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Molecular insights into skin pigmentation: Unraveling the role of key genes and miRNAs in melanogenesis

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Abstract

Human skin pigmentation is a complex phenotype governed by an interplay of genetic, biochemical, and physiological factors. Melanogenesis involves tightly regulated enzymatic pathways that control the balance between eumelanin and pheomelanin synthesis, ultimately determining individual skin color and influencing susceptibility to pigmentation disorders and UV-related health outcomes. An extensive literature review was conducted to construct a comprehensive molecular framework of skin pigmentation. Key genes involved in melanogenesis, including TYR, along with regulatory microRNAs (miRNAs), were systematically analyzed. Relevant studies addressing environmental influences-particularly ultraviolet (UV) exposure-and pigmentation disorders were also evaluated. This review elucidates the central roles of melanogenic genes and miRNAs in regulating pigment production and melanocyte function. Multiple miRNAs were identified as critical modulators of melanogenesis-related pathways. Furthermore, the molecular mechanisms underlying pigmentation disorders, including oculocutaneous albinism, were characterized. Environmental factors, especially UV radiation, were shown to exert significant effects on melanogenic signaling and skin color variation. Skin pigmentation is regulated through a multifaceted network of genetic, epigenetic, and environmental factors. By integrating current molecular insights, this review advances understanding of melanogenesis and associated disorders, providing a robust foundation for future research and potential therapeutic strategies targeting pigmentation-related conditions.

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Highlights

What is current knowledge?

Skin pigmentation is now understood as a highly regulated, multifactorial process shaped by genetic determinants such as key melanogenic enzymes (Including TYR), epigenetic regulators like microRNAs, and environmental influences-most notably UV radiation-which together control melanocyte function, melanin synthesis, and the balance between eumelanin and pheomelanin; current knowledge also clarifies the molecular bases of pigmentation disorders such as oculocutaneous albinism, highlighting how disruptions in these pathways lead to altered pigmentation phenotypes.

What is new here?

Skin pigmentation is already known to be controlled by a complex interaction of genetic, epigenetic, and environmental factors, but what is new in this review is the integrated framework it provides-bringing together melanogenic genes, regulatory microRNAs, UV responsive pathways, and the molecular basis of pigmentation disorders into a single cohesive model that clarifies how these layers collectively shape pigmentation biology.

Introduction

The skin, a remarkably versatile organ, performs far more than acting as a physical barrier (1). It is crucial for numerous life-sustaining physiological processes. This complex tissue defends the body against a range of external threats, including ultraviolet (UV), visible, and infrared radiation, environmental toxins, chemical agents, and physical trauma. Simultaneously, it prevents the loss of internal fluids and serves as the body's initial defense against microbial invaders (2). Beyond protection, the skin is vital for regulating body temperature, participating in immune responses, and performing endocrine and metabolic functions (3). Its role in sensory perception and the formation of personal identity further underscores its significance beyond simple physical safeguarding. These diverse functions are maintained by intricate biological systems governed by both protein-coding genes and non-coding RNA molecules (4).

A prominent visual characteristic of skin is its pigmentation, a result of precisely coordinated molecular and cellular interactions (5). Skin color originates from the production and distribution of melanin; a pigment synthesized within specialized cells called melanocytes through a process known as melanogenesis (4). The spectrum of human skin tones arises primarily from variations in the type and amount of melanin produced, factors influenced by both genetic makeup and environmental cues, particularly exposure to UV light (6). Melanocytes do not operate independently; they engage in close communication with neighboring keratinocytes and fibroblasts via paracrine signaling (7).

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This intercellular dialogue regulates various aspects of melanocyte behavior, including their survival, proliferation, and melanin synthesis. Keratinocytes produce an array of growth factors and cytokines that support and stimulate melanogenesis (8). A central regulator in this process is MITF (Microphthalmia-associated transcription factor), which integrates upstream signals and directs the expression of genes involved in melanin production (8,9). The actual synthesis of melanin occurs within melanosomes, specialized organelles within melanocytes that contain essential enzymes such as tyrosinase. Protein complexes ensure the correct localization and activity of these enzymes within the melanosomes (10). Following synthesis, melanosomes are transferred from melanocytes to keratinocytes, where they contribute to skin coloration and protection against light. In addition to these fundamental mechanisms, melanin production is also influenced by non-coding RNAs and modulated by both internal factors (Such as hormones and inflammation) and external factors (Such as UV radiation and pollutants) (11). These additional layers of regulation highlight the intricate nature of pigmentation control.

From a clinical and genetic standpoint, skin pigmentation extends beyond mere aesthetics. Differences in pigmentation affect an individual's susceptibility to UV damage and are associated with various dermatological conditions (12). Advances in genetic research have revealed that mutations in specific genes can disrupt pigmentation, leading to inherited disorders (1). The study of these genetic skin disorders has been crucial in identifying key regulators and pathways involved in pigment formation (3). This review aims to investigate the genetic underpinnings of human skin pigmentation and to elucidate the molecular mechanisms that govern pigmentation disorders. By gaining a deeper understanding of this complex trait, we can better inform strategies for disease prevention, diagnosis, and personalized treatment approaches.

Methodological framework for literature-guided gene prioritization

Data acquisition and preprocessing

To support our literature review with a structured gene prioritization framework, we adopted a previously curated list of 124 pigmentation-associated genes compiled by Baxter et al. (2019). Their integrative approach combined data from Gene Ontology (GO), Mouse Genome Informatics (MGI), and OMIM. This gene set served as a reference scaffold to guide our thematic synthesis of the molecular mechanisms involved in skin pigmentation (Supplementary Table 1) (13).

Constructing the protein-protein interaction network

To better contextualize the functional relationships among pigmentation-related genes, we utilized the STRING database (https://string-db.org/) to retrieve protein-protein interaction (PPI) data. This network-based perspective provided a systems-level view of potential interactions, which informed the thematic organization of our review. The integrated network served as a conceptual map to cluster genes into functional modules discussed in subsequent sections.

Network analysis and visualization

The NetworkX Python package (https://github.com/networkx/networkx) was employed for network visualization and analysis. We applied the concept of betweenness centrality (BC) to the merged STRING interaction data. In graph theory, BC reflects the influence of a node on network connectivity. A node with a high BC score signifies that its removal would disrupt network communication to a greater extent. This analysis was not intended as a standalone result but rather as a heuristic to prioritize genes for deeper literature-based exploration. The final network visualization (Figure 1) depicts node size proportional to BC score and node color corresponding to degree (Number of interacting partners). Darker and larger nodes represent proteins with greater influence on network connectivity. Edge width and color intensity indicate the strength of the predicted interaction between connected proteins.

