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The evolution of human skin colouration and its relevance to health in the modern world

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ABSTRACT
Functionally naked skin which comes in a range of colours is unique to the human species. This review summarises current evidence pertaining to the evolution of these attributes. The biggest changes in the integument occurred during the course of human evolution in equatorial Africa, under regimes of high daytime temperatures and high ultraviolet radiation (UVR). Loss of most functional body hair was accompanied by the evolution of an epidermis with a specialised stratum corneum and permanent, protective, eumelanin pigmentation. The main reason for the evolution of dark pigmentation was to protect against folate deficiency caused by elevated demands for folate in cell division, DNA repair, and melanogenesis stimulated by UVR. Dispersal out of tropical Africa created new challenges for human physiology especially because of lower and more seasonal levels of UVR and UVB outside of the tropics. In these environments, the challenge of producing a vitamin D precursor in the skin from available UVB was met by natural selection acting on mutations capable of producing varying degrees of depigmentation. The range of pigmentation observed in modern humans today is, thus, the product of two opposing clines, one favoring photoprotection near the equator, the other favoring vitamin D photosynthesis nearer the poles. Recent migrations and changes in lifestyle in the last 500 years have brought many humans into UVR regimes different from those experienced by their ancestors and, accordingly, exposed them to new disease risks, including skin cancer and vitamin D deficiency.

KEYWORDS Melanin, natural selection, vitamin D, migration, urbanisation, depigmentation

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EDUCATION

Human skin is functionally naked, sweaty, resistant to abrasion, colourful, and often deliberately decorated. This constellation of attributes makes human skin unique[1] and of great interest to comparative biologists and anthropologists. The range of colour exhibited by human skin is its most singular biological characteristic and the one of greatest social import because skin colour has been the primary trait used to classify people into races. Skin colour has been observed and studied by philosophers and scientists for over two millennia and yet there is still much about it that is not known. Research into the evolution and importance of skin pigmentation languished during much of the twentieth century because of legitimate concerns that study of the causes and ramifications of skin colour variation would be socially divisive. This situation has changed in the last twenty years partly because of the development of new genetic tools, which have allowed for rapid and wide-scale exploration of human variation. Study of variation in pigmentation also gained impetus because of the recognition that understanding and dispassionate discussion of the causes of visible human variation is important to human health and the future of societies. Here I review recent advances in knowledge of the evolution of skin pigmentation variation and the diverse effects that skin pigmentation has on health and wellbeing in the modern world.

THE EVOLUTION OF FUNCTIONAL NAKEDNESS AND ITS RELATIONSHIP TO SKIN PIGMENTATION

The evolution of skin pigmentation in humans is related to the evolution of hairlessness and enhanced sweating abilities.[2] The common ancestor of chimpanzees and humans lived about six million years ago in equatorial Africa, under conditions of high daytime temperatures and high UVR. This common ancestor probably had dark hair covering pale skin on most if its body, the condition common to catarrhine primates. The exposed skin on the face and on the dorsal surfaces of the hands and feet had active melanocytes capable of producing melanin in response to sun exposure, but unexposed skin remained unpigmented.[3] Loss of functional body hair occurred

early in the evolution of the genus Homo and was associated with the evolution of an efficient whole-body cooling system based on eccrine sweating.[3–6] Because sweating is most effective in cooling the body when there is less hair on the surface to slow evaporation, the evolution of increased density of eccrine sweat glands occurred pari passu with functional nakedness. Naked skin is more vulnerable to environmental influences, and that of humans differs from that of close but hairier primate relatives in its greater water resistance and resistance to abrasion.[1] These differences are due in part to genes related to the epidermal proteins that contribute to the barrier functions of the skin, the integrity of sweat glands, and the delicate and friable nature of body hair.[7,8] Naked skin is also more vulnerable to damage from solar radiation, including UVR,[9,10] and compensation for this came from evolution of increased thickness of the epidermis, especially the stratum corneum[1,11] and of permanent protective eumelanin pigmentation to prevent the most energetic and damaging wavelengths of UVR from penetrating the body.[3]

