suggest that common ancestor of humans diverged about 6–7 million years ago in Africa [3–5]. One of the oldest known hominids from that time was found in Chad [3,6]. He may have walked upright [4,7]. The African apes did probably change less than the human ancestors [5]. They have, and probably had, light skin under their dark hair. Skin in areas with little hair is light, but turns brown and gets freckles in the sun [8]. Many researchers believe that 7 million years ago the human ancestors resembled chimpanzees, as they appear today, with respect to characteristic features of hair and skin [8].

One of the oldest known human skeletons belongs to "Lucy", who lived in East Africa more than 3 millions years ago [9]. Later, 1.5 millions years ago, the "Turkana" boy lived in the same area [9,10]. He had longer legs than "Lucy". The hot sun of Africa may have led to modifications of the skin of early humans in order to avoid overheating of their brain [11]. The dense capillary network in the brain assures that its temperature closely follows arterial temperature and is controlled through systemic thermoregulation, independent of head surface temperature [12]. The brain can function optimally only within a narrow range of physiological temperatures. To reduce the chance of overheating, early humans probably lost most of their body hair and developed sweat glands [13]. Furthermore, bacteria and fungi are easier to fight in a hairless skin [14]. However, this may not be correct since we still have hair on our heads and on other vital body areas.

Before about 1.8 million years ago human evolution occurred only in Africa. Afterwards, humans migrated out of Africa for the first time and probably populated Asia first and Europe somewhat later, inhabiting non-equatorial regions for the first time [15]. Fig. 1 is a sketch of one of the models for the later part of human evolution [16]. Fig. 2 demonstrates the relationship between mean genetic diversity of human populations computed on the basis of autosomal microsatellite markers and their geographic distances in km from East Africa [17]. This figure shows genetic evidence documenting much later migrations out of Africa, only about 50,000 years ago [17]. These migrations lead to the spread of modern humans (Homo sapiens) throughout the world, and, as they spread, they largely replaced other human species, such as Neanderthals, whose ancestors had migrated from Africa 1.8 million years ago. This is the migration which is relevant for understanding the present-day patterns of skin color.

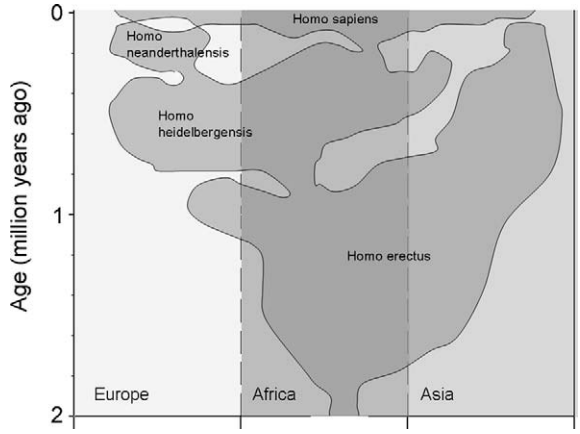

Fig. 1. One possible model of the origin of our species (adapted from Ref. [16]).

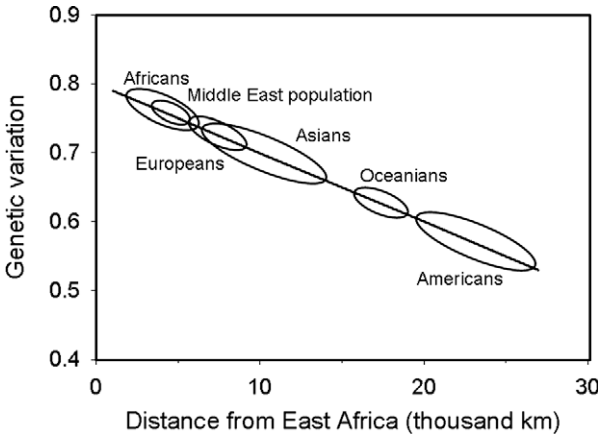

Fig. 2. Genetic variation versus distance from East Africa [17].

3. Hypotheses for skin darkening

At least six hypotheses have been proposed for skin darkening: (1) protection of sweat glands and cutaneous blood vessels, (2) protection against skin cancer, (3) protection against vitamin D overproduction, (4) camouflage, (5) combating microorganisms, and (6) protection of vital structures and molecules such as folates in the blood.

3.1. Protection of sweat glands and cutaneous vasculature

The strong African sun can easily damage sweat glands and blood vessels in a naked skin. Thus, thermoregulation will be impaired, and development of a dark, protective skin color may have been inevitable [18]. Fig. 3 shows the characteristics of different human skin types [19]. Before it gets burnt, dark skin tolerates several times more solar radiation than light skin does [20,21]. The

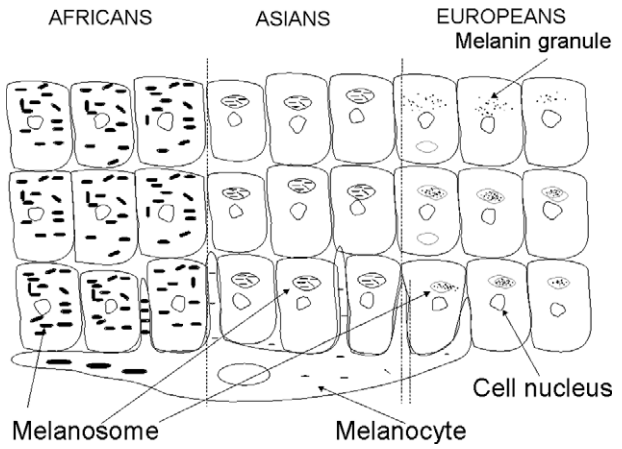

Fig. 3. Different skin types (adapted from Ref. [19]). Human skin of all types have the same total number of melanocytes, but the number, size, aggregation and distribution of melanosomes within the keratinocytes vary. Melanosomes in keratinocytes of dark skin are large, heavily pigmented and distributed individually, whereas those in keratinocytes of Caucasian skin are smaller, have less melanin and distributed in clusters. More melanosomes are in dark skin.

melanin is produced by melanocytes in the basal layer of the epidermis, from where it moves upwards as the basal cells divide and migrate to the stratum corneum, and, thus, protects all layers of the skin, as well as the blood vessels under it against sun damage [21–23]. However, it is a paradox that dark skin absorbs more solar radiation and gets warmer than light skin does [24].

3.2. Skin cancer protection

The hypothesis that the main purpose of a dark skin color is to protect against skin cancer is rather unlikely, because skin cancer usually develops late in human life, after the reproductive age [25–27], which was low for early humans [28]. The incidence rate of all types of skin cancer increases rapidly with age [25–27].

Furthermore, it is possible that older individuals may help to increase the overall success of reproduction of their kin with their knowledge or by providing for them. Individuals who remain alive and escape skin cancer would be able to help their family. This might lead to some selection for resistance against developing skin cancer.