Gene selection and functional annotation

Based on network centrality and interaction density, we selected a subset of 50 genes to anchor our literature synthesis. These genes were mapped to four major molecular pathways-melanogenesis, Fanconi anemia/DNA repair, cell cycle regulation, and MAPK signaling-which structure the thematic sections of this review (Table 1). This integrative approach allowed us to explore both well-established and emerging regulatory mechanisms in skin pigmentation.

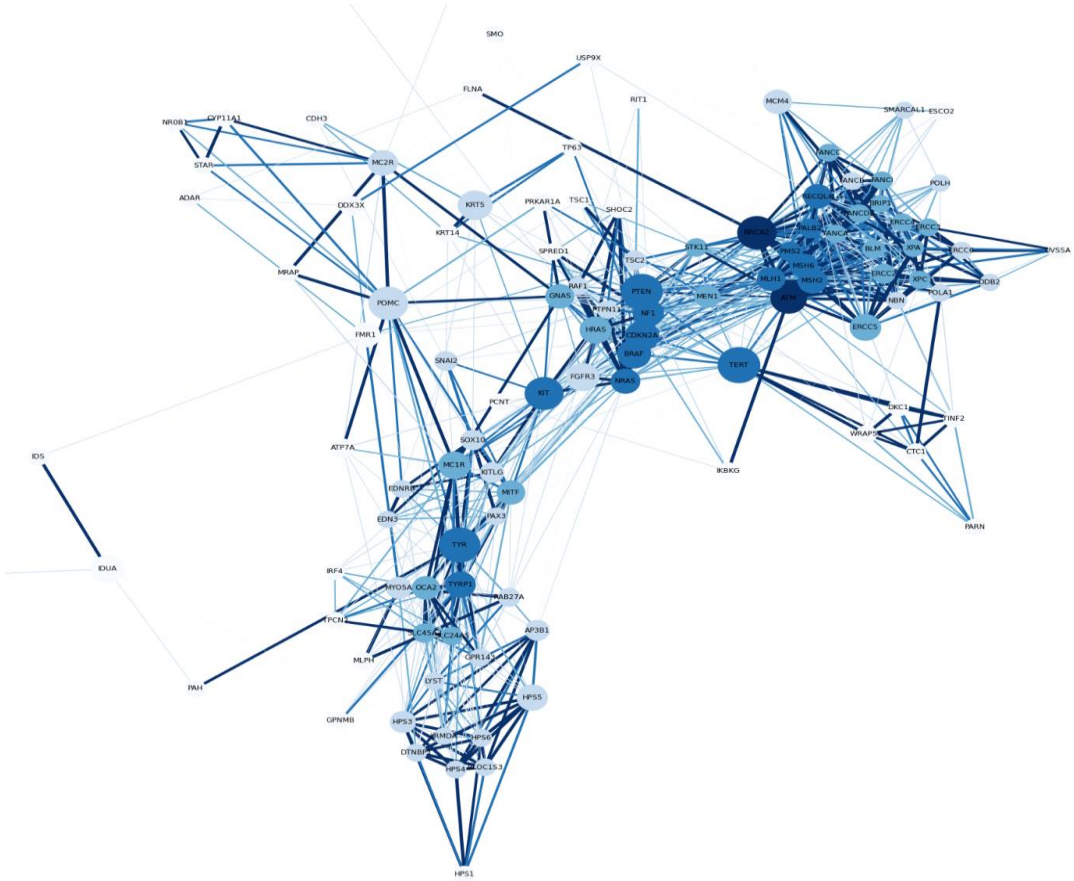

Figure 1. Interaction network of genes involved in human skin pigmentation

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Table 1. Functional pathways and associated genes in skin pigmentation disorders

Functional pathway	Genes	Gene function	Organ specificity	Ref
Melanogenesis	TYR, TYRP1, OCA2, SLC45A2, SLC24A5, MITF	Regulate the synthesis, transport, and distribution of melanin, influencing skin, hair, and eye pigmentation.	Skin Hair Eye	(96,97)
Fanconi anemia	FANCA, FANCC, FANCD1 (Also called BRCA2), FANCD2, FANCI, FANCJ (Also called BRIP1), and FANCN (Also called PALB2)	Essential for repairing interstrand cross-links in DNA, which helps maintain genomic stability and proper cellular function.	Heart Kidney Bone Skin	(22,98,99)
DNA Repair and cell cycle checkpoint	ATM, BLM, ERCC2, ERCC3, ERCC4, ERCC5, MSH2, MSH6, MLH1, PMS2, RECQL4, XPA, XPC, SMARCAL1, MCM4, PTEN, STK11, CDKN2A	Function in a diverse set of pathways that involve the recognition and removal of DNA. lesions, tolerance to DNA damage, and protection from errors of incorporation made during DNA replication or DNA repair.	All human body organs	(100,101)
MAPK signaling pathway	BRAF, HRAS, NRAS, KIT, NF1	Regulate gene expression, mitosis, metabolism, motility, survival, apoptosis, and differentiation.	All human body organs	(102)

Molecular pathways involved in skin pigmentation

Melanogenesis pathway

Melanin produced by melanocytes gives the skin its color. Variations in the amount, type, and distribution of melanin in the skin are responsible for the wide range of skin colors observed in humans. Melanogenesis refers to the biological process through which melanocytes synthesize melanin, the pigment responsible for the color of the skin, hair, and eyes. This process is tightly regulated and involves several key genes and proteins (Figure 2). The synthesis of melanin pigments occurs in specialized organelles within melanocytes called melanosomes. Within these melanosomes, melanogenic enzymes such as tyrosinase (TYR) and related proteins are involved in melanin synthesis. These enzymes are properly localized with the help of specific protein complexes. Once melanosomes are loaded with melanin, they are transferred to keratinocytes, the predominant cell type in the outermost layer of the skin (14-16).Variations in the amount, type, and distribution of melanin in the skin are responsible for the wide range of skin colors seen in humans Melanogenesis refers to the biological process through which melanocytes synthesize melanin, the pigment responsible for the color of our skin, hair, and eyes. This process is tightly regulated and involves several key genes and proteins. The synthesis of melanin pigments occurs in specialized organelles within melanocytes called melanosomes. Within these melanosomes, melanogenic enzymes such as tyrosinase (TYR) and related proteins are involved in the synthesis of melanin. These enzymes are addressed with the help of specific protein complexes. Once the melanosomes are loaded with melanin, they are then transferred to keratinocytes, the predominant cell type in the outermost layer of the skin.

TYR

Tyrosinase (TYR), located on chromosome 11q14.3, consists of six exons and is mainly expressed in the skin and eyes. It plays an important role in melanin biosynthesis by converting tyrosine into dopaquinone (DQ) through its enzymatic activities. Variants in TYR can lead to oculocutaneous albinism type 1 (OCA1), with OCA1A showing complete inactivity and OCA1B showing reduced activity. Nonpathologic alleles contribute to normal pigmentation variations. Dopa enhances TYR activity, promoting melanin synthesis (17,18).

