Influence of Ethnicities and Skin Color Variations in Different Populations: A Review

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Keywords

Skin color · Ethnicity · Genetic factors · Melanin

Abstract

Background: In the world scientific tradition, skin color is the primary physical characteristic used to divide humans into groups. Human skin has a wide range of tones and colors, which can be seen in a wide range of demographic populations. Many factors influence the color of people's skin, but the pigment melanin is by far the most important. Melanin is produced by cells called melanocytes in the skin and is the primary determinant of skin color in people with darker skin. Indeed, >150 genes have now been identified as having a direct or indirect effect on skin color. Vitamin D has recently been discovered to regulate cellular proliferation and differentiation in a variety of tissues, including the skin. The mechanisms through which the active vitamin D metabolite 1,25 dihydroxyvitamin D3 (or calcitriol) affects keratinocyte development are numerous and overlap with the mechanisms by which calcium influences keratinocyte differentiation. Ultraviolet (UV) is the most major modifiable risk factor for skin cancer and many other environmental-influenced skin disorders when it is abundant in the environment. Although the UV component of sunlight is known to cause skin damage, few researches have looked at the impact of non-UV solar

radiation on skin physiology in terms of inflammation, and there is less information on the role of visible light in pigmentation. **Summary:** The quantity and quality of melanin are regulating by the expression of genes. The enzyme tyrosinase is primarily responsible for the genetic mechanism that controls human skin color. Genetics determines constitutive skin color, which is reinforced by facultative melanogenesis and tanning reactions. High quantities of melanin and melanogenic substances are typically accepted in darker skin to protect against UV radiation-induced molecular damage. Previous research has proposed that skin color variation is caused by a dynamic genetic mechanism, contributing to our understanding of how population demographic history and natural selection shape human genetic and phenotypic diversity. However, the most significant ethnic skin color difference is determined by melanin content. This current review aimed to assess the influence of skin color variations in skin structure and functions as well as difference in dermatological disease patterns. Also, this article reviewed several cases of skin color adaptation in different populations. **Key Messages:** Skin color impacts the composition and activity. Therefore, the contrast of dermatological ailments between distinct race-related categories is remarkable. Skin color adaptation is a challenging procedure. Refinement of skin color is an age-old craving of humans with ever-evolving drifts.

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Introduction

One of the most striking examples of human phenotypic variability is skin color variation [1]. Melanin, a pigment produced by melanocytes at the base of the epidermis, is the most prominent pigment. Melanin has 2 forms, eumelanin (black-brown) and pheomelanin (yellow-reddish). The former is primarily collected in light-skinned people, while light-skinned persons are more likely to develop the latter [2, 3]. Furthermore, the size and number of melanin particles vary by the organism and are even more significant in determining human skin color than the proportions of the 2 types of melanin [4]. Some skin-related factors, such as keratin, also influence skin color [5, 6]. We know a lot about the genetic architecture of human skin color, but we do not know much about it, which can be related to climates, cultures, and continents. Historically, human skin color has been measured using subjective categories: “moderate brown, occasionally burns, tans easily.” Quantitative approaches focused on reflectance spectrophotometry have recently been used to differentiate between reddening induced by inflammation and increased hemoglobin and darkening caused by enhanced melanin [7, 8]. The organic polymer of melanin is made up of oxidative tyrosine derivatives in 2 types, including a cysteine-rich red-yellow form (pheomelanin) and a less soluble black-brown form (eumelanin). Chemical extraction is needed to distinguish between pigment types in biological samples, but it is worthwhile because pigment-type switching is one of the few things we learn about the most prevalent variations in human pigmentation [9, 10].