3.3. Protection against vitamin D overproduction

In 1967 Loomis proposed that a dark skin color had developed to prevent against vitamin D intoxication [29]. Already at that time it was known that solar radiation, notably at equatorial fluence rates, was an extremely efficient vitamin D producer and that high doses of vitamin D might have toxic effects [29]. This proposal is wrong because once previtamin D_3 is formed from 7-dehydrocholesterol in the skin, it either can isomerize to vitamin D_3 or absorb UVB radiation and isomerize into biologically inactive products, out of which lumisterol is the most abundant one [30]. For this reason vitamin D intoxication from sun-exposure has never been observed [31].

3.4. Camouflage

Camouflage plays a vital role for the survival of some animals, and for this purpose melanin is used [32]. Melanin pigments can get darker through a reversible, photochemical process or through spatial rearrangements of melanin structures. In human skin such rapid darkening is called immediate pigment darkening, IPD. It takes place within minutes upon exposure to UVA and visible radiation, reaches a maximum within 1–2 h and then fades [33–37]. IPD is most pronounced in individuals with a dark baseline (constitutive) pigmentation [34]. No photoprotective effects of the IPD, such as less skin cancers or sunburns, have been observed [36]. The evolutionary significance and the biological role of such darkening for humans can at present only be speculated on [35–37]. The early humans would have had to rely on concealment during hunting [38]. Maybe IPD acted as camouflage and led to decreased visibility in the sun?

3.5. Defense against microorganisms

Melanin producing cells may have immunological functions, and some scientists think that melanocytes should be regarded as true members of the immune system [39]. Bacteria and fungi are more abundant and troublesome in tropical regions than in cold regions. This supports the defense hypothesis, since people living in tropical regions usually have more melanin and a darker skin color than people living in colder regions at high latitudes [39]. Studies of populations living at low latitudes and high altitudes with a cold climate, as in Tibet, may help to evaluate this hypothesis.

3.6. Protection of folates in the blood

The so-called "folate-hypothesis" for darkening of skin was proposed in 1978 by Branda and Eaton [40]. Folates are vitamin B derivatives of utmost importance in DNA synthesis; i.e. in the biosynthesis of pyrimidines. Folate deficiency leads to infertility in men and neural tube defects of babies and other disorders of evident evolutionary significance [41–46]. Since a substantial fraction of the folates in humans are flowing in the blood, either in serum or in red cells, and since folates absorb and can be degraded by UVB radiation, and since blood is flowing in dermal microvessels that can be reached by solar UVB, brown or dark skin may have been developed to protect folates [8,40,47]. Some, but not all, in vivo investigations aimed at elucidating this question, indicate that intense solar radiation or artificial UVB radiation as used in the treatment of psoriasis, can lead to folate degradation, similar to what is found in test tubes [48,49]. Since folate antagonists, such as methotrexate, are used in cancer therapy with the hope that they can slow down tumor growth selectively [50], we have proposed that the observed variation of internal cancer prognosis with season of diagnosis can be related to folate photodegradation in the summer season [41]. Thus, prognosis is best when treatment starts in summer or autumn [51–54]. However, we found no decrease of folate levels in summer in Norway, and proposed that the prognosis was more likely to be related to vitamin D levels, which are significantly larger in the summer season than in the winter season [51,55].

More work, both measurements of penetration of UV and visible light to dermal vessels of dark and light skin and studies of folate photobiology are needed before the "folate hypothesis" can be finally evaluated.

4. Hypothesis of skin lightening

From the fact that skin lightening has occurred several times in the evolutionary history of humans [8], we can conclude that this process is an important factor in evolution. Four main hypotheses for skin lightening will be reviewed: that of the hypothesis of sexual selection, that of adaptation to colder climates through changes of heat exchange with the environment, that of need of more efficient vitamin D photosynthesis at high latitudes and that of genetic drift.

4.1. Sexual selection and sexual dimorphism in human skin color

In most populations women are slightly lighter than men, but the evolutionary purpose of such difference is unknown [8,56–58], few explanations have been proposed. One possible explanation of sexual dimorphism in skin pigmentation may be that vitamin D deficiency has larger negative evolutionary consequences for women than for men, due to their greater need for calcium and vitamin D during pregnancy and lactation [8,59].

Another possible explanation may be that men seem to prefer women with a light skin color [60], which can be regarded as a sign of youth and fertility [58,61]. Skin gets slightly darker upon ageing, notably during puberty [56,62].

A third hypothesis is that women's lighter skin can be regarded as a form of infantile mimicry [61,63,64]. Because light skin characterizes the early infant stage of primates, it may have become a visual cue that triggers appropriate adult behaviour toward infants, i.e., decreased aggressiveness and increased desire to provide care and protection.

These hypotheses are not mutually exclusive. Once women had acquired a visibly lighter skin, for whatever reason (greater need for vitamin D, infantile mimicry, etc.), men would have used this visual cue to identify women, particularly when searching for potential mates. Mate search would therefore be biased toward the lightest-skinned women. Although initially created by natural selection, the sex difference in skin color may thus have been further accentuated by sexual selection. This scenario is supported by the absence of a single physiological cause. Women are lighter-skinned not only because they have less melanin but also because they have less blood in the outer layers of the skin [65,66]. Selection may have acted via paleness, rather than solely via vitamin D production.

Both men and women seem to use skin color for sex identification. Subjects can distinguish a man's face from a woman's face even if both images are blurred and offer no other cue than skin tone. A key detail seems to be the contrast between the pigmentation of the face and that of the lips and eyes [67–69]. This visual cue may also influence sexual preferences. Women prefer darker male faces more during the oestrogen-dominant phase of their menstrual cycle than during the progesterone-dominant phase [70].

Variations in human skin color have been correlated to natural selection (latitude, UV radiation) and sexual selection (male mortality rates, incidence of polygyny, female participation in food gathering), and have been described in the literature [60,66,71]. Human skin color may sometimes correlate more with the incidence of polygyny than with latitude [71]. The association between very dark skin and low latitude exists mainly when polygynous societies are found at low latitudes, such as in sub-Saharan Africa [60,71]. Thus, just as weaker sexual selection may explain the unusually dark skin of sub-Saharan agricultural peoples, stronger sexual selection may explain the unusually light skin of northern and eastern Europeans, as well as other highly visible color traits [66,72].

In fact, already Darwin discussed the sexual selection hypothesis [58,73]. This hypothesis posits that human skin color results from an equilibrium between natural selection forced by solar UV (sunburn, skin cancer, vitamin D deficiency, etc.) and sexual selection by men for lighter skinned women [74].