TYRP1

TYRP1, also known as OCA3, is located on chromosome 9p23 and consists of eight exons. It encodes a melanosomal enzyme essential for eumelanin synthesis and stabilizes the TYR protein while modulating its activity. Defects in TYRP1 are linked to oculocutaneous albinism type III and rufous oculocutaneous albinism. It catalyzes the oxidation of DHICA to indole-5,6-quinone-2-carboxylic acid and can hydroxylate tyrosine, underscoring its role in pigmentation (19,20).

OCA2

OCA2 encodes the human equivalent of the mouse p (Pink-eyed dilution) gene, serving as an integral membrane transporter that facilitates the movement of small molecules, particularly tyrosine, crucial for melanin synthesis. It significantly influences skin and eye color variations (Brown or blue). Mutations in OCA2 are associated with type 2 oculocutaneous albinism (OCA2). The gene product contributes to a melanosome-specific chloride current, regulating pH to optimize TYR activity for melanin production and affecting TYR processing. Alternative splicing results in multiple transcript variants, highlighting its complex role in pigmentation (21,22).

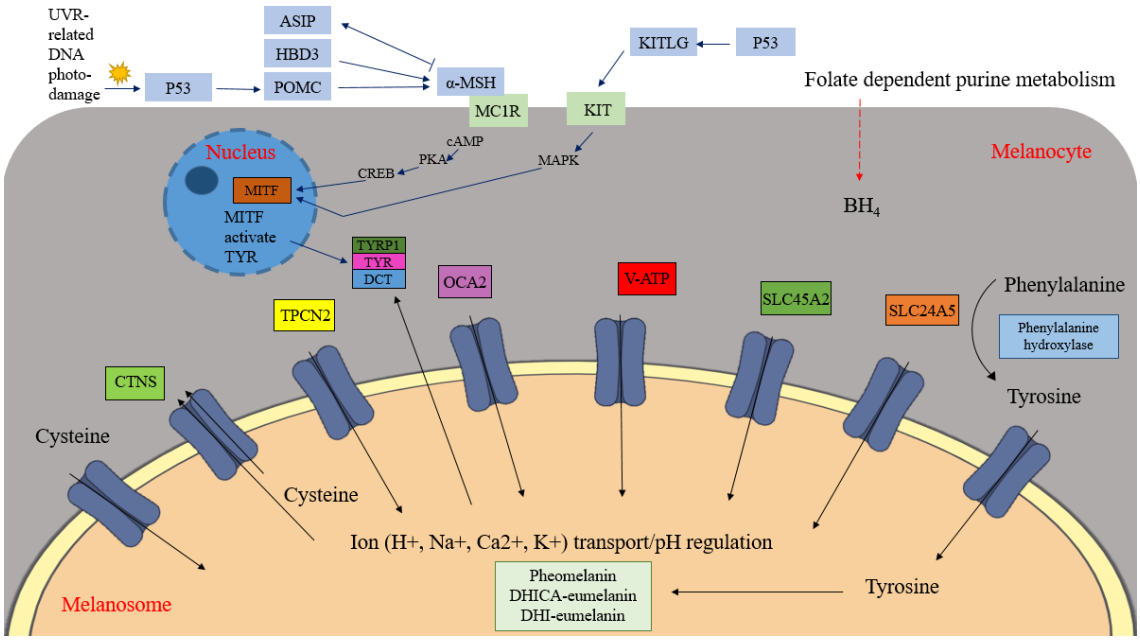

Figure 2. In the process of melanogenesis within melanocytes and melanosomes, various genes, proteins, and ion transport mechanisms play crucial roles. These components are intricately integrated to regulate melanin production.

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SLC45A2

SLC45A2, also known as OCA4, MATP, or SHEP5, is located on chromosome 5p12.2 and has seven exons. It encodes a carrier protein essential for melanin synthesis, expressed in various tissues, including skin and testicles. The protein regulates melanin formation by maintaining pH and ionic balance in melanosomes and facilitating tyrosine trafficking. Under normal conditions, it elevates melanosomal pH, enabling copper binding to TYR, which is critical for melanin production (23).

SLC24A5

SLC24A5, located on chromosome 5p13.2, also consists of seven exons and is expressed in tissues such as skin and kidney. It encodes a membrane-associated transport protein important for melanogenesis, facilitating tyrosine trafficking and proton transport to melanosomes. This regulation ensures optimal pH for TYR activity and melanin production. Mutations in SLC24A5 lead to oculocutaneous albinism type 4 (OCA4), while polymorphisms are associated with skin and hair color variations. The protein is notably expressed in melanoma cell lines, underscoring its significance in pigmentation and melanoma biology (24,25).

MC1R

MC1R (Melanocortin-1 receptor) is located on chromosome 16q24.3 and consists of a single exon. As a seven-transmembrane G protein-coupled receptor, it plays a key role in melanogenesis by being activated by melanocyte-stimulating hormones (MSH) and adrenocorticotropic hormone (ACTH). This activation stimulates eumelanin production via the cAMP pathway, promoting the conversion from pheomelanin (Red pigment) to eumelanin (Black pigment). MC1R also enhances the activity of TYR, TYRP1, and TYRP2. Mutations can lead to increased pheomelanin and lighter pigmentation, influencing sun sensitivity and melanoma risk. Over 30 variant alleles have been identified, highlighting its significance in pigmentation and UV response (26).

MITF

MITF (Melanocyte Inducing Transcription Factor) is encoded by a gene on chromosome 3p14.2 and features basic helix-loop-helix and leucine zipper domains. It regulates melanocyte survival, differentiation, and melanosome biogenesis by binding to promoter regions of key pigmentation genes such as TYR and TYRP1. MITF is also involved in nutrient response through the MTOR signaling pathway. Mutations in MITF are linked to auditory-pigmentary syndromes such as Waardenburg syndrome type 2 and Tietz syndrome, as well as cutaneous malignant melanoma. This transcription factor is essential for the development of various cell types, including melanocytes, mast cells, and retinal pigment epithelium (8,27).

Fanconi anemia pathway

The Fanconi anemia (FA) pathway primarily functions in DNA repair. However, studies have revealed that individuals with Fanconi anemia often exhibit skin abnormalities, including changes in skin pigmentation (28). Although the FA pathway itself may not directly affect skin color, the genes associated with this pathway play essential roles in maintaining skin health and preventing cancer (Figure 3). When the FA pathway is disrupted, it can lead to an increased risk of skin cancer and other malignancies (29). Thus, understanding these genetic connections is crucial for both skin health and overall well-being.