Melanin pigments are complex polymers that have a great capacity to absorb visible light, UVR, and ionizing radiation, and to neutralize the reactive oxygen species (ROS) created when these agents interact with skin cells.[12,13] Eumelanin is the dominant form of melanin found in human skin. It is intensely dark in its concentrated form because it absorbs broadly in the spectrum of visible light. Eumelanin polymers are intractably stable even when they are bombarded by high-energy radiation or ROS.[14,15] Ultraviolet radiation damages DNA and the constituents of cell membranes, causing a toxic cascade of events that produces ROS and disrupts normal chemical reactions in cells.[16,17] These processes are greatly attenuated by eumelanin, especially when it is present close to the surface of the skin.[18]

EVOLUTION OF PROTECTIVE EUMELANIN PIGMENTATION UNDER HIGH UVR CONDITIONS

Human skin pigmentation is highly correlated with latitude,[19–21] but is even more highly correlated (r^2=-0.93) with UVR, specifically the UV minimal erythemal dose or UVMED.[3,19,22,23] Skin pigmentation as measured by skin reflectance is more strongly correlated with UVMED than with any other single environmental factor.[22]

Many hypotheses have been advanced to account for the evolution of dark pigmentation under high UVR regimes, and these are reviewed at length elsewhere.[2] In brief, four major hypotheses proposed have described advantages under natural selection accruing from: 1) lowered mortality due to protection from sunburn and skin cancer; 2) enhancing survival through camouflage in poorly lit forested environments; 3) the antimicrobial properties of eumelanin in pathogen-rich environments; and 4) protection of folate metabolism against deficiencies caused by high UVR. Our research has focused on the last of these hypotheses.

The mostly deleterious effects of UVR on biological systems are well known.[16,24] Darkly pigmented, eumelanin-rich skin protects against much of the damage to DNA caused by UVR,[25] and is associated with much lower rates of skin cancer than lightly pigmented skin.[26–29] Heavily pigmented melanocytes are able to resume proliferation after UVB irradiation faster than lightly pigmented ones, and DNA from lightly pigmented melanocytes is more badly damaged after irradiation with increasing doses of UVB than is DNA from heavily pigmented ones.[17,27] By contrast, pheomelanin in lightly pigmented skin appears to increase the risk of oxidation stress in melanocytes. This, combined with the limited ability of pheomelanin to absorb UVR, leads to elevated skin cancer risk among light-skinned individuals.[26,30,31] The damaging effects of UVR on DNA structure are widely recognised and are associated with the initiation of skin cancers that mostly affect people toward the end or after their reproductive careers.[3,32] Cutaneous malignant melanoma is the only type with a high incidence rate among people of reproductive age, and overall incidence and mortality rates for melanoma prior to the mid-twentieth century were very low (<5 per 100,000).[33] Increases in the incidence of melanoma in the last fifty years are the result of lightly pigmented people being exposed to more intense or longer periods of sunlight and UVR[34] and experiencing more painful sunburns[35] because of migration to sunny places or recreational sun-tanning, the so-called 'vacation effect'.[36–38] These conditions were not typical of our species prior to the twentieth century, when most people moved very little during their lifetimes because they lacked the means of transportation to do so. It is difficult to quantify the relative importance of sunburns and skin cancer, specifically melanoma, as selective factors in the evolution of skin pigmentation, but available epidemiological evidence indicates that mortality of individuals of young reproductive age would have been extremely low. Thus, reduction of sunburn and melanoma risk probably contributed only to a minor extent in the evolution of darkly pigmented skin.

The deleterious effects of UVR are not limited to DNA, and it is probably the effects of UVR on folate metabolism that have been of greatest importance in the evolution of dark pigmentation in humans. The importance of folate in human development and health has been highlighted by studies demonstrating that interdiction of cell proliferation because of folate deficiency interferes with normal development, and causes birth defects. The role of folate deficiency in causing neural tube defects is now firmly established.[39–42] Folate sufficiency is also necessary for maintenance of active spermatogenesis[43,44] and in the formation of myelin

and the production of many neurotransmitters including serotonin.[45] Folate can only be obtained from foods such as green leafy vegetables, citrus fruits, and whole grains, or from supplements of the synthetic form of the vitamin, folic acid. Healthy levels of folate are difficult to maintain in the body because natural food folates are unstable, suffer from low bioavailability, and tend to break down when foods are boiled or stored.[46,47] Folate deficiencies can be caused by insufficient intake of folate, improper absorption of the vitamin from the gut, or the breakdown of folate or its main serum form, 5-methylhydrofolate (5-MTHF) by alcohol or UVR, in particular UVA.[48–50]