4.2. Adaptation to colder climates

When humans migrated away from equatorial area they came into colder climates. Did skin color play any role in this connection? It has been reported anecdotally from the Korean War and from Alaska that dark people are more prone to get frostbites than light people [75]. This was supposed to be caused by a higher emission of heat from dark than from light skin. According to one of the laws of physics a high absorption coefficient (dark skin) is linked to a high emissivity. Skin color would be important if human skin emitted light or infrared radiation up to a wavelength of about 2 μm. For these wavelengths dark skin has a higher absorption coefficient than light skin [76]. However, for a skin temperature of 32 °C, Wien's law of displacement says that the wavelength of maximal emission (λ_{max}) should be: $\lambda_{max}\,(\mu m) \approx 2900\ (\mu m \cdot K)/T\,(K) \approx 9.5\ \mu m$. Around this wavelength dark and light skin have similar absorption coefficients [77,78]. Thus, after being heated to skin temperatures, a kettle painted white loses its heat as fast a kettle painted black [79]. Even more than that, up to 2 μm dark skin will absorb more radiation from the environment and, therefore, keep the heat better than light skin. As far as we know, light and dark skin are similar with respect to vascularisation. Thus, there is weak evidence for this hypothesis for skin lightening.

4.3. The vitamin D hypothesis for skin lightening

Neanderthals probably had a light skin [80], and were better suited for a cold and challenging climate at the end of the last ice age than the incoming Cro-Magnons, our ancestors [81]. Neanderthals had, on average, larger brain sizes than present-day humans but not than contemporaneous modern humans, such as Cro-Magnons [10,82]. They had a larger ratio of body mass to body surface, which would reduce heat loss [81]. In the 1800s Rudolf Virchow introduced the possibility that Neanderthals might have suffered from rickets. The hypothesis that they died out because of vitamin D deficiency was supported by Ivanhoe in 1970s [83]. However, later several other fossils of Neanderthals have been analyzed and it has been concluded that they seem to be relatively healthy [84]. However, evidences from stable isotope ratios suggest limited intake of fish, but not of animal meat [85–87]. In contrast to fat fish, meat of animals contain almost no vitamin D [88]. The reasons why the Neanderthals disappeared remain a mystery. The Cro-Magnon people who replaced the Neanderthals were migrants from further south. This suggests that they would, at least initially, have had darker skin than the Neanderthals. This should have limited their vitamin D production from UVB relative to that of the Neanderthals. However, their diet was probably different from that of Neanderthals. Salmon bones, paintings of Salmon, trout, and pike in Cro-Magnon caves, indicate that fish was eaten [89,90]. Fatty fish, such as salmon and trout, are rich in vitamin D [91]. Fishing nets, fish hooks, rafts and canoes were invented by Cro-Magnon. This suggests that fish was regularly eaten.

A parallel observation with the disappearance of the Neanderthals, is that the Nordic people disappeared from West Greenland in a cold period (1350–1450), and their bones are also said to bear signs of vitamin D deficiency [92–94].

If we assume that vitamin D does not play any role in the development of human skin color, neither white nor dark people in the world would suffer from vitamin D deficiency. In contrast to this, a lot of people are vitamin D deficient, especially African Americans (even in southern Arizona) [95], aboriginal people in Canada [96], Greenlanders in Denmark [97], immigrants from Pakistan, Turkey and Somalia in Norway [98], etc. Dark skin needs about six times more UVB than light skin to generate a given amount of vitamin D [99,100]. In our opinion the vitamin D hypothesis is the most likely hypothesis, although, still there is no consensus about it.

4.4. Genetic drift

Another hypothesis for skin lightening is that genes that influence variation in skin and hair pigmentation are only under strong selection close to the equator, so selection is relaxed in human

populations living at higher latitudes [21,101,102]. Consequently, just by chance, there were changes in the allele frequencies of genes underlying skin pigmentation that happened to produce lighter skin in some populations. This hypothesis would predict the existence of some groups with light skin away from the equator but also some groups who maintain a dark skin (more variation in skin color).

5. The genetics of skin color

The genes controlling human skin color act mainly on melanin production and distribution [102,103]. Many genes are involved, some of them being recently discovered [101–109]. For the original, dark skin color, a functional melanocortin 1 receptor, MC1R, seems to be essential [110]. Africans generally have the wild type of the gene coding for MC1R [105]. When melanocortin binds to MC1R on melanocytes, it stimulates the production of two forms of melanin, eumelanin and pheomelanin, and determines the balance between them [101,104,105]. The MCIR gene has a wide range of alleles in non-tropical populations, particularly among Europeans, but these alleles mainly affect hair color. Only red hair is associated with a visible reduction in skin pigmentation [104]. Thus, most of Japanese and Inuits have the Arg163Gln variant of the gene, while red haired people have a number of other variants, such as Arg151Cys and Arg160Trp [101]. The ASIP gene may play a shared role in shaping light and dark pigmentation across the world [104]. A number of genes seem to be involved in the development of light skin (Fig. 4): MYO5A, DTNBP1, TYRP1, SLC24A5 and KITLG in Europeans [107,111–113], DCT, KITLG, EGFR, DRD2 in Asians [102,113]. SLC24A5 accounts for 25–38% of the difference between African and European skin color [112]. Genetic results support the hypothesis that skin pigmentation has not evolved neutrally in human species, but rather that populations "out of Africa" have undergone positive selection for skin pigmentation (for a review, see Ref. [114]). The allelic changes at the AIM1 (SLC45A2) gene are dated to around 11,000 BP among European populations [115]. Some alleles causing light skin are shared across Europe and East Asia, and some are specific to either Europe or East Asia [102,104,106,111,114,116,117]. So the two evolutionary trajectories are not entirely independent, but not entirely shared either.

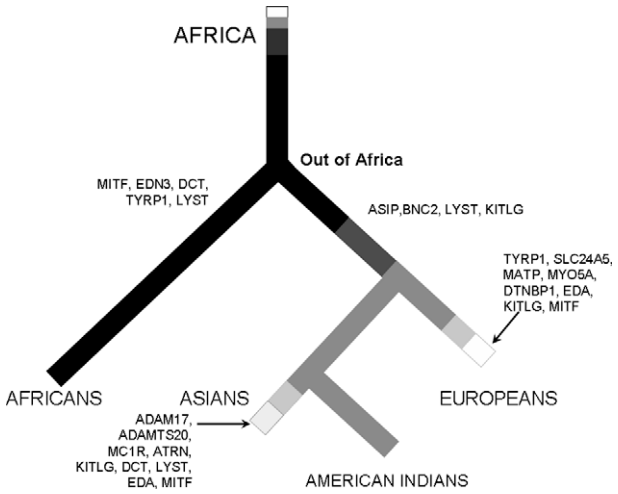

Fig. 4. Evolutionary-genetic model of human skin pigmentation (adapted from Refs. [21,114]).