FANC genes

An increased risk of aberrant skin alterations, such as hyper- or hypopigmentation, café-au-lait spots, wart growth, actinic keratosis, and melanoma and nonmelanoma skin malignancies, is a characteristic of Fanconi anemia (FA), a rare genetic condition (30). Because FA is associated with defective DNA repair pathways, patients are more susceptible to these diseases. It is therefore recommended that people with FA undergo annual full-body skin examinations from a young age until at least 18 years of age (1). FA is caused by genetic mutations in proteins necessary for activation of the Fanconi anemia pathway, which plays a crucial role in DNA damage repair (30). Defects within this pathway result in increased vulnerability to DNA damage and crosslinking, which can often be identified through chromosomal fragility tests (31). Although specific characterization of FA-associated skin findings is currently lacking, case series have reported that altered pigmentation is the most common cutaneous clinical feature, affecting up to 68% of FA patients (28). These pigment alterations appear as hypopigmented macules, flexural hyperpigmentation, and café-au-lait macules (32). Fanconi anemia is caused by mutations in the FANC genes, particularly those related to telomere maintenance and interstrand crosslink repair. Patients with FA frequently experience poikilodermatous skin changes, which are characterized by telangiectasia, hyperpigmentation, and hypopigmentation (33). DNA interstrand crosslinks (ICLs), which are covalent connections between two DNA strands, are actively repaired by FANC proteins. ICLs can cause genomic instability and are extremely hazardous. The Fanconi anemia core complex comprises FANC proteins, including FANCA, FANCB, FANCC, FANCD1 (Also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (Also called BRIP1), FANCL, FANCM, and FANCN (Also called PALB2). This complex is essential for identifying and repairing ICLs, thereby maintaining the integrity of skin genetic material (34). In addition, FANC proteins are involved in cellular defense mechanisms against reactive oxygen species (ROS) and oxidative stress (10). Decreased FANC protein function in FA patients affects the skin's cellular defense mechanisms and makes it more vulnerable to oxidative stress-induced damage because the skin is exposed to various environmental stimuli that can produce ROS and cause DNA damage (35).

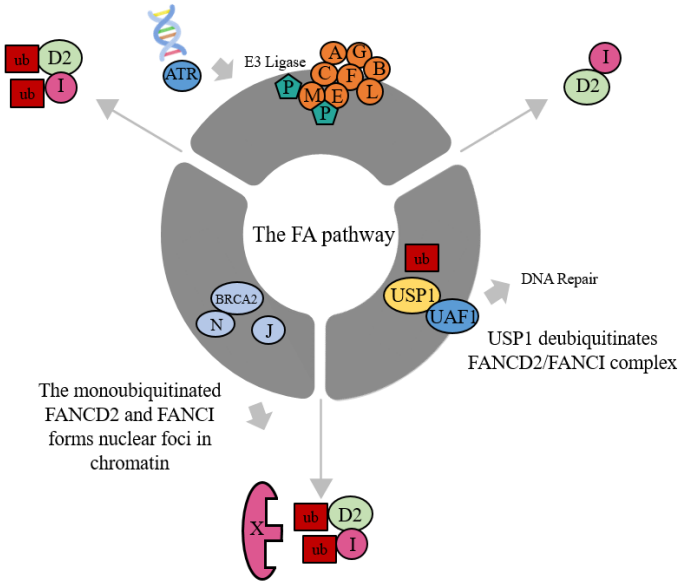

Figure 3. After DNA damage, the ATR kinase activates the FA core complex (Composed of FANCA/B/C/E/F/G/L/M). This complex acts as an E3 ubiquitin ligase, monoubiquitinating FANCD2 and FANCI. The monoubiquitinated FANCD2/FANCI complex then localizes to chromatin, where it interacts with other FA proteins and DNA repair factors. The USP1-UAF1 protein complex subsequently deubiquitinates FANCD2/FANCI, allowing their release from chromatin. Additionally, USP1 plays a role in directing FANCD2/FANCI to DNA repair foci.

DNA repair and cell cycle regulation

Cell cycle checkpoints

The integrity of our DNA is constantly under threat from various sources, including environmental factors like ultraviolet (UV) radiation. Cell cycle checkpoints: The integrity of DNA is constantly threatened by various sources, including environmental factors such as ultraviolet (UV) radiation. UV radiation can damage DNA within skin cells, leading to mutations. If left unrepaired, these mutations can lead to abnormal cell behavior, including altered pigmentation or even skin cancer (35). This is where DNA repair mechanisms come into play. They work to identify and correct damage that has occurred in DNA. For instance, if a skin cell's DNA is damaged by UV radiation, DNA repair mechanisms are activated to fix the damage (36). If the damage is too severe and cannot be repaired, the cell may undergo apoptosis, or programmed cell death (36,37). Cell cycle checkpoints are crucial in this process. They are control mechanisms that ensure the fidelity of DNA replication and division. Before a cell divides, it must pass through several checkpoints at which the cell's health and DNA integrity are assessed. If the cell's DNA is damaged, the cell cycle is halted at one of these checkpoints to allow DNA repair. If the damage is irreparable, the

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cell may be directed to undergo apoptosis (37). UV radiation can cause damage to the DNA within our skin cells, leading to mutations1If left unrepaired, these mutations can lead to abnormal cell behavior, including altered pigmentation or even skin cancer. They work to identify and correct any damage that has occurred to the DNA. For instance, if a skin cell's DNA is damaged by UV radiation, DNA repair mechanisms are activated to fix the damage. If the damage is too severe and cannot be repaired, the cell may undergo apoptosis, or programmed cell death. They are control mechanisms that ensure the fidelity of DNA replication and division. Before a cell divides, it must pass through several checkpoints where the cell's health and the integrity of its DNA are assessed. If the cell's DNA is damaged, the cell cycle is halted at one of these checkpoints to allow for DNA repair. If the damage is irreparable, the cell may be directed to undergo apoptosis

DNA repair mechanisms are divided into four categories

Base Excision Repair (BER) repairs single-base damage caused by oxidative stress, deamination, or other chemical modifications (Figure 4a). Specific DNA glycosylases recognize and remove damaged bases. Subsequently, DNA polymerase fills the resulting gap, and DNA ligase seals the nick. Nucleotide Excision Repair (NER) repairs bulky DNA lesions, such as UV-induced pyrimidine dimers and DNA crosslinks (Figure 4b). Key proteins involved in this pathway include XPC, XPA, and TFIIH. In NER, a short segment of the damaged DNA strand is excised, followed by DNA synthesis to restore the gap. Double-strand breaks (DSBs) are repaired by two major pathways (Figure 4c). Homologous Recombination (HR) repairs DSBs during the S and G2 phases of the cell cycle by using a homologous DNA template, typically the sister chromatid, to accurately restore the broken strand. Key proteins involved in HR include RAD51, BRCA1, and BRCA2. In contrast, Nonhomologous End Joining (NHEJ) repairs DSBs throughout the cell cycle by directly ligating broken DNA ends without requiring a homologous template, which may result in small insertions or deletions at the repair site. Mismatch Repair (MMR) corrects base-base mismatches and small insertion–deletion loops that arise during DNA replication. This pathway enhances replication fidelity by recognizing mismatched nucleotides, removing the error-containing strand, and resynthesizing DNA using the undamaged strand as a template (Figure 4d).