Skin color is significantly related to latitude and, more importantly, the ultraviolet (UV) radiation distribution in global populations. The skin of those who live near the equator is darker to shield themselves from UV rays, which can lower folic acid levels [11] and cause skin cancer [12, 13]. Higher latitude populations have lighter skin due to selection to protect vitamin D photosynthesis, which is a UV-dependent process [14]. While UV was formerly thought to be a driving force in the evolution of human skin tones, the specific genetic mechanism of selection is still unknown. Nevertheless, it is critical for understanding the microevolution of adaptive traits and reconstructing human evolutionary history. It would be impossible to give a comprehensive account of human regional skin color adaptation as it would need not only the genes that have been described as being under selection but also the extent to which these genes may be able to account for combined impacts, gene interactions, and

phenotypic variation and how they respond to external environments [15]. With these backgrounds, the current review is aimed to evaluate the influence of skin color variations in skin structure and functions. Also, this article reviewed several cases of skin color adaptation in different populations.

Methodology

A literature search was carried out on the following databases, including Google Scholar, MEDLINE, PubMed, Scopus, and Cochrane databases with the appropriate key terms. We were looking specifically for articles on the influence of ethnicities and skin color variations in different populations. The initial literature search revealed 8,667 articles, which is detailed in Figure 1. All the published articles were reports with a description of skin color variation, articles published in the English language, and all study designs were included in this review.

Results and Discussion

Variations in Skin Coloration

The difference in skin pigmentation between ethnic groups is the most prominent [16]. The amount of melanin in the skin, the amount of UV exposure, genetics, the quality of melanosomes, and pigments present in the skin all play a role in racial variation. The different colors present in human skin are caused by 4 chromophores: carotenoids, hemoglobin, melanin, and oxyhemoglobin. By absorbing unique light wavelengths and allowing red to be reflected, oxyhemoglobin and hemoglobin lead to the pinkish color of Caucasian skin. Melanin is responsible for the different brown shades seen in black and sun-tanned skin. Carotenoids cause yellow-orange pigmentation. A mixture of all the pigments causes other hues. Orthoquinones are produced during melanogenesis, and they have a high predisposition for interacting with protein and nucleic acids and covalently adhering to them.

As a consequence, melanogenesis is limited to specialized organelles known as melanosomes [17]. By the time the organelles are completely melanized and transported to keratinocytes as granules, the response of melanosomal proteins and intermediate quinines has resulted in a correct pattern of matrix deposition and inhibition of tyrosinase and other enzymes. Australian aborigines, African-blacks, and Americans have been found to have more melanosomes. Compared to other racial groups, these ethnic groups' melanosomes are also more scattered and larger individually. Melanosomes were present in Mon-

Fig. 1. PRISMA flowchart.

goloids, Chinese, Japanese, East Indians, and European-American Caucasians clustered together in complexes of 2 or more. Differences in skin pigmentation are caused by melanosome arrangement variations and the quantity of melanin present [16].

Melanogenesis, on the other hand, is a gradual process that happens following exposure to UV light. After a single UV dose, the quantity of melanin in black skin grew by 12%, white skin by 1%, and Asians by 4% after 7 days [18]. According to a report, basal keratinocytes in type III (French) skin lacked nuclear melanin capping in subjects tanned during their vacation time [19]. Recently, this has also been observed in Japanese individuals. This implies that the tanning process's first stages are the most crucial and are caused by the redistribution of already established melanin, and melanosomes that have already been synthesized are transferred to suprabasal keratinocytes. Human photobiology research has traditionally focused on UV radiation and, more recently, on visible light [20]. Visible light has wavelengths ranging from 400 to 700 nm, while it has been classified as covering the range of 380–780 nm CIE in various European Commission docu-

ments. In human skin, visible light has been shown to cause both transitory and long-term pigmentations [21]. Visible light-induced pigmentation has been demonstrated to last up to 8 weeks, and the amount of pigment created is proportional to the overall dose of light. A study of the effects of visible light on human skin, particularly in persons with darker complexions, found that the induction of pigmentation was not accompanied by any negative effects similar to those caused by UV radiation [20]. In contrast to these findings, Liebel et al. [22] demonstrated that visible light can cause considerable ROS generation in skin, resulting in the release of pro-inflammatory cytokines and the development of matrix metalloproteinases. A single UVB exposure can cause delayed pigment development, which is preceded by an erythema reaction. During the first minutes of exposure, UVA (320–400 nm) can cause immediate pigment darkening (IPD), which is a temporary kind of pigmentation that fades away within a few hours [23, 24], or persistent pigment darkening, which is a pigment darkening that emerges within hours of greater UVA exposure and lasts for several days or weeks [25, 26]. Single UVA exposure