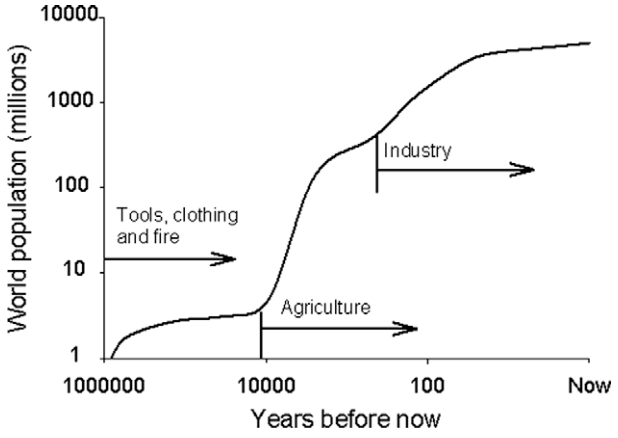

Fig. 5. The growth of human populations reveals population surges (adapted from Refs. [145,146]).

6. The introduction of agriculture and its relation to vitamin D and the Indo-European language

Agriculture was developed from 12,000 to 10,000 years ago [118], and led to a large expansion of the population: a given area of land can feed several times more people through agriculture than through gathering, hunting and fishing (Fig. 5). Keeping domestic animals improved the situation further, since it gave easier access to meat and made milk an alternative, nourishing food [28]. When the population expanded, it rapidly spread in many directions. The wave of people brought with them, not only agriculture and the habit of milk drinking and development of lactose tolerance [28], but also the Indo-European languages [119,120]. About five thousand years ago the wave of agriculture came to the Baltics, to Scandinavia and to England [119]. In England changes of the isotope ratio of ^{12}C–^{13}C have been found in bones from between 5500 and 5200 years before now. This shows that the food changed rapidly away from fish as an important food source [121]. Due to the Gulf Stream current northern Europe can sustain growth of barley and similar grains. All this together led to a rapid development of the lactose tolerance gene [28,122,123], and to light skin. The agricultural food was an insufficient source of vitamin D, and the fluence rate of UVB in the solar radiation was too low to produce enough vitamin D in dark skin. Development of agriculture has occurred in several places, and did not necessarily lead to skin lightening if the ambient UVB level was sufficiently high to allow adequate vitamin D synthesis. Cold climates and high latitudes would speed up the need for skin lightening.

It is possible that agriculture played a role in the evolution of light skin in modern humans, but the main objection to this hypothesis is its recency: A few thousands of years may not be enough for such genetic changes.

7. Health effects of vitamin D

A large number of health effects of an adequate level of vitamin D are now being revealed [124–134]. Many of them are of evolutionary relevance, and we will briefly list the most important ones: The incidence rates and the severity of coronary heart disease are reduced, the rates of diabetes, multiple sclerosis, rheumatoid arthritis, Crohn's disease, and several other immune deficiency-related diseases, such as defense against influenza, are reduced [124,126,131,134–138]. Furthermore, the incidence rates of most internal cancers are reduced, while their prognoses are improved, by a good vitamin D status [127–129,133,139–143]. Rickets and osteomalacia are practically abolished [125]. Finally, the risk of

getting children with schizophrenia is significantly reduced [130,132].

Yupiks and Inuits (Eskimo), who live far north, have a darker skin than Europeans. Some of them live inland, but may have a history of coastal habitation. Their original diet was traditionally rich in fish which contains a high level of vitamin D. It is believed that their diet compensated for the low fluence rates of vitamin D producing UVB radiation, and, therefore, there was no need for skin lightening in Eskimos. However, modern Inuits living on a westernized low vitamin D diet instead of tradition diet (rich vitamin D diet) suffer from vitamin D deficiency [97].

8. Skin lightening and skin darkening

Does development of light skin from dark skin and dark skin from light skin occur at similar rates? The fact that South American Indians, living in equatorial regions have a much lighter skin color than Africans living at the same latitude may offer a road towards an answer. The South American Indians came from high latitudes about 15,000 years ago [144]. During this time no extreme skin darkening has occurred. As discussed above, light skin was developed around 11,000 years ago [115]. Does this show that skin lightening is a faster and, from the evolution point of view, a more important process than skin darkening? Does it show that avoidance of vitamin D deficiency is more important than avoidance of skin cancer?