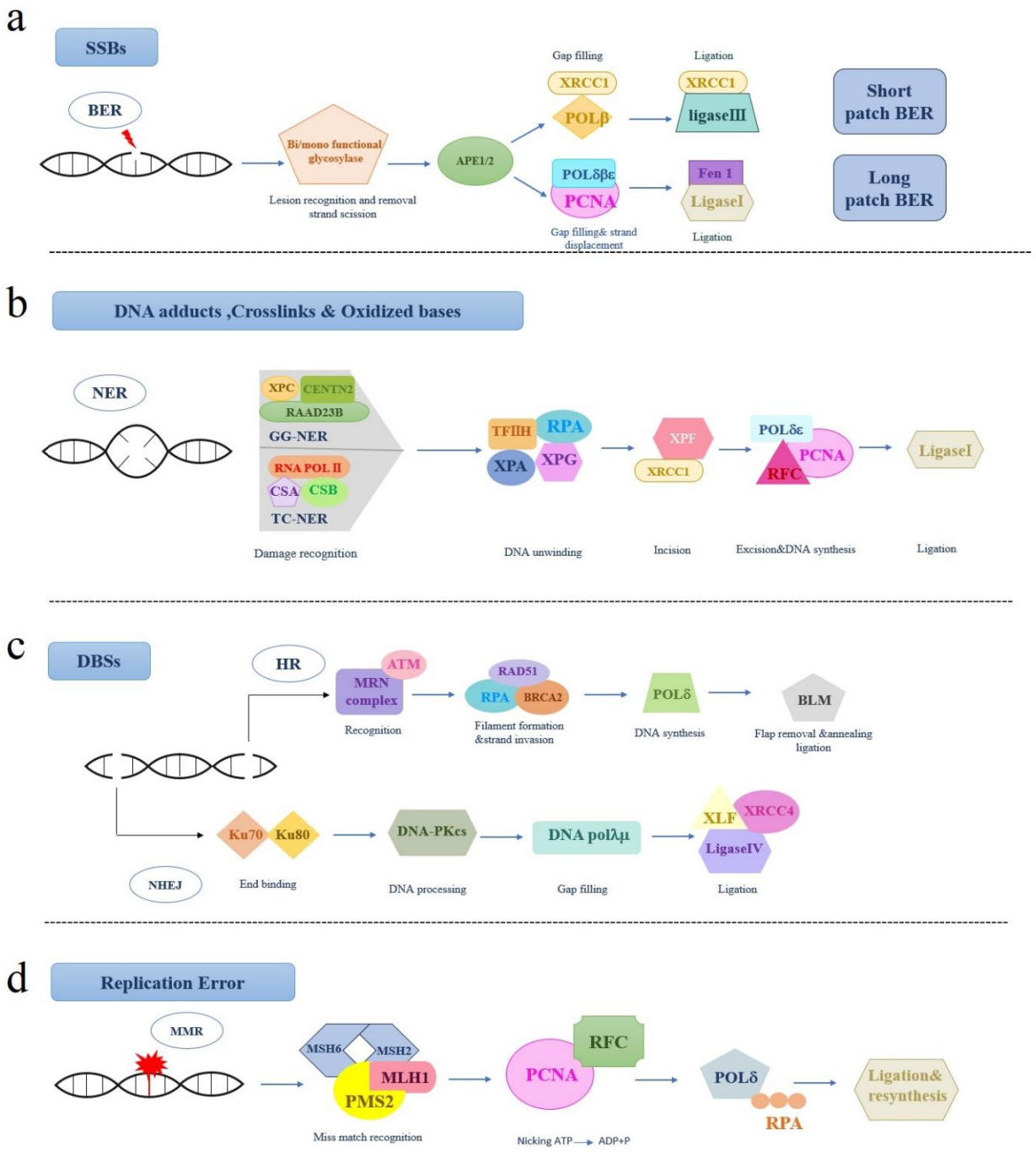

Figure 4. The key mechanisms for repairing various types of DNA damage: Base Excision Repair (a), Nucleotide Excision Repair (b), Double-Strand Breaks (c), and Nonhomologous End Joining (d).

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Relation of DNA repair to skin pigmentation: Skin pigmentation, or skin color, is primarily determined by melanin, a pigment produced by cells called melanocytes. When skin cells are exposed to UV radiation, DNA damage can occur, leading to melanin production as a protective response. This process, known as tanning, is essentially an adaptive response that protects the skin from further DNA damage (35). Therefore, although DNA repair and cell cycle checkpoints may not directly influence skin pigmentation, they play a crucial role in maintaining the health and normal function of skin cells, including melanocytes. Disruptions to these processes can potentially lead to abnormal skin pigmentation. In summary, DNA repair mechanisms and cell cycle checkpoints are essential for maintaining the health and normal function of all cells, including those involved in skin pigmentation. Although they may not directly regulate skin pigmentation, they help ensure that pigment-producing cells are healthy and that their DNA remains intact (35-37). When skin cells are exposed to UV radiation, it can cause DNA damage, leading to the production of melanin as a protective response. This process, known as tanning, is essentially an adaptive response to protect the skin from further DNA damage. Any disruptions to these processes can potentially lead to abnormal skin pigmentation. While they might not directly regulate skin pigmentation, they help ensure that the cells producing the pigment are healthy and their DNA is intact

ATM

The ATM (ATM Serine/Threonine Kinase) gene, located on chromosome 11 (11q22-23), consists of 66 exons and encodes a 370 kDa protein crucial for DNA repair and cell cycle regulation (38). Mutations in ATM are linked to ataxia telangiectasia. The ATM protein phosphorylates various downstream proteins to maintain genome stability and acts as a checkpoint kinase. Additionally, ATM influences melanin synthesis by affecting the transcription factor MITF (Microphthalmia-Associated Transcription Factor), which regulates pigmentation genes. When DNA damage occurs, ATM phosphorylates MITF at S414, redirecting its function from pigmentation to DNA repair (39).

BLM

The BLM gene, located on chromosome 15q26.1, consists of 22 exons and encodes the DNA helicase RECQL3, crucial for genome stability (40). Mutations in BLM lead to Bloom syndrome, an autosomal recessive disorder characterized by heightened sensitivity to sunlight and associated skin issues. A notable symptom is a butterfly-shaped rash on the nose and cheeks, which can also appear on other sun-exposed areas. This sensitivity arises from increased DNA damage and impaired repair mechanisms due to BLM mutations (41).