Table 1. Assessment of skin color variations among the different populations by using several devices

S. No	Authors	Condition studied	Population	Device
1	Huixia et al. [36]	Changes induced by whitening products, ITA, and pigmentation and skin tone measurement	Asian (China)	Chromosphere
2	Cust et al. [37]	Nevus phenotype measurement and skin pigmentation	Adults (Australia)	Spectrophotometer
3	Clarys et al. [38]	Skin color measurement	Adults (Belgium)	Dermaspectrometer, Chromameter, Mexameter
4	Stamatas et al. [39]	Pigmentation and in vivo skin erythema	White, Asian, Hawaiians or other Pacific Islanders, African-American, Latino, or Hispanic	Spectrophotometer
5	Xiao et al. [40]	Variation in skin color measurement	Kurdish, Thai (UK), Chinese, Caucasian	Spectrophotometer
6	Nam et al. [41]	Skin brightness measurement	Adults (Korea), Asian	Spectrophotometer
7	Everett et al. [42]	Skin color measurement	Asian, black or African-American, white, mixed origin (USA) Asian, black or African-American, Biracial (USA), white	Spectrophotometer
8	Wright et al. [43]	ITA and skin color measurement	Children (New Zealand)	Spectrophotometer Munsell color chart
9	Weatherall and Coombs [44]	Skin color measurement	Indian, Polynesian, mixed origin, Europeans, Chinese	Spectrophotometer
10	Park et al. [45]	Skin color changes after UVB and UVA, ITA, skin color measurement	Asian (Korea)	Spectrophotometer
11	Chardon et al. [46]	ITA, tanning, and skin color measurement	Caucasian (France)	Spectrophotometer
12	Chien et al. [47]	Pigmentation in aging	African-American (USA), Caucasian	Chromameter
13	Del Bino and Bernard [48]	ITA, UVR responses in ex vivo skin, skin color measurement	African descent, Asian, Caucasian, and Hispanic; adults (USA, France, Russia, Brazil, Japan, China, India, Thailand)	Spectrophotometer
14	Alaluf et al. [7]	Epidermal melanin impact on human skin color	Indian, black (South Africa), European, Mexican, Chinese	Chromameter
15	Wright et al. [49]	ITA, skin color measurement, and erythema sensitivity	Indian or Asian, white, mixed origin (South Africa), black	Colorimeter

UVR, ultraviolet radiation; ITA, individual typology angle.

has been proven to cause IPD and persistent pigment darkening, as well as erythema, in skin phototypes I and II [27], and some research in fair-skinned people has looked into the pigmentation growth following frequent UVA exposures [28–30]. Several reviews observed pigment changes accompanied by erythema. Researchers exposed people with skin types II, III, and IV to visible light and saw IPD, acute erythema, and a long-lasting delayed tanning reaction [31]. In their review, Mahmoud et al. [31] speculated that the discrepancy could be related to the use of nonstandardized light sources in investigations on the effects of visible light on human skin pigmentation, as well as the lack of such sources.

Nonetheless, as determined by p53 levels, 6-4 photo-products, and cyclobutane pyrimidine dimers, photo-

damage affects all SPTs to some extent [18]. Bonnet Duquennoy et al. [32] identified increased levels of p53 in Chinese subjects 24 h after one minimal erythema dose, and in comparison with sun-protected skin, these levels were higher in sun-exposed skin. Similarly, de Winter et al. [33] found that a single UV exposure in the epidermis increased the immunoreactivity of p53, with elevated levels in darker-skinned people. Similarly, in response to DNA damage, DNA repair enzymes are known to be upregulated by this tumor suppressor gene and regulate cell cycle progression, allowing for additional time for DNA repair. It also causes apoptosis in cells that have been severely damaged. The removal of cyclobutane pyrimidine dimers is less effective in the skin with light pigmentation. According to Wagner et al. [8], a significantly lower tanning