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References

[1] S.C. Anton, Climatic influences on the evolution of early Homo?, Folia Primatol (Basel) 78 (2007) 365–388.
[2] M.A. Maslin, B. Christensen, Tectonics, orbital forcing, global climate change, and human evolution in Africa: introduction to the African paleoclimate special volume, J. Hum. Evol. 53 (2007) 443–464.
[3] M. Brunet, F. Guy, D. Pilbeam, D.E. Lieberman, A. Likius, H.T. Mackaye, M.S. Ponce de Leon, C.P. Zollikofer, P. Vignaud, New material of the earliest hominid from the Upper Miocene of Chad, Nature 434 (2005) 752–755.
[4] C.P. Zollikofer, M.S. Ponce de Leon, D.E. Lieberman, F. Guy, D. Pilbeam, A. Likius, H.T. Mackaye, P. Vignaud, M. Brunet, Virtual cranial reconstruction of Sahelanthropus tchadensis, Nature 434 (2005) 755–759.
[5] B.J. Bradley, Reconstructing phylogenies and phenotypes: a molecular view of human evolution, J. Anat. 212 (2008) 337–353.
[6] M. Brunet, F. Guy, D. Pilbeam, H.T. Mackaye, A. Likius, D. Ahounta, A. Beauvilain, C. Blondel, H. Bocherens, J.R. Boisserie, L. De Bonis, Y. Coppens, J. Dejax, C. Denys, P. Duringer, V. Eisenmann, G. Fanone, P. Fronty, D. Geraads, T. Lehmann, F. Lihoreau, A. Louchart, A. Mahamat, G. Merceron, G. Mouchelin, O. Otero, P.P. Campomanes, M.P. De Leon, J.C. Rage, M. Sapanet, M. Schuster, J. Sudre, P. Tassy, X. Valentin, P. Vignaud, L. Viriot, A. Zazzo, C. Zollikofer, A new hominid from the Upper Miocene of Chad Central Africa, Nature 418 (2002) 145–151.
[7] B.G. Richmond, W.L. Jungers, Orrorin tugenensis femoral morphology and the evolution of hominin bipedalism, Science 319 (2008) 1662–1665.
[8] N.G. Jablonski, G. Chaplin, The evolution of human skin coloration, J. Hum. Evol. 39 (2000) 57–106.
[9] P.R. Ehrlich, Human Natures: Genes, Cultures, and the Human Prospect, Island Press, Washington, DC, 2000.
[10] H.M. McHenry, K. Coffing, Australopithecus to homo: Transformations in body and mind, Ann. Rev. Anthropol. 29 (2000) 125–146.
[11] A.I. Ibraimov, The evolution of body heat, conductivity, skin and brain size in human, J. Hum. Ecol. 21 (2007) 95–103.
[12] D.A. Nelson, S.A. Nunneley, Brain temperature and limits on transcranial cooling in humans: quantitative modeling results, Eur. J. Appl. Physiol Occup. Physiol. 78 (1998) 353–359.
[13] P.E. Wheeler, The evolution of bipedality and loss of functional body hair in hominids, J. Hum. Evol. 13 (1984) 91–98.
[14] M. Pagel, W. Bodmer, A naked ape would have fewer parasites, Proc. Biol. Sci. 270 (suppl. 1) (2003) S117–S119.
[15] F.A. Reed, S.A. Tishkoff, African human diversity, origins and migrations, Curr. Opin. Genet. Dev. 16 (2006) 597–605.
[16] C. Stringer, Human evolution: out of Ethiopia, Nature 423 (2003) 692–695.
[17] F. Prugnolle, A. Manica, F. Balloux, Geography predicts neutral genetic diversity of human populations, Curr. Biol. 15 (2005) R159–R160.
[18] A.L. Zihlman, B.A. Cohn, The adaptive response of human skin to the savanna, Hum. Evol. 33 (1988) 397–409.
[19] G.S. Barsh, What controls variation in human skin color?, PLoS Biol. 1 (2003) E27.
[20] N. Kollias, Y.H. Malallah, H. al-Ajmi, A. Baqer, B.E. Johnson, S. Gonzalez, Erythema and melanogenesis action spectra in heavily pigmented individuals as compared to fair-skinned Caucasians, Photodermatol. Photoimmunol. Photomed. 12 (1996) 183–188.
[21] E.J. Parra, Human pigmentation variation: evolution genetic basis and implications for public health, Am. J. Phys. Anthropol. Suppl. 45 (2007) 85–105.
[22] H.F. Blum, Does the melanin pigment of human skin have adaptive value? An essay in human skin have adaptive value? An essay in human ecology and the evolution of race, Q. Rev. Biol. 36 (1961) 50–63.
[23] A.L. Kadekaro, R.J. Kavanagh, K. Wakamatsu, S. Ito, M.A. Pipitone, Z.A. bdel-Malek, Cutaneous photobiology. The melanocyte vs. the sun: who will win the final round?, Pigment Cell Res 16 (2003) 434–447.
[24] J.M. Hanna, D.E. Brown, Human heat tolerance: an anthropological perspective, Ann. Rev. Anthropol. 12 (1983) 259–284.
[25] S.A. Holme, K. Malinovszky, D.L. Roberts, Changing trends in non-melanoma skin cancer in South Wales 1988–1998, Brit. J. Dermatol. 143 (2000) 1224–1229.
[26] A.V. Giblin, J.M. Thomas, Incidence mortality and survival in cutaneous melanoma, J. Plast. Reconstr. Aesthet. Surg. 60 (2007) 32–40.
[27] A. Katalinic, U. Kunze, T. Schafer, Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumour stages and localization (epidemiology of skin cancer), Brit. J. Dermatol. 149 (2003) 1200–1206.
[28] C.E. Finch, The Human Life Span: Present, Past, and Future. The Biology of Human Longevity, Academic Press, Burlington, 2007.
[29] W.F. Loomis, Skin-pigment regulation of vitamin-D biosynthesis in man, Science 157 (1967) 501–506.
[30] M.F. Holick, J.A. MacLaughlin, S.H. Doppelt, Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator, Science 211 (1981) 590–593.
[31] M.F. Holick, Photobiology of Vitamin D, in: F. David, J.W. Pike, H.G. Francis (Eds.), Vitamin D (2), Academic Press, Burlington, 2005, pp. 37–45.
[32] A. Slominski, D.J. Tobin, S. Shibahara, J. Wortsman, Melanin pigmentation in mammalian skin and its hormonal regulation, Physiol. Rev. 84 (2004) 1155–1228.
[33] G.E. Costin, V.J. Hearing, Human skin pigmentation: melanocytes modulate skin color in response to stress, FASEB J. 21 (2007) 976–994.
[34] A.R. Young, Acute effects of UVR on human eyes and skin, Prog. Biophys. Mol. Biol. 92 (2006) 80–85.
[35] H. Honigsmann, G. Schuler, W. Aberer, N. Romani, K. Wolff, Immediate pigment darkening phenomenon. A reevaluation of its mechanisms, J. Invest. Dermatol. 87 (1986) 648–652.
[36] H. Beitner, Immediate pigment-darkening reaction, Photodermatology 5 (1988) 96–100.
[37] C. Routaboul, A. Denis, A. Vinche, Immediate pigment darkening: description, kinetic and biological function, Eur. J. Dermatol. 9 (1999) 95–99.
[38] R.B. Cowles, Black pigmentation: adaptation for concealment or heat conservation?, Science 158 (1967) 1340–1341.
[39] J.A. Mackintosh, The antimicrobial properties of melanocytes, melanosomes and melanin and the evolution of black skin, J. Theor. Biol. 211 (2001) 101–113.
[40] R.F. Branda, J.W. Eaton, Skin color and nutrient photolysis: an evolutionary hypothesis, Science 201 (1978) 625–626.
[41] A.H. Steindal, A.C. Porojnicu, J. Moan, Is the seasonal variation in cancer prognosis caused by sun-induced folate degradation?, Med Hypothes. 69 (2007) 182–185.
[42] U. Mathur, S.L. Datta, B.B. Mathur, The effect of aminopterin-induced folic acid deficiency on spermatogenesis, Fertil. Steril. 28 (1977) 1356–1360.
[43] B. Landau, R. Singer, T. Klein, E. Segenreich, Folic acid levels in blood and seminal plasma of normo- and oligospermic patients prior and following folic acid treatment, Experientia 34 (1978) 1301–1302.
[44] M.J. Cosentino, R.E. Pakyz, J. Fried, Pyrimethamine: an approach to the development of a male contraceptive, Proc. Natl. Acad. Sci. USA 87 (1990) 1431–1435.
[45] J.M. Scott, Reduced folate status is common and increases disease risk. It can be corrected by daily ingestion of supplements or fortification, Novartis. Found. Symp. 282 (2007) 105–117.
[46] T. Forges, P. Monnier-Barbarino, J.M. Alberto, R.M. Gueant-Rodriguez, J.L. Daval, J.L. Gueant, Impact of folate and homocysteine metabolism on human reproductive health, Hum. Reprod. Update. 13 (2007) 225–238.
[47] N.G. Jablonski, G. Chaplin, Skin deep, Sci. Am. 287 (2002) 74–81.
[48] M.K. Off, A.E. Steindal, A.C. Porojnicu, A. Juzeniene, A. Vorobey, A. Johnsson, J. Moan, Ultraviolet photodegradation of folic acid, J. Photochem. Photobiol. B 80 (2005) 47–55.
[49] A.H. Steindal, A. Juzeniene, A. Johnsson, J. Moan, Photodegradation of 5-methyltetrahydrofolate: biophysical aspects, Photochem. Photobiol. 82 (2006) 1651–1655.
[50] F.M. Huennekens, The methotrexate story: a paradigm for development of cancer chemotherapeutic agents, Adv. Enzyme Regul. 34 (1994) 397–419.