Ultraviolet radiation and the ROS generated by UVA lower levels of folate 5-MTHF in the body because competition for folate is intense when high UVR simultaneously stimulates multiple folate-requiring processes, including cell division, DNA repair, and melanogenesis. Reduction of levels of folate and 5-MTHF is particularly serious if the body's demand for folate is high – as in pregnancy – or if folate levels are already low because of low intake. The essential connections between folate metabolism and the evolution of dark skin pigmentation are, firstly, the relationship between UVR exposure and folate deficiency and, secondly, the relationship between UVR-induced folate deficiency and reduced fitness due to failures of normal embryogenesis and spermatogenesis.[3,51] High concentrations of melanin significantly reduce folate destruction *in vitro* through absorption and scattering of UVA.[18] Research into the UVR-mediated dynamics of folate metabolism is active and continuing, especially in the laboratory of Johan Moan of the University of Oslo.[52]

This evidence supports the theory that the major factor contributing to the evolution of dark skin pigmentation was the reduction of fitness brought about by UVR-induced folate deficiency. Supporting evidence also comes from epidemiological studies, which indicate trends associating dark pigmentation with lower rates of neural tube defects.[53–55] Much research remains to be done in this area, including further *in vivo* studies of folate metabolism in humans subjected to UVR, and prospective epidemiological studies which can further probe the relationship that skin pigmentation and dietary intake of folate have on rates of birth defects.

The importance of the maintenance of dark pigmentation under high UVR conditions has been underlined by studies of the MC1R (melanocortin 1 receptor) locus, one of several genes that contributes to skin, hair, and eye pigmentation. In modern Africans, this gene exhibits no variation, but outside of Africa it is highly variable. The absence of variation in African forms of the gene provides evidence of strong positive selection or selective sweep occurring around 1.2 million years ago[56] and the maintenance of a functional constraint on variation (purifying selection) in Africa thereafter.[57–59] The ancestral form of *MC1R*, along with probable contributions from other pigmentation genes (Shriver et al 2003,[60] Norton et al 2007[61]), makes possible the production of large amounts of eumelanin in the melanocytes of the skin and appears to have been so effective in improving health and reproductive success that people carrying it quickly outnumbered and replaced those who did not.

EVOLUTION OF DEPIGMENTATION UNDER LOW UVR CONDITIONS

The evidence that permanent dark skin pigmentation evolved as protection against the deleterious effects of UVR is overwhelming, but it does not explain the clinal distribution of increasingly lightly pigmented skin outside of the tropics. The strength of UVR, and of UVB in particular, declines greatly north of the Tropic of Cancer and south of the Tropic of Capricorn.[22,62–64] Low levels of UVR are not beneficial despite the fact that most UVR radiation is harmful. This is because UVR has one overwhelmingly positive action, photosynthesis of vitamin D_3 (cholecalciferol) in the skin by UVB.[65–67] Vitamin D_3 is made in the skin when UVR penetrates the skin and is absorbed by 7-dehydrocholesterol (7-DHC) in the epidermis and dermis to form pre-vitamin D_3. This reaction only occurs in the presence of wavelengths of 290–315 nm in the UVB range, with peak conversion occurring at 295–297 nm, and is dependent upon season and latitude, time of day, and on the amount of pigment and thickness of the skin.[68,69] The reaction becomes less efficient with advancing adult age because of age-dependent decline in 7-DHC in the skin.[70,71] Circulating levels of pre-vitamin D_3 are tightly controlled because continued sunlight exposure causes the photoisomerization of pre-vitamin D_3 to lumisterol and tachysterol.[72] Biologically active vitamin D_3 is produced by two successive hydroxylation steps in the liver and then in the kidney to form the active metabolite, $1,25(OH)_2D_3$ (calcitriol). This is the form that acts as a steroid hormone through binding to its specific intranuclear receptor, the vitamin D-receptor (VDR), and subsequently modulates the transcription of responsive genes such as that of calcium binding protein, which regulates mineral ion homeostasis.[68,73] Vitamin D is also available in low quantities in some foods, but vitamin D_3 is found in physiologically significant quantities in oily fish and liver.[74] Dietary sources of vitamin D must be converted into the biologically active form via the same hydroxylation steps undergone by cutaneously produced vitamin D_3.

