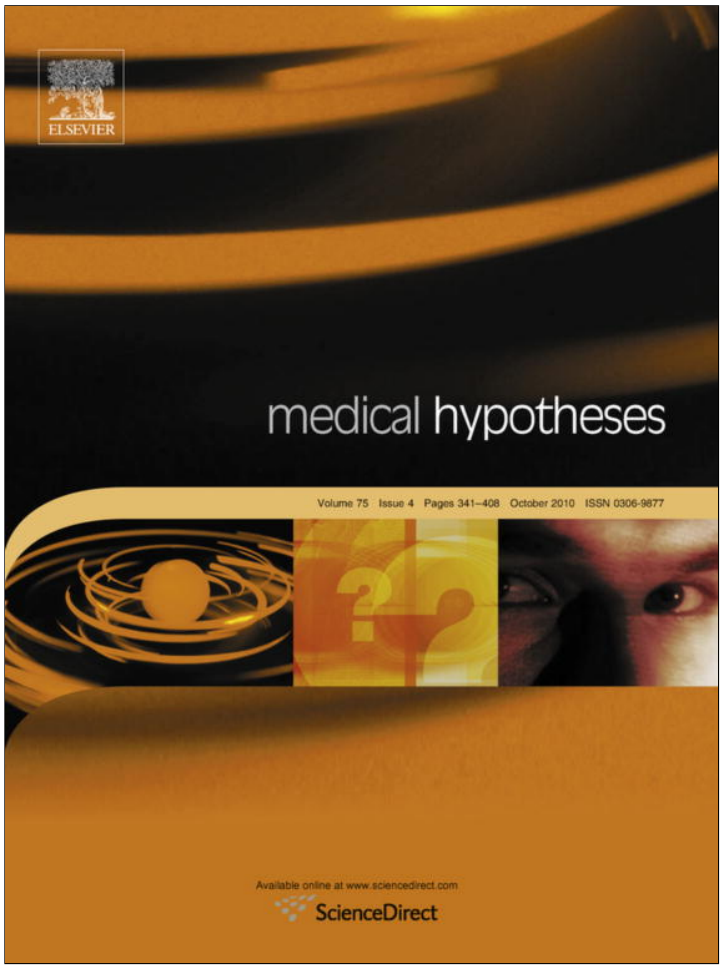

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# Diet, disease and pigment variation in humans

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SUMMARY

There are several hypotheses which explain the de-pigmentation of humans. The most prominent environmental explanation is that reduced endogenous vitamin D production due to diminished radiation at higher latitudes had a deleterious impact on fitness. This drove de-pigmentation as an adaptive response. A model of natural selection explains the high correlations found between low vitamin D levels and ill health, as vitamin D's role in immune response has clear evolutionary implications. But recent genomic techniques have highlighted the likelihood that extreme de-pigmentation in Eurasia is a feature of the last 10,000 years, not the Upper Pleistocene, when modern humans first settled northern Eurasia. Additionally the data imply two independent selection events in eastern and western Eurasia. Therefore new parameters must be added to the model of natural selection so as to explain the relatively recent and parallel adaptive responses. I propose a model of gene-culture co-evolution whereby the spread of agriculture both reduced dietary vitamin D sources and led to more powerful selection on immune response because of the rise of infectious diseases with greater population densities. This model explains the persistence of relatively dark-skinned peoples at relatively high latitudes and the existence of relatively light-skinned populations at low latitudes. It also reinforces the importance of vitamin D as a micronutrient because of the evidence of extremely powerful fitness implications in the recent human past of pigmentation.