ERCC2

Located on chromosome 19q13.3, the ERCC2 gene, also known as XPD, consists of 23 exons spanning about 54,000 base pairs. It encodes the XPD protein, a component of the TFIIH complex, which is essential for DNA repair and gene transcription (42). A primary function of ERCC2 is to repair UV-induced DNA damage. Mutations in this gene can disrupt the Nucleotide Excision Repair (NER) pathway, leading to the accumulation of DNA damage, such as cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs). This accumulation can interfere with melanin production, affecting skin pigmentation. Individuals with ERCC2 mutations may develop xeroderma pigmentosum, increasing their risk of skin and eye cancers due to heightened UV sensitivity (43).

ERCC3

The ERCC3 gene, or XPB, is located on chromosome 2q21 and encodes a 782-amino-acid protein that is part of the TFIIH complex. This complex includes an ATP-dependent DNA helicase crucial for transcription initiation and DNA repair through transcription-coupled repair (TCR) and NER pathways (44). ERCC3 also influences skin biology, particularly pigmentation. UV radiation stimulates melanocytes to increase melanin production, a protective response against UV damage. This process involves various factors, including DNA damage and interactions among skin cells (2).

ERCC4

The ERCC4 gene, located on chromosome 16p13.12, encodes the XPF protein through its 11 exons. Together with ERCC1, XPF forms a nuclease essential for DNA repair and chromosome stability (45). Mutations in ERCC4 can lead to hereditary conditions such as Fanconi anemia, segmental XFE progeroid syndrome, and xeroderma pigmentosum (XP-F) (46,47). XPF is crucial in the nucleotide excision repair (NER) pathway, which addresses UV-induced DNA damage in skin cells, including melanocytes. When DNA lesions occur, XPF activates the NER pathway to repair the damage. However, mutations impair XPF function, reducing the ability to repair UV damage and affecting melanocyte behavior, potentially leading to pigmentation abnormalities (2).

ERCC5

Also known as XPG, the ERCC5 gene is located on chromosome 13q22-33 and consists of 15 exons and 14 introns. It plays an important role in DNA repair mechanisms (45,48). Mutations in ERCC5 can cause XP-G, a severe subtype of xeroderma pigmentosum. Individuals with XP-G often exhibit abnormal skin pigmentation, such as lentigines and hypo- or hyperpigmentation in sun-exposed areas. The enzyme encoded by ERCC5 is critical for repairing UV-induced DNA damage, and mutations disrupt this function, leading to genomic instability and pigmentation issues in XP-G and other NER disorders (2).

MSH2, MSH6, MLH1, and PMS2

Lynch syndrome is an autosomal dominant condition that increases the risk of colorectal cancer (CRC), endometrial cancer (EC), and other cancers, linked to four mismatch repair (MMR) genes: MSH2, MLH1, MSH6, and PMS2 (49). MSH2 encodes a 935-amino-acid protein located on chromosome 2p21-22, while MLH1 is found on chromosome 3p21 and encodes a 756-amino-acid protein. MSH6, located on chromosome 2 (2p15-16), encodes a 1360-amino-acid protein (153 kDa), and PMS2 is situated on chromosome 7p22.1. MLH1 forms a heterodimer with PMS2, and MSH2 pairs with MSH6. The MLH1/PMS2 complex identifies mismatched nucleotide base pairs and initiates repair, whereas the MSH2/MSH6 complex functions as an endonuclease. These genes are responsible for correcting errors during DNA replication, such as improper base pairing or slippage of DNA polymerization. Failure in mismatch repair results in a mutator phenotype characterized by microsatellite instability (MSI) (50,51). UV radiation can cause DNA strand breaks, which are repaired by mechanisms including base excision repair (BER), nucleotide excision repair (NER), and MMR. While BER and MMR specifically address non-bulky lesions, NER repairs bulky lesions. Ineffective repair pathways due to excessive UV exposure can increase the risk of mutagenesis and allow photoproducts to persist (52).

RECQL4

The RECQL4 gene, located on chromosome 8q24.3, encodes a 1208-amino-acid helicase that plays an important role in nucleotide excision repair (NER), essential for genomic integrity (53,54). Mutations in RECQL4 are linked to Rothmund-Thomson syndrome (RTS), which causes photosensitivity and skin abnormalities due to increased UV sensitivity in affected cells. Following UV exposure, RECQL4 relocates to nuclear foci and enhances the resolution of DNA lesions; its depletion slows this process. RECQL4 interacts with XPA, a key NER protein, suggesting it may assist in unwinding DNA post-damage verification. Although its exact role in skin pigmentation is unclear, RECQL4's involvement in NER indicates a potential influence on melanocyte function, warranting further research into its interactions and implications for pigmentation disorders (5,55).

SMARCAL1

Also known as HARP, the SMARCAL1 gene is found on chromosome 12q24.31 and is crucial for chromatin remodeling and transcription regulation. As a member of the SWI/SNF family, SMARCAL1 possesses ATPase and helicase functions, converting single-stranded DNA bound by Replication Protein A (RPA) into double-stranded DNA (56). Mutations in SMARCAL1 are associated with Schimke immune-osseous dysplasia (SIOD), characterized by growth dysfunctions and T-cell immunodeficiency. This disorder likely arises from impaired stabilization of replication forks during DNA damage. Recent studies indicate that SMARCAL1 deficiency alters gene expression in dermal fibroblasts, affecting stress response, signaling, and cell cycle regulation. These findings suggest that SMARCAL1 is important for maintaining skin integrity, and its dysregulation could contribute to skin disorders. Further research is needed to clarify SMARCAL1's role in skin biology and explore potential therapeutic applications (57).

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XPA and XPC

The XPA and XPC genes are critical components of the nucleotide excision repair (NER) mechanism, which addresses DNA damage from ultraviolet (UV) radiation, a major cause of skin cancers like squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) (58). XPA is the first human NER protein that preferentially binds to damaged DNA and acts as a nucleation center for other repair proteins, facilitating the excision and synthesis of new DNA. Mutations in XPA can lead to severe forms of Xeroderma Pigmentosum (XP), characterized by excessive UV sensitivity and a heightened risk of skin cancers (59). In contrast, XPC is essential for the initial detection of DNA damage, binding tightly to damaged regions and altering their structure to recruit additional repair factors. XPC's recruitment is influenced by p38 MAPK signaling, which regulates chromatin relaxation and protein degradation, and is also controlled by p53 and promoter methylation (60).