The most obvious function of vitamin D in humans is in the building and maintenance of the bony skeleton. The essential connection between vitamin D status and bone health was established because vitamin D in the form of cod liver oil was found to cure nutritional rickets.[75] Vitamin D exerts its effects on bone indirectly through regulation of absorption of calcium and phosphorus from the gut, and directly modifies the activity of osteoblasts and chondrocytes, and many other non-classical target

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tissues.[65,73] The presence of VDRs in tissues of the brain, heart, stomach, pancreas, skin, gonads, in the activated T and B lymphocytes of the immune system, and many sites elsewhere in the body has heightened awareness of the varied and important roles vitamin D plays in the body. Chronic deficiencies in vitamin D have been associated recently with breast, prostate, colon, ovarian, and possibly other cancers,[76,77] and research in this area is extremely active. Low vitamin D status is also linked to impaired immune system activity, specifically Th1-mediated autoimmunity and infectious immunity[76] and to abnormal development and function of the brain.[77,78]

The theory that light skin pigmentation evolved in order to permit cutaneous vitamin D production under conditions of reduced sunlight at high latitudes is an old one that has considerable new, positive support from clinical, nutritional, epidemiological, genetic, and other observational studies.[3,81,82] The extent of vitamin D's importance to health is evidenced by the seriousness and diversity of problems related to hypovitamosis D[83–85] afflicting people throughout the life cycle. In the musculoskeletal system, nutritional rickets in children is now probably overshadowed by sarcopenia and osteomalacia in adults, the latter being silent afflictions that can lead to increased morbidity from accidental falls.[86] And, as mentioned earlier, vitamin D deficiency and insufficiency, especially beginning in infancy or childhood, are associated with increased, but still not rigorously quantified, risk of certain cancers, autoimmune and infectious diseases. The global disease burden linked to the vitamin D deficiencies caused by low UVR exposure now exceeds that connected with high UVR exposure.[87]

The clinical and observational evidence discussed above provides the setting for the probable action of natural selection. Genetic evidence now strongly supports this. Depigmentation is the result of positive selection in humans inhabiting low UVR environments, and this has been demonstrated in molecular genetic studies that indicate that lightly pigmented skin phenotypes in humans evolved multiple times and has been maintained by purifying selection.[88,89,61]

Eumelanin competes with 7-DHC for UVB photons to greatly slow production of pre-vitamin D_3 to the extent that people with lightly pigmented skin produce pre-vitamin D_3 in their skin at a rate 5–10 times faster than those with darkly pigmented skin.[3,74,90–96] This poses strict geographic limits on the distribution of darkly pigmented people outside of high UVB areas unless vitamin-D-rich foods or vitamin D supplements are consumed.[63] Thus, skin pigmentation in modern humans is the result of the action of two reciprocal clines working to promote the UVB-induced photosynthesis of pre-vitamin D3 in the skin on the one hand and prevent the damage caused by UVB and UVA on the other.[3,63]

Members of the human lineage dispersed many times independently into non-tropical latitudes, and evolved depigmented phenotypes by numerous and different genetically based means, some of which remain to be illuminated. Habitation of middle latitudes between approximately 23° and 46° with seasonally high loads of UVB favored the evolution of partially depigmented phenotypes capable of tanning.[63] Among people of European ancestry, genes related to tanning ability are similar to those related to hair colour.[97] The genetic basis of skin pigmentation now is becoming better understood, but considerable research remains to be done on the relationships between skin, hair, and eye pigmentation genes,[12,98] on the convergent evolution of skin pigmentation phenotypes including those in the New World,[99] and on rates of skin pigmentation evolution.

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