[51] T.E. Robsahm, S. Tretli, A. Dahlback, J. Moan, Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway), Cancer Causes Control 15 (2004) 149–158.
[52] Z. Lagunova, A.C. Porojnicu, A. Dahlback, J.P. Berg, T.M. Beer, J. Moan, Prostate cancer survival is dependent on season of diagnosis, Prostate 67 (2007) 1362–1370.
[53] J. Moan, A. Porojnicu, Z. Lagunova, J.P. Berg, A. Dahlback, Colon cancer: prognosis for different latitudes, age groups and seasons in Norway, J. Photochem. Photobiol. B 89 (2007) 148–155.
[54] A. Porojnicu, T.E. Robsahm, J.P. Berg, J. Moan, Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: a possible role of sun-induced Vitamin D, J. Steroid Biochem. Mol. Biol. 103 (2007) 675–678.
[55] A.C. Porojnicu, T.E. Robsahm, A. Dahlback, J.P. Berg, D. Christiani, O.S. Bruland, J. Moan, Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role?, Lung Cancer 55 (2007) 263–270.
[56] A.K. Kalla, Ageing and sex differences in human skin pigmentation, Z. Morphol. Anthropol. 65 (1973) 29–33.
[57] L. Madrigal, W. Kelly, Human skin-color sexual dimorphism: a test of the sexual selection hypothesis, Am. J. Phys. Anthropol. 132 (2007) 470–482.
[58] K. Aoki, Sexual selection as a cause of human skin color variation: Darwin's hypothesis revisited, Ann. Hum. Biol. 29 (2002) 589–608.
[59] F.R. Perez-Lopez, Vitamin D: the secosteroid hormone and human reproduction, Gynecol. Endocrinol. 23 (2007) 13–24.
[60] P. Frost, Geographic distribution of human skin color: A selective compromise between natural selection and sexual selection?, Hum Evol. 9 (1994) 141–153.
[61] P.L. van den Berghe, P. Frost, Skin color preference, sexual dimorphism and sexual selection: a case of gene culture co-evolution?, Ethnic Racial Stud 9 (1986) 87–113.
[62] Y. Miyamura, S.G. Coelho, R. Wolber, S.A. Miller, K. Wakamatsu, B.Z. Zmudzka, S. Ito, C. Smuda, T. Passeron, W. Choi, J. Batzer, Y. Yamaguchi, J.Z. Beer, V.J. Hearing, Regulation of human skin pigmentation and responses to ultraviolet radiation, Pigment Cell Res. 20 (2007) 2–13.
[63] R.D. Guthrie, Evolution of human threat display organs, Evol. Biol. 4 (1970) 257–302.
[64] P. Frost, Human skin color: a possible relationship between its sexual dimorphism and its social perception, Perspect. Biol. Med 32 (1988) 38–58.
[65] E.A. Edwards, S.Q. Duntley, The pigments and color of living human skin, Am. J. Anat. 65 (1939) 1–33.
[66] P. Frost, Sexual selection and human geographic variation, J. Cult. Evol. Psychol. (2008) 26–48.
[67] R. Russell, Sex, beauty, and the relative luminance of facial features, Perception 32 (2003) 1093–1107.
[68] R. Russell, P. Sinha, I. Biederman, M. Nederhouser, Is pigmentation important for face recognition? Evidence from contrast negation, Perception 35 (2006) 749–759.
[69] M.J. Tarr, D. Kersten, Y. Cheng, B. Rossion, It's pat! sexing faces using only red and green, J. Vision 1 (2001) 337a.
[70] P. Frost, Preference for darker faces in photographs at different phases of the menstrual cycle: preliminary assessment of evidence for a hormonal relationship, Percept. Mot. Skills 79 (1994) 507–514.
[71] J.T. Manning, P.E. Bundred, F.M. Mather, Second to fourth digit ratio sexual selection and skin color, Evol. Hum. Behav. 25 (2004) 38–50.
[72] P. Frost, European hair and eye color: a case of frequency-dependent sexual selection?, Evol Hum. Behav. 27 (2006) 85–103.
[73] C. Darwin, The Descent of Man, Murray, London, 1871.
[74] P. Frost, Human skin-color sexual dimorphism: a test of the sexual selection hypothesis, Am. J. Phys. Anthropol. 133 (2007) 779–780.
[75] P.W. Post, F. Daniels Jr., R.T. Binford Jr., Cold injury and the evolution of "white" skin, Hum. Biol. 47 (1975) 65–80.
[76] C.R. Simpson, M. Kohl, M. Essenpreis, M. Cope, Near-infrared optical properties of ex vivo human skin and subcutaneous tissues measured using the Monte Carlo inversion technique, Phys. Med. Biol. 43 (1998) 2465–2478.
[77] J. Steketee, Spectral emissivity of skin and pericardium, Phys. Med. Biol. 18 (1973) 686–694.
[78] B.F. Jones, A reappraisal of the use of infrared thermal image analysis in medicine, IEEE Trans. Med. Imaging 17 (1998) 1019–1027.
[79] R.A. Bartels, Do darker objects really cool faster?, Am J. Phys. 58 (1990) 244–247.
[80] C. Lalueza-Fox, H. Rompler, D. Caramelli, C. Staubert, G. Catalano, D. Hughes, N. Rohland, E. Pilli, L. Longo, S. Condemi, M. de la Rasilla, J. Fortea, A. Rosas, M. Stoneking, T. Schoneberg, J. Bertranpetit, M. Hofreiter, A melanocortin 1 receptor allele suggests varying pigmentation among Neanderthals, Science 318 (2007) 1453–1455.
[81] H. Helmuth, Body height body mass and surface area of the Neanderthals, Z. Morphol. Anthropol. 82 (1998) 1–12.
[82] C.B. Ruff, E. Trinkaus, T.W. Holliday, Body mass and encephalization in Pleistocene Homo, Nature 387 (1997) 173–176.
[83] F. Ivanhoe, Was Virchow right about Neandertal?, Nature 227 (1970) 577–579.
[84] M. Kricun, J. Monge, A. Mann, G. Finkel, M. Lampl, J. Radovic, The Krapina Hominids. A Radiographic Atlas of the Skeletal Collection, Croatian Natural History Museum, Zagreb, 1999.
[85] M.P. Richards, P.B. Pettitt, E. Trinkaus, F.H. Smith, M. Paunovic, I. Karavanic, Neanderthal diet at Vindija and Neanderthal predation: the evidence from stable isotopes, Proc. Natl. Acad. Sci. USA 97 (2000) 7663–7666.
