Color by Numbers: When Population Skin Pigmentation Is not Political but a Polytypical Evaluation Exercise to Measure Vitamin D, Diseases, and Skin Pigmentation

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VITAMIN D HAS RECEIVED MUCH ATTENTION IN nutrition science, public health, and other disciplines because of its associations with falls, cancer, women in reproductive years, hypertension, cognition, and mortality.[1-6] Subpopulations with predispositions of poor vitamin D status are associated with increased disease risks and medical conditions.[7-9] National Health and Nutrition Examination Survey (NHANES) results have highlighted variations in vitamin D nutriture according to federal classifications of ethnicity and race.[8-10] These include the separate and distinct identities of ethnicity (Hispanic/Latino or not Hispanic/Latino) and race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or white). Estimates depend on obtaining a representative proportion of a specific racial category, which has led NHANES to use predominantly three categories: non-Hispanic black, non-Hispanic white, and Mexican American.

Fuller[7] proposed that race and racism underscored health disparities and challenged us to "reframe" our approach to health disparities in evaluating population vitamin D nutriture. One approach could dissuade use of social categorical constructs of skin pigmentation such as the federal classification system. A clearer measure related to capturing the continuous and polytypical nature of skin pigmentation would borrow from the fields of anthropology and dermatology; that is, using reflectance spectrophotometry in examinations of associations between subpopulations and vitamin D nutriture.

FROM MYTHS TO EMPIRICISM: THE ORIGINS AND RELEVANCE OF SKIN PIGMENTATION

How did we get to aggregating heterogeneous traits into homogenous groupings? Speculation on the origins of skin pigmentation can be traced back to ancient civilization, including the Greek myth of Phaethon, the son of the sun god Helios.[11] While charioting the sun across the sky, Phaethon lost control, burning the people of the African continent as he approached too close to Earth while turning others pale from the cold as he drove too far away. During the early 18th century, intellectuals representing many disciplines that spanned across botany, philosophy, mathematics, medicine, and anatomy began to examine pigmentation as a scientific and social construct. John Mitchell, an 18th century naturalist, surmised that skin pigmentation was related to latitudinal gradient, with depigmentation reflecting man's migration from the equator to more northern latitudes.[12] The naturalist Georges-Louis Leclerc speculated that skin pigmentation resulted from variations in climate, food, and way of life.[13]

Toward the later 19th century, a peculiar approach of measuring craniology (skull sizes) and anthropometry inferred what is now accepted as a racist mode of inquiry.[14,15] Advanced by the physical anthropologist Paul Broca, he later introduced a 34-shade chromatic scale for skin color that soon proved unreliable due to inconsistencies in measurement. The anthropologist Paul Topinard, Broca's student, moved away from numerical skin matching and reverted to description, albeit this would present similar challenges to Broca's color scale.[16] Topinard's reversion to description may have been a precursory indication that skin pigmentation was a continuous and not categorical variable.

In more contemporary times, following the discovery of *Ardipithecus ramidus*, the oldest human skeleton to date, genomic studies have shown that modern man originated in Africa.[17,18] Approximately 80,000 years ago, human beings migrated out of Africa to more temperate regions of more northern latitude that eventually favored cutaneous depigmentation. A review of photobiological and photobiophysical hypotheses indicates that skin pigmentation originated from selective pressures for the protection of two micronutrients essential to human health.[19] Accordingly, dark pigmentation inhibits photolysis by UV radiation (UVR)

of the light-sensitive nutrient folate, as would occur in equatorial regions of high UVR. Depigmentation allowed for UVR synthesis of vitamin D, a process that would be difficult at latitudes with low UVR.[20] Today individuals settling in northern latitudes and bearing dark skin pigmentation are at an increased risk of vitamin D deficiency and all the resultant associated health conditions, supporting the contention provided through NHANES that this nutrient is a biological determinant of health disparities.[21] Interestingly, depigmentation, as a consequence of adaptation necessary to allow for cutaneous synthesis of vitamin D, may also be associated with additional disparities in health. There is controversial but inconclusive concern about the adverse effects of folic acid supplementation among subpopulations in the United States. For example, there is a body of evidence that suggests high folate status is associated with an increased risk of colorectal cancer,[22] a leading cause of cancer-related death in examinations of population-based cancer registries.[23] Surveillance data suggest that there are variances in race in the United States as demonstrated by high incidences of colorectal cancer in African-, Hispanic-, and Asian-American men and women.[24,25] Ongoing randomized, controlled screening trials suggest that this may be due partially to disparities in early detection and treatment[26]; however, data from both national prospective and genetic studies have also proposed a biological component.[27,28] Of note, global rates of colorectal cancer are significantly higher in developed countries (ie, Europe and North America) than in developing countries (ie, Africa and South Central Asia).[23] Although there may be several underlying factors, consideration of the hypothesis that skin pigmentation may be a contributing factor merits further investigation.