PTEN

The PTEN gene, located on chromosome 10q23.31, encodes a protein that functions as a lipid and protein phosphatase, crucial for cell division, growth, and survival (61). Reduced levels of PTEN have been linked to various nonmelanoma skin cancers, including skin papilloma and SCC. PTEN regulates global genomic nucleotide excision repair (GG-NER), which repairs UVB-induced DNA damage. A decrease in PTEN compromises GG-NER, increasing skin cancer risk, and this process is also affected by the AKT/p38 signaling pathway. In PTEN-deficient cells, restoring XPC levels can recover GG-NER capability. Additionally, reduced PTEN expression is observed in melanoma, where its loss activates AKT, promoting carcinogenesis. While PTEN's role in skin pigmentation is not fully understood, its association with MC1R and influence on the NER pathway likely affect skin tone (62,63).

MCM4

MCM4 (Minichromosome maintenance complex component 4) is a gene on chromosome 8q11.21, part of the MCM complex crucial for DNA replication initiation and elongation in eukaryotic cells. The complex consists of six subunits: MCM2, MCM3, MCM4, MCM5, MCM6, and MCM7, with helicase activity primarily mediated by trimeric complexes of MCM4, MCM6, and MCM7. Up-regulation of MCM4 and related genes (MCM5, MCM6) is associated with DNA damage response, cell cycle regulation, and the G1/S phase transition. Mutations in MCM4 are linked to steroidogenic disorders affecting cortisol production and skin pigmentation, though the exact relationship remains unclear (64-66).

STK11

STK11 (Also known as LKB1) is located on chromosome 19p13.3 and encodes a protein that acts as a tumor suppressor, regulating cell division and proliferation. It is part of the AMPK signaling pathway, which maintains cellular energy balance and influences melanocyte function, the cells responsible for melanin production. Mutations in STK11 are associated with Peutz-Jeghers syndrome, characterized by intestinal polyps and pigmented skin lesions, suggesting a potential link between STK11 and skin pigmentation (67,68).

CDKN2A

CDKN2A is a gene located on chromosome 9p21 that encodes two tumor suppressor proteins, p16 and p14ARF. These proteins are essential for regulating the cell cycle, preventing uncontrolled cell division and facilitating cell repair (69). While CDKN2A is linked to cancer development, it does not directly regulate skin pigmentation. Mutations in this gene increase the risk of melanoma, a skin cancer that may show abnormal pigmentation, but this is a result of the cancer process rather than a direct effect on pigmentation genes (70).

MAPK signaling pathway

Skin color is primarily determined by melanin, a pigment produced by melanocytes within the basal layer of the epidermis. Melanogenesis, the process of melanin production, is tightly regulated by various signaling pathways, the MAPK pathway plays a critical role in determining skin color, influencing the function of melanocytes, the cells responsible for melanin production. Activation of this pathway influences melanocyte proliferation, melanin synthesis, and the response to ultraviolet (UV) radiation, thereby contributing to skin pigmentation and protection against UV damage (6). Mitogen-Activated Protein Kinase (MAPK) signaling pathways are vital for regulating cellular processes including differentiation, cell growth, proliferation, and survival. Regarding skin color, the MAPK pathway plays a major role in melanocyte proliferation and migration (71). These MAPKs can be grouped into four main families; extracellular-signal-regulated kinase (ERKs) which are also known as classic pathways, the c-Jun N-terminal Kinase (JNK), p38 p38/SAPK pathways (72), and the ERK5 pathway. Each of these pathway families is initiated by an extracellular signal that leads to sequential activation of MAP kinase kinase kinase (MAPKKK). Then this MAPKKK initiates a MAP kinase kinase (MAPKK) which phosphorylates MAP kinase. Activation of a MAP kinase subsequently leads to triggering cellular responses that result in MAPK pathway activation (73-75). A large-scale molecular profiling of human cancers has expanded the understanding of the role of MAPK pathways in different human cancers (76). Skin cancers are mostly the result of the mutation in ERK1/2 pathways (74,77). In the investigation of finding the pathways of skin color the first layer is the embryonic crucible, where melanocyte precursors, arising from the neural crest, move toward the epidermis. This migration and development of melanocytes is caused by signaling prowess of Stem Cell Factor (SCF), which binds to its receptor KIT (Known as c-Kit or CD117) on the surface of melanoblasts (Melanocyte precursor cells). This interaction activates the MAPK pathway, promoting the development and migration of melanocytes from the neural crest to the epidermis during embryogenesis. Previous studies have proven that stem cell factor, α-melanocyte hormone, and other factors can activate signaling pathways that promote melanogenesis-related gene expression (Figure 5) (78).

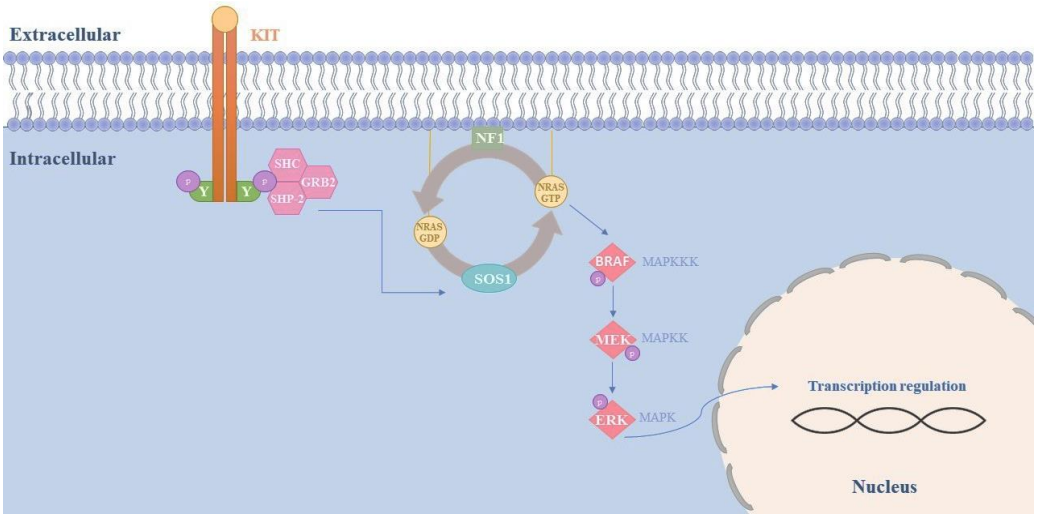

Figure 5. The MAPK signaling pathway is initiated by the conversion of GDP to GTP, activating Ras. Active Ras then binds and activates Raf, leading to the activation of MAPKKK. MAPKKK, also known as active Raf, further activates MAPKK, which in turn activates MAPK. The activated MAPK molecule moves to the nucleus, where it triggers the activation of diverse transcription factors.