[86] V. Balter, L. Simon, Diet and behavior of the Saint-Césaire Neanderthal inferred from biogeochemical data inversion, J. Hum. Evol. 51 (2006) 329–338.
[87] B. Bogin, L. Rios, Rapid morphological change in living humans: implications for modern human origins, Comp. Biochem. Physiol. A-Mol. Integr. Physiol. 136 (2003) 71–84.
[88] C. Lamberg-Allardt, Vitamin D in foods and as supplements, Prog. Biophys. Mol. Biol. 92 (2006) 33–38.
[89] R. Lewis, Can Salmon make a comeback?, BioScience 41 (1991) 6–10
[90] P.B. Moyle, M.A. Moyle, Introduction to fish imagery in art, Environ. Biol. Fishes 31 (1991) 5–23.
[91] Z. Lu, T.C. Chen, A. Zhang, K.S. Persons, N. Kohn, R. Berkowitz, S. Martinello, M.F. Holick, An evaluation of the vitamin D3 content in fish: Is the vitamin D content adequate to satisfy the dietary requirement for vitamin D?, J Steroid Biochem. Mol. Biol. 103 (2007) 642–644.
[92] W. Hovgaard, The Norsemen in Greenland: recent discoveries at Herjolfsnes, Geogr. Rev. 15 (1925) 605–616.
[93] H. Chick, The relation of ultra-violet light to nutrition, Lancet 220 (1932) 377–384.
[94] C. Gini, The extinction of the Norse settlements in Greenland, Acta Genet. Stat. Med. 6 (1956) 404–407.
[95] E.T. Jacobs, D.S. Alberts, J.A. Foote, S.B. Green, B.W. Hollis, Z. Yu, M.E. Martinez, Vitamin D insufficiency in southern Arizona, Am. J. Clin. Nutr. 87 (2008) 608–613.
[96] Vitamin D supplementation: Recommendations for Canadian mothers and infants, Paediatr. Child Health 12 (2007) 583-598.
[97] L. Rejnmark, M.E. Jorgensen, M.B. Pedersen, J.C. Hansen, L. Heickendorff, A.L. Lauridsen, G. Mulvad, C. Siggaard, H. Skjoldborg, T.B. Sorensen, E.B. Pedersen, L. Mosekilde, Vitamin D insufficiency in Greenlanders on a westernized fare: ethnic differences in calcitropic hormones between Greenlanders and Danes, Calcif. Tissue Int. 74 (2004) 255–263.
[98] A.A. Madar, L.C. Stene, H.E. Meyer, Vitamin D status among immigrant mothers from Pakistan, Turkey and Somalia and their infants attending child health clinics in Norway, Brit. J. Nutr. (2008) 1–7.
[99] T.L. Clemens, J.S. Adams, S.L. Henderson, M.F. Holick, Increased skin pigment reduces the capacity of skin to synthesize vitamin D3, Lancet 1 (1982) 74–76.
[100] M.F. Holick, The photobiology of vitamin D and its consequences for humans, Ann. NY. Acad. Sci. 453 (1985) 1–13.
[101] R.M. Harding, E. Healy, A.J. Ray, N.S. Ellis, N. Flanagan, C. Todd, C. Dixon, A. Sajantila, I.J. Jackson, M.A. Birch-Machin, J.L. Rees, Evidence for variable selective pressures at MC1R, Am. J. Hum. Genet. 66 (2000) 1351–1361.
[102] O. Lao, J.M. de Gruijter, D.K. van, A. Navarro, M. Kayser, Signatures of positive selection in genes associated with human skin pigmentation as revealed from analyses of single nucleotide polymorphisms, Ann. Hum. Genet. 71 (2007) 354–369.
[103] R.A. Sturm, R.D. Teasdale, N.F. Box, Human pigmentation genes: identification, structure and consequences of polymorphic variation, Gene 277 (2001) 49–62.
[104] H.L. Norton, R.A. Kittles, E. Parra, P. McKeigue, X. Mao, K. Cheng, V.A. Canfield, D.G. Bradley, B. McEvoy, M.D. Shriver, Genetic evidence for the convergent evolution of light skin in Europeans and East Asians, Mol. Biol. Evol. 24 (2007) 710–722.
[105] J.L. Rees, The melanocortin 1 receptor (MC1R): more than just red hair, Pigment Cell Res. 13 (2000) 135–140.
[106] R.A. Sturm, A golden age of human pigmentation genetics, Trends Genet. 22 (2006) 464–468.
[107] S. Myles, M. Somel, K. Tang, J. Kelso, M. Stoneking, Identifying genes underlying skin pigmentation differences among human populations, Hum. Genet. 120 (2007) 613–621.
[108] N. Izagirre, I. Garcia, C. Junquera, R.C. de la, S. Alonso, A scan for signatures of positive selection in candidate loci for skin pigmentation in humans, Mol. Biol. Evol. 23 (2006) 1697–1706.
[109] J. Han, P. Kraft, H. Nan, Q. Guo, C. Chen, A. Qureshi, S.E. Hankinson, F.B. Hu, D.L. Duffy, Z.Z. Zhao, N.G. Martin, G.W. Montgomery, N.K. Hayward, G. Thomas, R.N. Hoover, S. Chanock, D.J. Hunter, A genome-wide association study identifies novel alleles associated with hair color and skin pigmentation, PLoS. Genet. 4 (2008) e1000074.
[110] P.R. John, K. Makova, W.H. Li, T. Jenkins, M. Ramsay, DNA polymorphism and selection at the melanocortin-1 receptor gene in normally pigmented southern African individuals, Ann. NY. Acad. Sci. 994 (2003) 299–306.
[111] B.F. Voight, S. Kudaravalli, X. Wen, J.K. Pritchard, A map of recent positive selection in the human genome, PLoS. Biol. 4 (2006) e72.
[112] R.L. Lamason, M.A. Mohideen, J.R. Mest, A.C. Wong, H.L. Norton, M.C. Aros, M.J. Jurynec, X. Mao, V.R. Humphreville, J.E. Humbert, S. Sinha, J.L. Moore, P. Jagadeeswaran, W. Zhao, G. Ning, I. Makalowska, P.M. McKeigue, D. O'donnell, R. Kittles, E.J. Parra, N.J. Mangini, D.J. Grunwald, M.D. Shriver, V.A. Canfield, K.C. Cheng, SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans, Science 310 (2005) 1782–1786.
[113] C.T. Miller, S. Beleza, A.A. Pollen, D. Schluter, R.A. Kittles, M.D. Shriver, D.M. Kingsley, cis-Regulatory changes in Kit ligand expression and parallel evolution of pigmentation in sticklebacks and humans, Cell 131 (2007) 1179–1189.