The theory of gene–culture coevolution may provide another plausible explanation for this dimorphism. It suggests an interaction between culture and environment to the extent that new selective pressures lead to adaptation to support successful survival.[29] This is not dissimilar to Fuller's argument. Fuller contended that the issue with vitamin D is not one of race and racism but rather of phenotype and environment.[7] Furthermore, Fuller's reminder to us that race does not exist as a biological truth affirms the conviction that as scientists we should look for scientific ways to examine issues concerning diverse individuals. Doing otherwise, such as by assigning categorical social designations, obliterates the rich ancestry we have inherited. Consider the consequences of assessing the vitamin D status of individuals who were formerly deemed "other" as now either strictly "black" or "white."

THE NUTRITIONAL BASIS FOR SKIN PIGMENTATION

The skin is the largest human organ, and among its various roles is to regulate the amount of UVR penetration (specifically, ultraviolet B [UVB] light) for the synthesis and protection of vitamin D and folate, respectively. Thus, it can be argued that skin pigmentation was born from a health concern. Experimental investigations have demonstrated this. We know that dark skin pigmentation is rich in eumelanin, a photoprotective compound, which prevents UVR destruction of the light-sensitive nutrient folate.[30] Folate is essential for the biosynthesis of nucleotides that are the backbone of DNA and RNA and required for embryonic neural tube development. Therefore, a deficiency would compromise successful reproduction. Folate also is used for eumelanin synthesis by its production of the eumelanin substrate guanosine triphosphate (Figure 1).[31] Moreover, as an antioxidant,[32] folate can scavenge epidermal reactive oxygen species generated from exposure to UVR,[33,34] thereby inhibiting cellular DNA damage that can lead to sun-induced cancer.[35]

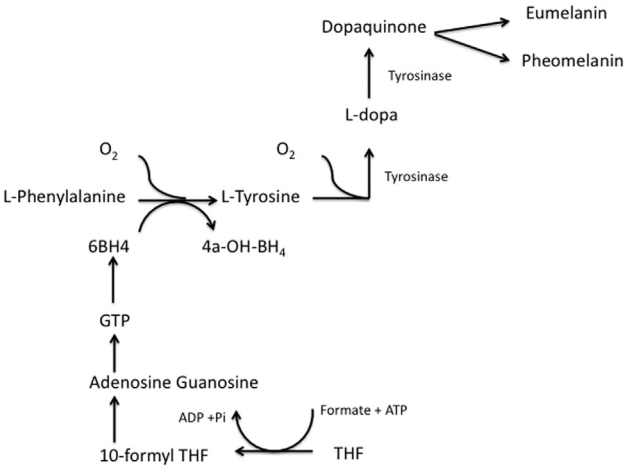

Figure 1. Folate–melanin (eumelanin and pheomelanin) pathway. $6BH_4$=6R-L-erythro 5,6,7,8-tetrahydrobiopterin. 4a-OH-BH_4=4a-hydroxy-tetrahydrobiopterin. GTP=guanosine triphosphate. Pi=inorganic phosphate. THF=tetrahydrofolate.

According to the vitamin D hypothesis, positive selection favored depigmentation following human beings' migration to more northern latitudes for the UV cutaneous synthesis of previtamin D-3. This is the substrate from which active vitamin D is derived. Vitamin D synthesis begins with absorption of UVB by 7 dehydrocholsterol that is found in the skin leading to the formation of previtamin D-3. Previtamin D-3 is then converted in two hydroxylation reactions in the liver and kidney to the active form of vitamin D, 1,25 dihydroxyvitamin D (1,25$(OH)_2$D).[36] The main circulating form of vitamin D in humans is 25(OH)D. Interestingly, the observation that women of all populations are lighter in pigmentation than their male counterparts may suggest a trait favored by natural selection possibly due to greater vitamin D requirements during pregnancy and lactation.[20,37] Today there is concern for subpopulations because investigations report higher eumelin content, as found in darker-pigmented individuals, may inhibit UVB synthesis of vitamin D, thereby placing darker-pigmented individuals at high risk for vitamin D deficiency.[38] This is of concern to all respective subpopulations living at more northern latitudes than our original equatorial ancestors.

The vitamin D receptor is ubiquitous in the human body. Following its identification in tissues throughout the human body, it became recognized that vitamin D's actions go beyond its original role of maintaining bone integrity and calcium homeostasis to affect several chronic conditions and events such as cancer, cardiovascular disease, autoimmune disorders, hypertension, and falls.[1-4,39,40] The observation that vitamin D is a biological determinant of health