Table 2. Association of genes and their function in the African population

S. No	SNP	Allele	Gene	Function
1	rs10424065	T	<i>MFSD12</i>	Intronic
2	rs56203814	T	<i>MFSD12</i>	Synonymous
3	rs2240751	G	<i>MFSD12</i>	Tyr 182 His
4	rs7948623	T	<i>DDB1</i>	Intergenic
5	rs6497271	G	<i>HERC2</i>	Intronic
6	rs4932620	T	<i>HERC2</i>	Intronic
7	rs1800404	T	<i>OCA2</i>	Synonymous
8	rs12913832	A	<i>HERC2</i>	Intronic
9	rs1426654	A	<i>SLC24A5</i>	Ala 111 Thr

SNP, single-nucleotide polymorphism.

response than East Asians and Hispanics and European Americans with low constitutive pigmentation had a much larger burn reaction indicating that they burnt more and browned less than those with higher pigmentation. In this line, Rijken et al. [34] analyzed white and black skin responses to solar-simulating radiation. They discovered that, unlike Caucasians, participants with skin color did not reveal any diffuse keratinocyte activation, active proteolytic enzymes or increase in neutrophils, and the suprabasal epidermis, except for minor DNA damage. As a result, other than melanin, Asian skin appears to have systems to protect against UV irradiation. It is probably due to dietary factors, but it is also possible to link to the DNA repair enzymes and p53 induction [35]. Several devices were used to assess skin color variations among different populations, listed in Table 1.

Genetics of Skin Color

Heritability overall is the most crucial issue for any quantitative trait with multiple contributing components, the number of genes that are likely to be implicated, and the most effective methods for identifying specific genes. The broad-sense heritability of skin color is very high [50], provided one can account for sunlight exposure as the most crucial nongenetic component. Several pieces of research have made claims about the number of genes in the skin color of humans; one of the most comprehensive is by Harrison and Owen [51] who evaluated the skin reflectance measurements among 70 Liverpool inhabitants who were their grandparents, parents or both were of European or West African ancestry and who were divided into “backcross” and “hybrid” classes based on this. An effort to partition and evaluate the backcross

groups’ variance yielded marginal estimations of 3–4 “efficient variables,” in this case, segregating genes independently. To put it another way, the average skin reflectance of “backcross hybrid” groups is half that of their parental groups. One of the earliest models to identify and investigate gene function and interaction was mouse coat color genetics, which has been used to consider the number of possible human pigmentation genes. Approximately, 100 different genes have been identified for mouse coat color genetics [52].

In nontropical populations, especially among Europeans, the *MC1R* gene has a wide range of alleles, but these alleles primarily affect hair color. Only red hair is linked to a decrease in skin pigmentation [53]. The Arg163Gln version of the gene is found in most Japanese and Inuits, while red-haired people have a variety of other variants, including Arg160Trp and Arg151Cys. The *ASIP* gene can influence light and dark pigmentation in people all over the world. The production of light skin appears to be influenced by a variety of genes: *DRD2*, *EGFR*, *DCT*, and *KITLG* in Asians; *KITLG*, *SLC24A5*, *TYRP1*, *DTNBP1*, and *MYO5A* in Europeans; and *SLC24A5* which is responsible for 25–38% of the variation in skin color between Africans and Europeans [53, 54]. Several genes and their functions were associated with the African population listed in Table 2.

Role of Vitamin D

Vitamin D is synthesized in the human skin, which also serves as a target organ for the biologically active version of the vitamin. Vitamin D has an impact on a variety of skin activities, including apoptosis, differentiation, and keratinocyte proliferation, as well as immunoregulatory mechanisms and barrier maintenance. Vitamin D is also being evaluated as a treatment option for a variety of skin conditions [55]. Vitamin D has been found to have a dose-dependent influence on keratinocyte proliferation and differentiation in numerous in vitro investigations. 1,25(OH)2D3 was found to stimulate keratinocyte proliferation at low concentrations (10⁻⁹M or less), but inhibited proliferation and promoted differentiation at high concentrations (>10⁻⁸M) [56, 57]. The effect of vitamin D on in vitro keratinocyte proliferation is influenced by a number of other parameters, including calcium concentrations, cell density, and the absence or presence of serum [58]. Vitamin D has a dose-dependent influence on keratinocyte apoptosis, similar to its effect on cellular growth. Vitamin D protects apoptosis produced by different proapoptotic stimuli such as TNF, UV radiation, ceramide, and others at normal quantities, whereas it causes apoptosis in keratinocytes