## Introduction

Hypotheses abound for human variation in pigmentation. These models are more concerned with de-pigmentation than the state of pigmentation, which is assumed to be ancestral to our species. From inspecting the variation around the *MC1R* locus, which is necessary for the regulation of pigmentation across mammalian taxa, researchers have adduced that dark skin emerged in our lineage during the period of *Homo erectus*, approximately one million years before the present [1]. It is suggested that a dark complexion was necessary as the hominin lineage became hairless and its skin exposed to solar radiation [1]. The character of the damage wrought upon skin by sun exposure is manifold [2]. But a plausible evolutionarily oriented hypothesis is that folate deficiency induced by the destruction of its precursor, folic acid, through interaction with ultraviolet radiation was the primary selective pressure which resulted in the development of dark skin [2]. Folate deficiency has a deleterious effect on the reproductive fitness of females because of its correlation with birth defects [2]. The strength of this model in relation to other deleterious consequences of radiation exposure upon skin, such as cancers, is that it has a powerful immediate relevance to fitness, and therefore evolution. Cancers strike later in life beyond the peak of one's direct reproductive years, and the human susceptibility to cancers may actually be a consequence of evolution itself due to antagonistic pleiotropy [3]. The variation in genes known to control pigmentation in very dark-skinned populations who are otherwise not closely related tends to reflect strong selective constraints, meaning that the genetic variants which confer dark skin are prevented by negative selection from mutating to another state [2]. The genetic architecture of Melanesian pigmentation is more similar to that of Africans than that of East Asians, though genome-wide Melanesians are far closer to East Asians than Africans [4].

The question then shifts to the other half of the equation, the populations which have become de-pigmented. This is where competing models offer sharply different explanations as to the dynamics of de-pigmentation. They fall into three broad categories, those of behavioral selection, environmental adaptation, and decay of a relict trait. The behavioral hypotheses begin with the axiom that light skin is attractive to humans, whether to mothers or the opposite sex, due to innate cognitive biases [5,6]. Social or sexual selection hinges on predispositions coded into our aesthetic preferences, and the general signals of health, youth and fertility which light skin connotes. Infants and younger women tend to be more lightly complected than adults or males [5]. This is possibly due to the fact that melanin production pathways are embedded in more complex biochemical networks, and up-regulation of testosterone has the side effect of increasing production of melanin [7]. By contrast, the environmental selection models rest upon the

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conjecture that light skin is an adaptation to factors operative at higher latitudes. The most prominent hypothesis is that vitamin D synthesis is enhanced by lighter complexion, and vitamin D is an essential micronutrient, rickets being the most well known pathology engendered by its deficiency [2]. Finally, there is the model whereby lighter pigmentation is simply the byproduct of the relaxation of the adaptive constraint; once selection is no longer operative on a trait it decays and mutations break the original functionality of the genes [8]. This model points to the inference that variation in complexion among Europeans may be conceived so that more darkly pigmented individuals simply exhibit a vestigial trait.

*New findings from evolutionary genomics*

The last hypothesis now seems unlikely. Several of the genes which encode for lighter pigmentation have increased in frequency within the last 10,000 years. They do not bear the hallmarks of incremental and steady decay through mutation and drift. The exception to this may be *MC1R*. Many genes are implicated in pigment variation. Of these, *SLC24A5*, *SLC45A2* and *OCA2*, the last of which encodes for blue-brown eye color variation as well as skin pigmentation, have been shaped by powerful selective forces so that whole genomic regions are homogenized [9,10]. This could not be if constant background mutation were the dominant evolutionary parameter.

Over the past decade a new class of findings utilizing computational methods has revolutionized our understanding of the overall patterns of natural selection in the human genome [10,11]. With much larger genomic data sets in the wake of the Human Genome Project and the International HapMap Project researchers have been able to develop methods which hinge on detecting patterns of variation directly from DNA sequences. The pattern of sequence variation gives clues as to the action of disparate evolutionary forces, such as natural selection and random genetic drift. In particular, many regions of the human genome are arranged as "haplotype blocks", haplotypes being genetic sequences which carry the same cluster of variants and so indicate phylogenetic relationships. These long haplotype blocks can emerge from processes such as population bottlenecks, whereby chance dictates the rise in frequency of one genetic variant among many [12]. But another dynamic is natural selection, which can take a favored fitness-enhancing variant and push its frequency far higher, in the process allowing adjacent sections of the genome to "hitchhike" along with the selective sweep. In this fashion one genetic variant can replace many others within a population by natural selection. The most prominent case of this is the longest haplotype block in the European genome, that around the gene *LCT*, which has embedded within it a genetic variant conferring the ability to digest milk as an adult, lactase persistence [13].

