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Review

Evolutionary perspective in skin color, vitamin D and its receptor

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Evolutionary pressures due to variation in climate play an important role in shaping phenotypic variation among and within species and have been shown to influence variation in phenotypes such as body shape and size among humans.[1] Here we review the evidence for migration and change of living latitude in the evolution of skin color genes and the vitamin D receptor (VDR).

Originated by Murray in 1934,[2] the vitamin D hypothesis was revived and popularized by Loomis in 1967,[3] and more recently refined by Jablonski and Chaplin.[4,5] In this article, some of the current evidence for what has been termed the "vitamin D theory" is summarized. We focus on hominins and view the case of human vitamin D as part of an evolutionary complex that adapts hominins to changing UV radiation, an idea that has been around for decades.[2,6,7] This review adds a new level of complexity by discussing not only vitamin D but also the evolution of its receptor, the VDR.

Key words: Evolution, MC1R, Rickets, Skin color, Vitamin D

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SKIN COLOUR AND THE GEOGRAPHICAL LATITUDE

The "vitamin D hypothesis" to explain skin pigmentation is based on the observation that the skin color of the world's indigenous peoples follows geographical distribution: the darkest populations inhabit the equatorial and tropical belt, the most pale-skinned the regions above 50^0N, and those of intermediate pigmentation the middle latitudes.[4]

The skin of chimpanzees is light coloured, but covered by dark hair. As the human lineage left the forest for the savannah and lost its hair, the skin would be exposed to much higher levels of UV radiation. Then, as hominins ventured out of Africa they received significantly less UVB radiation and their skin depigmented to a degree that permitted UVB-induced synthesis of previtamin D3 in northern and southern latitudes where UV radiation is less intense. Exposure to UV light has to balance the need for UVB for vitamin D photosynthesis and damage by UV for folic acid generation. This balance is maintained by melanism. Melanism determines skin color, which may be quantified by reflectance spectrophotometry.[8] Based on reflectance measurements, an exhaustive compilation of skin colors of indigenous peoples is now available, showing strong correlation with the geographical latitude.[4] Thus, skin colour of humans correlates with geographical latitude and UV radiation levels.[4,9-11] The latitudinal correlation reflects a compromise solution to the conflicting physiological need for vitamin D, as an essential component for

the maintenance of calcium homeostasis and skeletal metabolism, and the detrimental effect of UV on folic acid generation.[12] Evolution has used skin pigmentation as a tool for that balance.

DOUBTS ABOUT THE "VITAMIN D THEORY"

The vitamin D theory has recently been disputed as one that explains the evolution of human skin color[3,13] namely that reduced levels of pigmentation in human skin were selected to facilitate absorption of UV radiation. The claim was supported by evidence that people can produce enough vitamin D in their skin, regardless of pigmentation, if they are not pursuing a modern lifestyle. The assertion was that rickets was the only selective force that could have influenced the evolution of light pigmentation because other detrimental effects of vitamin D deficiency are unproven. As rickets is increased by industrialization, vitamin D status could not have constituted the fitness differential between lightly pigmented and darkly pigmented individuals at high latitudes that favored the evolutionary selection of the former.[13]

Yet, the evidence still holds explanatory scope and predictive success. Whatever be its specific actions, vitamin D is the only agent that can account for the observation that light skin is actively selected in areas where UV radiation is seasonal, scarce, or variable. In areas where UV is strong and unwavering, dark skin is positively selected.

SKIN COLOR GENES

Human pigmentation is a polygenic trait which may be shaped by different kinds of gene-gene interactions. A multi-stage genome-wide association study of natural hair color identified several loci highly associated with hair color.[14-16] The *IRF4* SNP was associated with skin color and skin tanning response to sunlight, and one variant in the melanocyte differentiation antigen *MATP* and *HERC2* genes; the latter was implicated in hair and eye pigmentation, skin sensitivity to sun, and freckling.[17] Recent studies have revealed that interactive effects between *HERC2* and the melanosomes-regulating *OCA2* gene may be responsible for blue eye color determination in humans. In a recent population associations study comparing important polymorphisms within the *HERC2* and *OCA2* genes with genotyping data for the human melanocortin-1 receptor (*MC1R*), Agouti-signaling protein (*ASIP*) and the MATP melanoma antigen *SLC45A2*, an interaction between *MC1R* and *HERC2* in the determination of skin and hair color was reported.[18] However the strongest determinant of skin color remains *MC1R*, a G-protein coupled receptor involved in the regulation of pigmentation. Several *MC1R* variant alleles are associated with red hair, fair skin and increased skin cancer risk.[19,20] A systematic functional analysis of 9 common *MC1R* variants by *in vitro* expression studies revealed variant receptors with normal to reduced cell surface expression and a corresponding normal to impaired cAMP coupling.[21] Comparison of the *in vitro* receptor characteristics with skin and hair color data of individuals both homozygous and heterozygous for *MC1R* variant alleles revealed parallels between variant *MC1R* cell surface expression, functional ability, dominant negative activity and their effects on human pigmentation.[21]

Because of the role of UV radiation in vitamin D synthesis, we propose that the VDR gene is epistatic with skin color-determining genes for the phenotype of fitness. Interestingly, both *MC1R* and the VDR are strongly implicated in immune system regulation, with obvious fitness consequences.[22,23]