at high concentrations [58]. The Tanzanian Hadza, a dark-skinned hunter-gatherer population who live traditionally and expose much of their skin to intense sun, have a high vitamin D status, with typical 25(OH)D3 blood levels in the order of 110 nmol/L [59].

Antimicrobial peptide synthesis has been reported to be regulated by vitamin D through mechanisms other than direct transcriptional activation. Serine proteases KLK5 and KLK7 regulate the action of cathelicidin and other antimicrobial peptides in human skin [60]. Vitamin D also plays a vital role in the development of certain inflammatory skin diseases. Many observational studies, including a meta-analysis, have found that levels of serum vitamin D are lower in adults and children with atopic dermatitis (AD) than in controls and that vitamin D insufficiency is linked to the risk of atopic eczema [61–63]. Many investigations have found a shortage or insufficiency of serum vitamin D in psoriatic patients, indicating that vitamin D plays an important role in the disease [64, 65]. Several case-control studies have found that psoriatic patients have significantly lower levels of serum 25(OH)D than controls, as well as an inverse relationship between serum 25(OH)D and disease severity [66, 67]. Future studies, utilizing the most current technology, will be required to mechanistically and intensively investigate the particular pathways influenced by vitamin D and to determine the efficacy and safety of vitamin D-based treatment regimens in the treatment of a variety of inflammatory skin conditions.

The Influence of Skin Color on the Skin Structure

Skin color is influenced by the type of melanin present, UV exposure, genetics, the content of melanosomes, and other chromophores in the skin [16]. The presence of various 4 chromophore combinations influences skin color perception in part: carotenoids, melanin, oxyhemoglobin, and hemoglobin. Because of the different light reflections and absorption caused by the mixture of these chromophores, the skin appears in various shades. The combination of oxyhemoglobin and hemoglobin developed a pink color in white skin, and the interaction of melanin and carotenes developed a yellow-orange color in brown skin [68]. Melanocytes are skin cells that produce the color melanin. Melanosomes are the organelles within melanocytes that create, deposit, and transmit melanin pigment. Skin color variances are caused by changes in the size, volume, and keratinocyte and melanocyte distributions, not by variances in the number of melanocytes between ethnic groups [69, 70]. Lightly colored skin has smaller melanosomes clustered in secondary lysosomes,

whereas darkly colored skin has larger melanosomes scattered singly within lysosomes. The varied hues of skin color that exist even within ethnic groups are due to changes in melanosome density and size, with varied proportions of larger single dispersed melanosomes and smaller aggregated melanosomes based on the pigmentation degree [70].

Skin color affects the position of melanosomes within the epidermis. Melanosomes are found throughout the epidermis, but in darkly colored skin, they are concentrated and evenly distributed over the basal layer, whereas melanosomes break down more quickly in white skin, resulting in noticeable absence in the epidermis' upper layers and small clusters of melanosomes in the Malpighian layers and basal cells [71]. Compared to lighter shaded black skin, more basal layer melanosomes are found in darkly colored black skin within an ethnic group. Similar conclusions are obtained when darker white skin and darker Asian skin are compared to their lighter equivalents [72]. Other components of melanogenesis differ depending on skin color, resulting in changes in melanin synthesis. The optimal pH for melanin synthesis is 6.8, which black skin's melanosomes come near, whereas white skin's melanosomes have a more acidic pH [73]. Melanosome transport to keratinocytes is another biological mechanism that affects pigmentation. This process is mediated by the protease-activated receptor 2. Compared to lighter pigmented skin, protease-activated receptor 2 is found in greater abundance in darker pigmented skin. Additionally, the induction of protease-activated receptor 2 is delayed in lighter skin [74].