These haplotype blocks prove useful in population genetics, yielding the measurement of "linkage disequilibrium" across the genome, a powerful signaler of correlated genetic variants within a population. With time, they break down; mutations along the genetic sequence of haplotypes result in their divergence from their common ancestor. After a haplotype block rises rapidly in frequency it will diversify into many lineages and lose its coherence as linkage disequilibrium decays. Thus, it can be assumed that the longer the block, and the greater the extent of linkage disequilibrium, the more recent the evolutionary genetic event which occurred to substitute one genetic variant for all the others in the population [10,11].

These assumptions produce a treasure trove of inferences. Though there are a wide range of suppositions and clues as to the evolutionary history of the human species, it is striking that many of the genetic variants which reduce the pigmentation of individuals seem to have emerged only within the last ten thousand years or so. This falsifies the hypothesis that lighter complexion arose through random walk processes of decay, as modern humans have been extant at high latitudes for tens of thousands of years [14]. On the other hand, for the hypotheses of sexual or social selection to hold, one must posit some change within the last ten thousand years which occurred simultaneously across the entire span of Eurasia to drive the evolution of lighter skin. Sexual or social selection models have great power as catchall explanations, but on their own unfortunately they often prove an empty *deus ex machina*, able to explain everything and so nothing. If historically attested aesthetic preferences are a guide to the past, one cannot explain why sexual or social selection did not result in the de-pigmentation of our species tens of thousands of years earlier, when natural environmental constraint was presumably removed as modern human bands moved north.

## Hypothesis

*Environment and culture co-evolve*

It is the last class of models, predicated on environmental forces, which offers a possible model to resolve this paradox. In its broad outlines it resembles the emergence of lactase persistence, it too being a hypothesis that hinges upon gene-culture co-evolution and interaction. The challenge is to explain why light skin evolved simultaneously in both eastern and western Eurasia after the last Ice Age. The causal chain is that reduced intensity of solar radiation entails reduced vitamin D production, which is necessary for optimal physiological function. But sunlight did not decrease after the last Ice Age. So more is needed than a simple model with latitude as its only predictive variable. Endogenous synthesis from the interaction of sunlight with skin is not the only source of vitamin D. One can also imbibe it via wild game and particularly seafood [15]. Perhaps the need for greater endogenous production of vitamin D through one's skin is a function not of the end of the Ice Age, but the rise of agriculture. This theory has a long history, but previously we did not have any understanding of when European and Asian populations lost their pigmentation, so its explanatory power was less unmistakable [16,17]. The theory has become crucial now that new genomic techniques have shown radical de-pigmentation to have occurred relatively recently. The model holds that the rise of agriculture replaced a diverse array of foods rich in micronutrients with carbohydrates comparable in calories but poor in micronutrients. The switch to a high-carbohydrate diet did have an effect on the production of digestive enzymes, so evolutionarily, we know it to be a significant transition [18]. Because of the lack of meat and fish in the diet of the new farmers, vitamin D intake would have been drastically reduced, putting all the pressure on endogenous production from exposure of skin to solar radiation. Another essential variable which might have been operative is the ubiquity of infectious disease predicated upon larger human population's resident at higher densities [19]. Pandemics and virulent endemic infectious diseases were almost certainly subsequent to the advent of agriculture and mass society. When Eurasian populations arrived in the New World, their vast suite of immunities wreaked havoc on Amerindian groups because the latter had no resistance to Old World diseases [20]. The same occurred in the Andaman Islands when Indians and the British made contact with the indigenous populations [21]. Events such as the Plague of Justinian, the introduction of malaria to Italy during the Dark Ages, and the Black Plague, show the power of pathogens in shaping human history and genomes [22]. Especially in an interconnected world with innumerable hosts the fitness effect of disease has likely been increasing, not decreasing [23]. Studies

which enumerate regions of the genome dense with signatures of adaptation consistently reinforce the fact that genes relevant to immune function have been targets of selection [10].