The *MC1R* gene reveals a significant molecular signature of selection as humans diverged from chimpanzees, with an excess of amino acid substitutions.[24] This pattern is consistent with directional selection on the *MC1R* gene as the human lineage adapted to the increased UV radiation on exposed skin. Evolutionary analyses indicate that dark skin is the ancestral condition for modern humans, consistent with the evolution of the human lineage in sub-Saharan Africa in an area of high UV intensity.[4] The *MC1R* displays a significant molecular signature of selection within sub-Saharan African populations of purifying selection to maintain its protein state.[24] Molecular phylogeographic analyses based on 25 regions of the human genome including *MC1R* indicate that the human lineage first expanded out of sub-Saharan Africa into Eurasia 1.9 million years ago, a figure consistent with the fossil record.[25,26] This initial colonization of Eurasia was followed by two other major expansions of human populations out of Africa into Eurasia, one at around 650,000 years ago that is consistent with

the expansion of the Acheulean tool culture out of Africa, and the next at around 100,000 years ago that marked the spread of several anatomically modern traits out of Africa.[25,26] The common ancestral form of the human *MC1R* gene dates back to 850,000 years ago and spread out of Africa during the Acheulean expansion.[27] As humans spread out of Africa into Eurasia, and then more recently into the Pacific and the Americas, they experienced a more diverse UV environment and the global patterns of skin color variation indicate a rapidly evolved adaptation to UV due to intense natural selection.[28] The molecular signature of selection at the *MCR1* changed from purifying selection in sub-Saharan Africans to one suggestive of diversifying selection in non-Africans.[19] The latter article is an excellent review on *MC1R* polymorphism across the entire human species, the role of selection in shaping *MC1R* diversity and *MC1R* polymorphism and evolution in non-human primates.

Variation in human skin pigmentation is due to varied amounts of melanin, particle size, shape and distribution of eumelanin (dark melanin) and phaeomelanin (red/yellow melanin) that are produced by the melanocyte. The dark melanin pigment absorbs and scatters the UVB wavelengths that catalyze vitamin D3 synthesis. In general, high concentration of dark melanin slows cutaneous synthesis of vitamin D3, and dark-skin individuals require six-time longer exposure to sunlight as compared to fair-skin subjects to achieve the same vitamin D serum levels.[29,30]

EVOLUTIONARY PERSPECTIVE IN VITAMIN D AND ITS RECEPTOR

Vitamin D is one of the oldest hormones; it is photosynthesized in all forms of life from the phytoplankton (750 million years ago) to mammals. Whereas its role in calcium and bone metabolism makes it clear why terrestrial animals need it, it is less clear why marine and fresh water, invertebrates and plants generate vitamin D.

Vitamin D3 synthesized in the skin requires successive hydroxylations in the liver and kidney to be converted to its biologically active form, 1α,25-dihydroxyvitamin D3, which in turn binds to a specific vitamin D receptor (VDR) that belongs to the superfamily of nuclear hormones receptors. 1α,25-dihydroxyvitamin D3 and the VDR are important for calcium absorption, skeletal development and mineralization, but also for the regulation of normal cell growth and inhibition of cancer cell growth.[31-39]

The evolution of VDR is not as ancient, yet there has been substantial evolution of VDR in vertebrates.[40] Nuclear hormone receptors are strongly conserved between vertebrate species and few examples of molecular adaptation within this superfamily have been demonstrated. The sequence of VDR is well conserved from *Xenopus* to mammals.[41] The VDR and the pregnane X receptor (PXR) are thought to have arisen from duplication of an ancestral gene. When compared in detail across a range of contemporary vertebrate species, VDRs were found to have similar ligand selectivities for vitamin D derivatives.[42] In contrast, zebrafish showed evidence of PXR-mediated induction of P450 3A and P450 2C enzyme expression following exposure to known PXR activators. Tight conservation of ligand selectivity of VDRs is found across all vertebrate species studied so far, including the VDR from the sea lamprey, a jawless fish that lacks a calcified skeleton. It was proposed that, in the evolutionarily ancient vertebrate, the jawless fish, VDR may function in part like pregnane X receptors and constitutive androstane receptors, to induce P450 enzymes for xenobiotic detoxification.[43] Using a genomic approach, it was suggested that VDR may be the original nuclear receptor gene.[42]

The abundance of VDR may be also related to the multitude of recent reports claiming a role for vitamin D in cell differentiation and proliferation, immune function, muscle strength, blood pressure control and more.[44]

POLYMORPHISM OF THE VDR

The *VDR* gene has four major polymorphic SNPs in humans and several other rare ones. Since the original suggestion that osteoporosis is associated with *VDR* polymorphism, a dozen articles reported conflicting results, which have been meta-analyzed to show that only the *VDR B* allele was significantly associated with bone mineral density at the spine.[45,46] Studies on polymorphism in the *VDR* gene suggested a role in skeletal mineralization, with the restriction fragment length polymorphism *F/f*, as defined by the

endonuclease FokI,[46] conferring a greater transcriptional VDR activity for the *F* than the *f* allele.[47] This has been questioned by others. In a study of *VDR* gene polymorphism in patients with rickets in Turkey and Egypt, we found the *VDR* BsmI genotypes to differentiate patients with vitamin D deficiency from those with calcium insufficiency.[48] The single site polymorphisms in the *VDR* gene can also be assembled into multi-site haplotypes. Haplotypes in the *VDR* locus have been shown to have significant phenotypic associations (susceptibility to bladder cancer, tuberculosis and fracture risk) that were not detectable using the individual SNPs that defined the haplotypes.[48,49]

PERSPECTIVES

The above-cited studies show that the polymorphic variation at the VDR locus has functional significance, although none of the above-mentioned studies has investigated if this functional significance extends to interactions with skin color even though there is a direct physiological link.[48,49] Polymorphism in the 5' ends of the *VDR* gene (FokI) is strongly related to large adenoma risk among subjects with low dietary calcium intake, low dietary vitamin D intake or dark skin color.[50] This polymorphism also interacts with skin color.[51] We therefore propose that along with the changing skin color based on *MC1R* and other skin color genes, the highly polymorphic *VDR* gene is part of an evolutionary complex that adapts humans to changing UV radiation.

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