In hyperpigmentation development, the enhanced activity of protease-activated receptor 2 could have a role, which is more common in those with darker skin. Aside from pigmentation, changes in the dermis of skin and epidermis structure of different colors have been observed. Differential responses to aging have been related to the reduction in epidermal structure across skin colors. Sun-exposed black skin, for example, has a more compact stratum lucidum, whereas sun-exposed white skin has a more hypercellular and edematous stratum lucidum. The epidermis of intensely pigmented samples is low dyskeratotic and vacuolated compared to samples of the epidermis of more minor pigmented. Although there is no discernible skin thickness difference between white and black skin, black skin possesses more corneocytes in the stratum corneum than white skin, implying a more dense and compacted layer [75, 76]. Black skin has a higher mean electrical resistance than white skin, which is most likely due to this compaction [77]. According to further research, in white, black, and Asian skin, the corneocytes

are all the same size, and there are no differences in the maturation of corneocytes, according to further research [78]. The epidermis appears to have the highest ceramide concentration in Hispanic and Asian skin and low concentration in black skin [79, 80]. There was no change in the surface of skin pH between the ethnic groups [81, 82]. On black skin, *Candida albicans*, *Cutibacterium acnes*, and aerobic bacteria are all more common than on white skin [83].

Skin Color as It Influences Skin Function

Small sample sizes, inadequate study designs, and contradicting results have hampered investigations into functional variations in the skin between individuals of different skin hues. Two investigations comparing the absorption of topical medicines through black and white skin found no differences in percutaneous absorption [84, 85], whereas 3 other investigations found that black skin inhibited the absorption of topical medicines [86]. There were no variations in absorption between white and Hispanic skin in research [87], but in a study comparing Asian skin to white skin, it was discovered that Asian skin absorbs less than white skin [88]. While there were no significant variations in skin physiological characteristics, morphological study of hair follicles found that Caucasians had much larger terminal hair follicles than Asians and Africans, among other things [89].

Erythema is a subjective criterion impacted by skin color, and it is typically misunderstood in pigmented skin. According to studies that employ erythema as an endpoint, lighter white skin is the most vulnerable and black skin is less susceptible to contact irritants than white skin [90, 91]. One explanation why black nursing home residents are 2–4 times more likely than white patients to develop decubitus ulcers has been suggested: it is challenging to recognize erythema in darker skin colors [92]. Transepidermal water loss as a function of stratum corneum integrity is another endpoint used to measure skin irritation. Even when employing this criterion, the results have been mixed, with some research claiming that white skin is more inflamed than Asian and black skin [93], whereas others find no difference between groups [94]. The primary endpoint was skin water vapor loss; a study comparing 11 dark-skinned Indians, 12 dark-skinned Malaysians, and 15 light-skinned Chinese patients found no significant differences in skin irritation across the groups. When patients were asked to self-assess their skin, there was no variation in the incidence of sensitive skin by ethnic group [95]. UV radiation damages skin in variable degrees, regardless of pigment. The num-

ber of pyrimidine dimers and 6-4 photoproducts formed in UV-exposed cells' DNA can be used to measure the extent of the damage, as well as the activity of the p53 gene in those cells [18]. This gene acts to prevent the development of cancer and tumor suppressor. According to studies, black skin has higher p53 gene activity than white skin following UV exposure [33]. When Asian skin was compared to white skin, a similar outcome was found [32], implying that this gene's activation is one of the mechanisms that protect different skin types from developing skin malignancies [96].

Prevalence of Skin Disorders between Ethnic Groups

The top 5 dermatologic diagnoses made by dermatologists in the USA have been ranked according to population: dyschromia, seborrheic dermatitis, acne, dermatitis, and AD are the top 5 diagnoses in black communities; benign neoplasms, psoriasis, warts, acne, and dermatitis are the top 5 diagnoses in Hispanic populations and seborrheic keratosis, acne, benign neoplasms, dermatitis, and psoriasis are the top 5 diagnoses in Asian communities, while nonmelanoma skin cancer, acne, actinic keratoses, dermatitis, and benign neoplasms are the top 5 diagnoses in white people [97]. Melanoma is more common in nonsun-exposed parts of the body, such as the palms and soles, in black, Hispanic, and Asian people, with acral lentiginous melanoma being the most prevalent kind of melanoma in these groups. Compared to white receivers, malignant neoplasms that develop in black and Hispanic transplant patients are more likely to appear in sun-protected areas [98].