*The genetic architecture of pigmentation*

Over the last 10 years the genetic architecture of pigmentation has been well characterized by the genome-wide associations. The method involves comparing cases and controls within a subject population where ancestral variation is not a confound, and then noting which genetic variants are overrepresented or underrepresented within the various phenotypic classes. When the frequency of genetic variants is modest these methods have great power to detect associations. The genetics of human populations in regards to pigmentation has been an ideal target for these studies because of the relatively smaller number of genes of large effect size and their diversity across populations.

According to genome-wide association studies, about a dozen genes are responsible for almost all the skin color variation across populations. Most of the variation is due to only to three or four genes. Approximately 20–45% of the skin color difference between Sub-Saharan Africans and Europeans is controlled by variation on one gene, *SLC24A5*, with another 25% of the variation between these two groups controlled by another locus, *KITLG* [24]. With relation to *SLC24A5* all Europeans have one variant, and all Sub-Saharan Africans have the other. The African variant, which is shared with East Asians, is ancestral, while the European variant, which is distributed across West Asia and North Africa, is derived [4]. Additionally, analysis of the genetic variation around this gene with haplotype-based methods suggests that the derived European variant began to rise in frequency on the order of 6000 years ago [25]. The relatively recent date of this selection event combined with the very high frequency of its variant in Europeans, nearly 100%, leads us to infer that the factor driving natural selection must have been very powerful, generating on the order of 10% fitness increase per generation to those carrying the new variant in relation to the population average. This is a very high rate of adaptation, to the extent that individuals may have observed changes in their own populations in their lifetimes.

*SLC24A5* is also responsible for approximately the same proportion of the skin color variation in South Asians [26]. The European variant of *SLC24A5* is extant at frequencies of ~50% among South Indians and Sri Lankans, and ~80–90% in Pakistan, exhibiting a southeast–northwest cline [27]. This gene has had a rapid rise and wide sweep across western Eurasia and North Africa after the last Ice Age. Different genes also seem to have arisen in East Asia recently, conferring lighter pigmentation on those populations [6]. These data imply strongly that the relatively lightly pigmented phenotype of modern Europeans post-dates the last Ice Age, and those modern humans were relatively dark-skinned at higher latitudes for several tens of thousands of years. Only with the arrival of agriculture do the new methods suggest that genes responsible for light skin in modern populations began to rise in frequency. Such strong evidence for natural selection necessitates that we look more closely at the candidate traits which might have driven adaptation.

*Vitamin D deficiency as an inevitability of agriculture*

The physiological fitness implications of low basal vitamin D levels and its relationship to disease have been well attested in the literature. Correlations between low levels of vitamin D and elevated risk for cancer, heart disease and respiratory ailments have all been reported [28–30]. Physicians now widely recommend Vitamin D supplementation as a preventative measure against ill health [31]. Research also implies that vitamin D deficiency may be chronic in much of the modern world. The seasonal cycle of flu epidemics, concentrated during winter's low levels of sunlight, may be a result of reduced vitamin D production during that time of year [30]. The ultimate reason for this micronutrient's relationship to disease is likely that vitamin D binds to receptors which are found in immune system cells, so it may be an essential element of a robust response to infection and important in reducing the likelihood of long-term pathology [32]. The combination of a diet deficient in vitamin D and the rise of endemic infectious diseases might have been what triggered the shift toward lighter skin all across Eurasia; light skin evolved at a time when both vitamin D production was particularly critical, and dietary sources had collapsed due to a lifestyle transition [33].