[114] B. McEvoy, S. Beleza, M.D. Shriver, The genetic architecture of normal variation in human pigmentation: an evolutionary perspective and model, Hum. Mol. Genet. 2 (15 Spec No. 2) (2006) R176–R181.
[115] M. Soejima, H. Tachida, T. Ishida, A. Sano, Y. Koda, Evidence for recent positive selection at the human AIM1 locus in a European population, Mol. Biol. Evol. 23 (2006) 179–188.
[116] M. Soejima, Y. Koda, Population differences of two coding SNPs in pigmentation-related genes SLC24A5 and SLC45A2, Int. J. Legal Med. 121 (2007) 36–39.
[117] S. Alonso, N. Izagirre, I. Smith-Zubiaga, J. Gardeazabal, J.L. az-Ramon, J.L. az-Perez, D. Zelenika, M.D. Boyano, N. Smit, R.C. de la, Complex signatures of selection for the melanogenic loci TYR TYRP1 and DCT in humans, BMC Evol. Biol. 8 (2008) 74.
[118] P. Heather, The slow birth of agriculture, Science 282 (1998) 1446.
[119] R.D. Gray, Q.D. Atkinson, Language-tree divergence times support the Anatolian theory of Indo-European origin, Nature 426 (2003) 435–439.
[120] J. Adams, M. Otte, Did Indo-European languages spread before farming?, Curr Anthropol. 40 (1999) 73–77.
[121] M.P. Richards, R.J. Schulting, R.E. Hedges, Archaeology: sharp shift in diet at onset of Neolithic, Nature 425 (2003) 366.
[122] A. Beja-Pereira, G. Luikart, P.R. England, D.G. Bradley, O.C. Jann, G. Bertorelle, A.T. Chamberlain, T.P. Nunes, S. Metodiev, N. Ferrand, G. Erhardt, Gene-culture coevolution between cattle milk protein genes and human lactase genes, Nat. Genet. 35 (2003) 311–313.
[123] A. Gibbons, Human evolution. There's more than one way to have your milk and drink it too, Science 314 (2006) 1672.
[124] Y. Arnson, H. Amital, Y. Shoenfeld, Vitamin D and autoimmunity: new aetiological and therapeutic considerations, Ann. Rheum. Dis. 66 (2007) 1137–1142.
[125] J.L. Berry, M. Davies, A.P. Mee, Vitamin D, metabolism rickets, and osteomalacia, Semin. Musculoskelet. Radiol. 6 (2002) 173–182.
[126] J.J. Cannell, R. Vieth, J.C. Umhau, M.F. Holick, W.B. Grant, S. Madronich, C.F. Garland, E. Giovannucci, Epidemic influenza and vitamin D, Epidemiol. Infect. 134 (2006) 1129–1140.
[127] J.C. Fleet, What have genomic and proteomic approaches told us about vitamin D and cancer?, Nutr Rev. 65 (2007) S127–S130.
[128] C.F. Garland, W.B. Grant, S.B. Mohr, E.D. Gorham, F.C. Garland, What is the dose-response relationship between vitamin D and cancer risk?, Nutr Rev. 65 (2007) S91–S95.
[129] M.F. Holick, The vitamin D epidemic and its health consequences, J. Nutr. 135 (2005) 2739S–2748S.
[130] A. Makay-Sim, F. Feron, D. Eyles, T. Burne, J. McGrath, Schizophrenia vitamin D, and brain development, Int. Rev. Neurobiol. 59 (2004) 351–380.
[131] C. Mathieu, C. Gysemans, A. Giulietti, R. Bouillon, Vitamin D and diabetes, Diabetologia 48 (2005) 1247–1257.
[132] J.J. McGrath, F.P. Feron, T.H. Burne, A. kay-Sim, D.W. Eyles, Vitamin D3-implications for brain development, J. Steroid Biochem. Mol. Biol. 89-90 (2004) 557–560.
[133] G.E. Mullin, A. Dobs, Vitamin D and its role in cancer and immunity: a prescription for sunlight, Nutr. Clin. Pract. 22 (2007) 305–322.
[134] A. Zittermann, Vitamin D and disease prevention with special reference to cardiovascular disease, Prog. Biophys. Mol. Biol. 92 (2006) 39–48.
[135] M. Cutolo, K. Otsa, M. Uprus, S. Paolino, B. Seriolo, Vitamin D in rheumatoid arthritis, Autoimmun. Rev. 7 (2007) 59–64.
[136] J. Gilman, F. Shanahan, K.D. Cashman, Determinants of vitamin D status in adult Crohn's disease patients, with particular emphasis on supplemental vitamin D use, Eur. J. Clin. Nutr. 60 (2006) 889–896.
[137] E. Ginanjar, Sumariyono, S. Setiati, B. Setiyohadi, Vitamin D and autoimmune disease, Acta Med. Indones. 39 (2007) 133–141.
[138] E.D. Michos, M.L. Melamed, Vitamin D and cardiovascular disease risk, Curr. Opin. Clin. Nutr. Metab. Care 11 (2008) 7–12.
[139] B.K. Armstrong, A. Kricker, Sun exposure and non-Hodgkin lymphoma, Cancer Epidemiol. Biomarkers Prev. 16 (2007) 396–400.
[140] E.R. Bertone-Johnson, Prospective studies of dietary vitamin D and breast cancer: more questions raised than answered, Nutr. Rev. 65 (2007) 459–466.
[141] S. Mordan-McCombs, M. Valrance, G. Zinser, M. Tenniswood, J. Welsh, Calcium, vitamin D and the vitamin D receptor: impact on prostate and breast cancer in preclinical models, Nutr. Rev. 65 (2007) S131–S133.
[142] D.M. Freedman, A.C. Looker, S.C. Chang, B.I. Graubard, Prospective study of serum vitamin D and cancer mortality in the United States, J. Natl. Cancer Inst. 99 (2007) 1594–1602.
[143] E. Giovannucci, Y. Liu, E.B. Rimm, B.W. Hollis, C.S. Fuchs, M.J. Stampfer, W.C. Willett, Prospective study of predictors of vitamin D status and cancer incidence and mortality in men, J. Natl. Cancer Inst. 98 (2006) 451–459.
[144] T. Goebel, M.R. Waters, D.H. O'Rourke, The late Pleistocene dispersal of modern humans in the Americas, Science 319 (2008) 1497–1502.
[145] B.A. Tinsley, Technical development and colonization as factors in the long-term variation in limits to growth, Cosmic Search 2 (1980) 10–12.
[146] E.S. Deevey Jr., The human population, Sci. Am. 203 (1960) 195–204.