In nonwhite populations, melanoma is more likely to be identified after spreading and has a poor prognosis. Black individuals have a 66.7% 5-year melanoma survival rate compared to 92.5% for white patients. These disparities are presumably the result of several socioeconomic variables, including educational gaps, health-care professional education gaps, and health-care access disparities. Keloids are a scarring phenomenon that varies in occurrence by ethnic group, though it is unclear if this is due to skin color or other causes. The incidence of keloids is higher in black patients than white patients [99] and higher in Chinese patients than Indian and Malaysian patients [100]. As previously stated, determining whether or not there is an actual difference in contact dermatitis prevalence between ethnic groups has proven problematic, probably due to most research using erythema as the endpoint [101]. Compared to white people, Asian and black people are more likely to develop AD, especially in youngsters. The odds ratio of developing AD is 1.9 for Hispan-

ics, 2.2 for black patients, and 3.1 for Asians. Even when sociodemographic characteristics and vitamin D levels are considered, this preponderance remains [102]. Because much of the evidence for systemic therapy for AD in the USA has typically been based on randomized studies conducted in Europe, where ethnic diversity is lower than in the USA, making it difficult to generalize the results, the gap in prevalence has significant implications for treatment [103].

Modern Eurasians' Skin Color Adaptation

The golden genes *SLC45A2* and *SLC24A5* are connected to Europeans' light skin color development [104, 105]. The NCKX5 protein, a transmembrane protein that regulates calcium concentration in the melanosome, belongs to the transmembrane protein family encoded by *SLC24A5* [106]. In zebra fish and mice, pigmentation is influenced by this gene [107]. In *SLC24A5*, the derived allele of rs1426654 was nearly fixed in Europeans but virtually missing in groups without European ancestry [108]. In Europeans, a 78-kb haplotype around *SLC24A5*, which is in linkage disequilibrium with rs1426654, has been discovered to accumulate [109]. Many animals, including birds, horses, fish, and mice, have a similar pattern at rs16891982 in *SLC45A2*, associated with pigmentation [110, 111]. In Europeans, other variants in this gene, such as rs40132, rs2287949, and rs26722, have also been associated with coloration [109, 112]. Melanocortin 1 receptor (*MC1R*) is another essential pigmentation-related gene discovered in Europeans [113]. This gene is found in melanocytes and controls the transition from pheomelanin to eumelanin [114]. In a range of animal species, pigmentary traits connected to *MC1R* have been studied [115, 116]. Despite its small size (951 bp), *MC1R* has a large number of variants, including rs1805008, rs3212357, and rs1805007 [117, 118]. The rs1900758 in *OCA2*, rs2733831 in *TYRP1*, and rs1393350 in *TYR* are other important European-specific loci [119, 120]. According to statistical analysis, the frequencies of derived alleles at these loci are higher in Europeans but lower in East Asians and Africans, suggesting that Europeans have been subjected to positive selection [121].

Genes involved in the adaptation of skin color in East Asians have received less attention than genes involved in skin color adaptation in Europeans. *MC1R* and *OCA2* are 2 well-known examples. The rs885479 in *MC1R* and rs1800414 and rs74653330 in *OCA2* are examples of non-synonymous mutations [122, 123], which have high derived allele frequencies in East Asians but low-derived allele frequencies in Europeans and Africans. The *OCA2* pro-

tein is assumed to be a mature membrane protein found on melanosomes. That may help transport proteins into melanosomes [124]. In a study of Han Chinese people using the melanin index to measure skin color, the skin lightening was assumed to be caused by the derived allele at rs1800414 [125]. Another pigmentation-related nonsynonymous variation in *OCA2*, rs74653330, was discovered [126]. The rs1407995 in *DCT* and rs10809814 in *TYRP1* are 2 more pigmentation-related alleles specific to East Asians that display a difference between non-Asians and Asians [125], and Asians show signs of positive selection are very strong [127].