*Explaining pigmentation variation, agriculture and epidemics*

The fact that different subgroups of Eurasians exhibit different genetic architectures for pigmentation implies that the necessity of adaptation to new conditions was so strong that selection drove frequencies up before gene flow could introduce one dominant variant across populations [34]. Something occurred simultaneously in the several millennia after the Ice Age to isolated populations which sent them on parallel tracks when it came to complexion. We know to a modest level of certainty that agriculture inevitably produces a suite of traits which we might term "civilization". The New World serves as a time-delayed independent experiment, whereby the stages of Old World cultural evolution were recapitulated by the Aztecs, Maya and Inca, at the time of the arrival of the Europeans [35]. But Old World populations which have gone through the Neolithic Revolution tend to have robust immune responses to its variegated suite of endemic pathogens. Colonization by Europeans in Asia and Africa did not result in population replacement [36]. It did in South Africa in the lands of the Khoisan, as it did in pre-agricultural Australia. We see then that agriculture tends to set off a chain of events which makes particular changes and responses inevitable in human societies, changes which may make members of those societies lethal to other, unaffected groups.

The essential dynamic connection between disease, diet and vitamin D synthesis also explains the fact that South Asians have been getting lighter in complexion according to the genomic data, while anthropology tells us that Tasmanians were dark-skinned. The populations of southern Australia and Tasmania are at latitudes which would imply that they should be the complexion of the peoples of the Mediterranean and East Asia, and yet the ethnography is clear that they are relatively dark [2]. In the case of the Tasmanians, their proximity to the ocean, and dependence on ocean-derived subsistence, might have resulted in greater absorption of vitamin D from their environment. Additionally, their island population is likely to have been small enough to discourage the incubation of many infectious diseases. Though much ink has been spilled on the genocide of the Tasmanians by white settlers, like Amerindians, it is likely that as many or most succumbed to infectious diseases [37]. In the case of the Australian Aboriginals their relative nudity, combined with their diverse diet, and dispersed population, might have resulted in their escaping any pressure to evolve lighter skin. Over time the decay hypothesis would hold that these populations would have grown lighter, and there is some data which suggests that southern Aboriginal populations are more lightly complected than northern ones. But, if it is true that the populations of Australia and Tasmania were descendants of the first settlers, then it brings into doubt the power of drift and decay to generate light skin over time scales of 50,000 years [38]. In India, there is contemporary evidence for vitamin D deficiency, which suggests that even at relatively low latitudes, without adequate nutrition or sufficiently light skin deficiencies can

emerge [39]. It is notable that African populations have recently been less subject to malnourishment than Asian ones, so the same drive toward lighter skin to compensate for a switch to agriculture might not have been operative on that continent as it was in the case of South and Southeast Asians because of the less advanced state of mass society [40].

Finally, there is the data from the New World. Amerindian populations are relatively genetically and phenotypically homogeneous, and though they exhibit skin color variation from north to south, these populations are neither as dark-skinned as Africans, nor as pale as the peoples of Europe or even East Asia [41,42]. Rather, they run the gamut from light to dark bronze. The current evidence is that the ancestors of these peoples arrived from Siberia, on the order of 10–20,000 years before the present [43]. These populations have had many generations to evolve light skin. One explanation for the relative uniformity of pigmentation may be that the populations were too small and did not have extant genetic variation. The fact that East Asia and Europe simultaneously forged different genetic pathways toward light skin weighs against this. Additionally, light skin is a loss mutation, the breaking of genetic function. These mutations emerge relatively frequently, as there are many more ways to lose function than gain it. Another model is that agriculture started late among these populations. On average, this is true, but it seems likely that groups in Central America have been farming at least as long as the Swedes, though the latitude is far lower [35]. A final issue is that the New World seems to have very few indigenous human-specific pathogens. This is a function of natural history: hominoids did not inhabit the New World until very recently, so there were few pathogens extant which could "jump" to *Homo sapiens* from closely related taxa [44]. Therefore, I would offer that the relative lack of endemic disease in the New World in relation to the Old World is the missing piece of the puzzle. These populations not only did not reach the same stage of agricultural intensity as those of the Old World, but their pathogen environment was relatively benign, resulting in a weaker selective pressure upon their immune systems.