The Admixed Populations' Skin Color Adaptation

Because their ancestral groups have such a wide range of skin colors, current study into pigmentation genes in admixed people is essential and mainly included those with European and African ancestry, such as Latin Americans, European Africans, and African-Americans. These 3 populations have different ancestral genetic makeups. Mestizos from Latin America have the smallest percentage of African ancestry (~10%). African-Americans had the highest genetic contribution from their African ancestors (~80%) [128, 129], while in European Africans, the genetic components inherited from Europeans (~42%) and Africans (~58%) are comparable [130]. Native American ancestry accounts for a large share of the population (~45%) occur in Latin Americans, which is unique [129, 131]. Furthermore, the proportion of ancestry in each admixed population varies significantly on an individual basis. For example, among African-Americans, the percentage of European ancestry ranges from 2 to 98% [128]. Since there is a strong link between ancestry proportion and skin color in admixed people, their wide skin color may be due to their highly diverse genetic makeup [130, 132]. Admixture mapping or interaction studies in admixed populations have also identified many well-known pigmentation candidate genes in Europeans. For example, tyrosinase (*TYR*) has the rs1042602 nonsynonymous substitution (S192Y), which was identified in European Africans from Cape Verde [130] and African-Americans [133]. Variants in Agouti-signaling protein (*ASIP*), such as rs6058017, have been found in various populations around the world at varied rates [134] and were also reported to be connected with brown eyes and dark hair in European Americans, Brazilians, and African-Americans [15]. Furthermore, in African-Americans, *KITLG* displayed strong selective sweep signals, and people with a high melanin index have a marked prefer-

ence for homozygotes of the African-specific gene (ancestral allele) at rs642742 (dark skin) [133].

However, some research represents contradictory findings. There is a connection between Native American ancestry and skin pigmentation in a Hispanic population that was not observed in a group of Puerto Rican women [132]. When tested in African-Americans and a combined population of African-Caribbeans and African-Americans, one of the critical single-nucleotide polymorphism loci in OCA2, rs1800404, had a significant impact on skin pigmentation but was absent in an independent investigation of African-Caribbean samples [133]. It is crucial to note that distinct genetic pathways for skin color variation exist in different populations; however, when evaluating detailed data, including ancestral populations and sample size utilized to evaluate admixed populations, caution should be exercised, as these could lead to skewed results [129, 133].

Current Trends in Improvement of Skin Color

In cosmetics, beauty therapy, and dermatology, current applications for the treatment of skin pigmentation defects and the enhancement of skin tone are relevant aspects. Inhibition of enzymes involved in various stages of melanogenesis, such as microphthalmia transcription factor (*MITF*), *TYR*, *MC1R*, laser therapies, ultrasound, dermabrasion, exfoliation, destruction of melanocytes, interfering with melanosomal maturation and melanin transfer and melanosomes' number and size. Effective treatments typically incorporate 2 or more approaches that have a synergistic effect. Active ingredients are chosen for their ability to monitor pigmentation while staying low in toxicity from both natural and synthetic sources [135]. The comprehensive structure-activity relationship studies will also be used to identify new and advanced combinations of ingredients with given therapeutic profiles and mechanisms. Although all of these applications

inhibit melanogenesis, just a few made it to the commercial product due to clinical trials, cutaneous absorption, and cytotoxicity [136, 137].

Conclusion

Skin color unquestionably impacts the composition and microenvironment activity. Therefore, the contrast of dermatological ailments between distinct race-related categories is remarkable. Skin color adaptation is a challenging procedure since different populations have shared and separate genetic processes involving many genes with different impact advantages on the phenotypes. An enormous collection of phenotype data and high-coverage whole-genome sequences could help researchers develop more accurate gene-environment interactions and genetic architecture models and learn more about minor ethnic groups. Refinement of skin color is an age-old craving of humans with ever-evolving drifts.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Both authors contributed equally to conception, preparing, drafting, editing, revising, finalizing, and approving the manuscript.

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