### *Environmental and behavioral selection as complements*

This hypothesis does not necessarily exclude those of sexual or social selection. There is robust cross-cultural data on a preference for lighter skin, especially for women, in most agricultural societies [45]. But it seems likely that agriculturalists had no greater power to enforce their aesthetic preferences in the game of mate selection than hunter–gatherers; both lived in a Malthusian world [46]. Therefore it is more likely that behavioral selection forces derive from the environmental factors. That is, light-skinned partners may have been more robust in the face of disease, resulting in higher fitness for those individuals who assortatively mated. This model aims to explain the more recent genomic data which seem inexplicable without an exogenous environmental factor to effect change concurrently in both eastern and western Eurasia.

## Consequences

There are medical and social implications for these evolutionary genomic findings and the model that vitamin D synthesis was a target of selection through de-pigmentation relatively recently. Debate rages today over whether vitamin D levels are correlated with ill health and subdued immune response, but not causally implicated [47]. In other words, does ill health result in less efficient production of vitamin D? If so, then serum levels of the latter serve simply as a signal. If the above elaborated model is correct, that the rise of agriculture drove the shift toward lighter skin so as to increase endogenous vitamin D production in the face of disease, then the relationship is more likely to be causal. That vitamin D does have a causal relationship to physiological fitness is more likely if it seems probable that endogenous production of this micronutrient was the target for natural selection. More importantly, the signatures of selection are particularly strong, indicating the adaptive significance of de-pigmentation [48]. The new findings from evolutionary genomics also lead one to conclude that de-pigmentation was concomitant with the advent of mass society and the diseases which are fostered by large human populations. Vitamin D supplementation then would be an efficacious action in response to worries about infectious disease susceptibility in modern populations, but in particular among darker-skinned populations at higher latitudes, and those of indigenous origin from groups which have not practiced intensive agriculture. Additionally, vitamin D micronutrient supplementation should be a high priority for development aid across the world, as there is evidence that its production has been a target of powerful natural selection. Supplementation would presumably result in decreased susceptibility to illness and so reduce societal morbidity.

## Testing the model

To establish the tightness of the fit of agriculture with changes in genes more results need to obtain by extracting ancient DNA from subfossils. There have already been many successful extractions on the order of 10,000 years, so the limitations are of scale. As there have been extractions of Neandertal DNA, it is also likely that modern humans from the late Pleistocene will also be analyzed in the near future. Recent findings also imply that there were long periods of coexistence between agriculturalists and hunter–gatherers, and that the former replaced the latter genetically, as opposed to a process of cultural diffusion [49]. If Europeans and Eurasians in general, became de-pigmented because of the agricultural lifestyle, then a synthesis of genomics and archaeology should establish a very strong correlation. If the selection coefficients were on the order of 0.10 then time series data should eventually emerge to validate the arc of natural selection. A second component would be to confirm the causal relationship of low vitamin D levels with suppressed immune systems more generally. Some randomized trials have already shown health correlations, though more need to be done for widespread seasonal ailments which might affect children (and so have evolutionary consequences) such as flu [50]. If the general immunosuppressant effect of vitamin D deficiency is established medically for common infectious diseases with a focus on mortality and morbidity early in life, then that would increase the probability of selection having operated to maintain levels of vitamin D through endogenous production.

## Conflict of interest statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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