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BRAF

BRAF is a kinase in the RAF family that plays a key role in the MAPK pathway, crucial for melanocyte function. Mutations in the BRAF gene, particularly the V600E mutation, are common in melanoma and lead to uncontrolled melanocyte proliferation, contributing to changes in skin color, such as darkened lesions. BRAF phosphorylates and activates MEK1 and MEK2, which then activate ERK1/2, ultimately stimulating transcription factors such as MITF that regulate melanin synthesis. This dysregulation can result in variations in skin pigmentation by upregulating melanogenic genes such as TYR and DCT (12,79,80)

HRAS and NRAS

HRAS and NRAS are GTPases that act as upstream regulators of BRAF in the MAPK signaling pathway. They are activated by external factors such as UV radiation and growth factors, initiating the MAPK cascade. Proper regulation of HRAS and NRAS is essential for melanocyte survival and differentiation. Mutations in these genes can disrupt this regulation, leading to abnormal melanocyte function and changes in skin pigmentation (81,82).

KIT

The KIT gene encodes a receptor tyrosine kinase crucial for melanocyte development, survival, and pigmentation. It activates the MAPK pathway through its ligand, stem cell factor (SCF), and facilitates melanosome transfer to keratinocytes, ensuring even skin pigmentation. Dysregulation can lead to disorders such as piebaldism and familial progressive hyperpigmentation (83,84).

NF1

NF1 (Neurofibromin 1) serves as a negative regulator of RAS proteins, enhancing their GTPase activity to convert active RAS-GTP to inactive RAS-GDP. This regulation is vital for maintaining MAPK signaling balance in melanocytes. Mutations in NF1 can lead to MAPK pathway hyperactivation (85).

Other genes

MEN1

The MEN1 gene, located on chromosome 11q13, consists of 14 exons and encodes the menin protein, a tumor suppressor linked to multiple endocrine neoplasia type 1 (MEN1). Recent studies indicate that MEN1 also plays a role in skin pigmentation by regulating melanocyte development and function through interactions with key transcription factors and signaling pathways. Menin influences the expression of essential genes like MITF (Microphthalmia-associated transcription factor), which is critical for melanocyte development and melanin production. Mutations in the MEN1 gene have been associated with changes in melanin production and distribution, leading to variations in skin pigmentation (86,87).

TERT

The TERT gene, located on chromosome 5p15.33 and consisting of 16 exons, encodes the catalytic subunit of telomerase, a vital enzyme that maintains telomere ends by adding the repeat sequence TTAGGG. This enzyme includes a protein component with reverse transcriptase activity and an RNA component that serves as a template for telomere synthesis. While TERT is traditionally linked to cellular senescence and cancer, emerging research suggests it may also affect skin pigmentation. Evidence indicates that TERT activity could influence melanocyte proliferation and survival, which are crucial for determining skin pigmentation. Additionally, TERT's role in chromosomal repair may further impact melanocyte function and pigmentation regulation (88).

GNAS

The GNAS gene, located on chromosome 20q13.32 and consisting of 13 exons, is essential for skin pigmentation by regulating melanocyte function and melanin synthesis. As a complex imprinted gene, it encodes several proteins, including the stimulatory G protein alpha subunit (Gsα), which mediates signaling from G protein-coupled receptors (GPCRs). Gsα pathways are crucial for melanin production, proliferation, and differentiation in melanocytes. Mutations or dysregulation of GNAS are linked to pigmentation disorders such as McCune-Albright syndrome and pseudohypoparathyroidism, highlighting its role in melanocyte biology (89-91).

KRT5

The KRT5 gene, found on chromosome 12q13.13 with 15 exons, encodes keratin 5, a protein vital for the structural integrity of epithelial cells, particularly in the skin. Keratin 5 is mainly expressed in the basal epidermis, forming heterodimers with keratin 14 to provide mechanical strength. It also regulates melanocyte function by influencing their proliferation, migration, and melanin production. Mutations in KRT5 are associated with skin disorders such as epidermolysis bullosa simplex, which can affect pigmentation, underscoring its significance in skin integrity and pigmentation regulation (10).

cAMP Pathway

The cAMP signaling pathway, mediated by genes such as MSH (Melanocyte-stimulating hormone) and POMC (Pro-opiomelanocortin), plays a pivotal role in regulating skin pigmentation. MSH, a cleavage product of POMC, acts as a potent stimulator of melanogenesis by binding to melanocortin receptors (MC1R) on melanocytes (92). Upon activation, MC1R triggers adenylate cyclase to produce cyclic adenosine monophosphate (cAMP), initiating downstream signaling cascades (93). One key effector of cAMP signaling is protein kinase A (PKA), which phosphorylates CREB (cAMP response element-binding protein), thereby upregulating the transcription of melanogenic enzymes, including TYR, TRP1, and tyrosinase-related protein 2 (TRP2) (94). These enzymes are essential for melanin synthesis, the pigment responsible for skin coloration. Dysregulation of the MSH/POMC/cAMP pathway is associated with various pigmentary disorders, such as vitiligo and hyperpigmentation conditions, underscoring its importance in skin pigmentation regulation (95).

miRNAs and lncRNAs involved in skin pigmentation

The primary pigment responsible for determining skin and hair color in humans is called melanin, which is present in large amounts in the skin, mucosa, retina, pia mater, gallbladder, and ovary (4). Melanocytes are specialized cells that produce melanin. The single melanocyte that connects 10-36 neighboring keratinocytes via dendrites to produce the epidermal melanin unit (EMU) is the "factory" of melanogenesis (96). Not only is the type of melanin produced important, but its final location within the tissue also has a significant impact on visible color, which in turn determines the functions of the pigment, including photoprotection (97). Melanin shields the skin from detrimental UV radiation by absorbing both UV and visible light. Additionally, it has antioxidative and radical scavenging properties, which limit the adverse effects of UV radiation on cellular macromolecules, particularly DNA. Consequently, it protects cells from genotoxic harm (11). Melanogenesis is a complex process involving over 150 genes and signaling networks, involving the growth, viability, and specialization of melanocytes. Epigenetic events such as DNA methylation, chromatin modification, and non-coding RNA classes affect gene expression, including miRNAs (98). miRNAs are small, single-stranded, non-coding RNAs with an average length of 21 to 23 nucleotides and are evolutionarily conserved molecules. A specific form of non-coding RNAs that is crucial in controlling gene expression is known as microRNAs, or miRNAs, most miRNAs are produced by transcription from DNA sequences and then processed into primary miRNAs, precursor miRNAs, and mature miRNAs. miRNAs often cause translational repression and mRNA degradation by interacting with the 3′ untranslated region (3′ UTR) of target mRNAs via the RISC complex (99). miRNAs play a crucial role in skin development, regulating specific skin processes like melanogenesis, both in normal and pathological conditions (100). The miRNAs involved in melanogenesis are categorized into five groups based on their various origins and targets (4) (Table 2). It has been predicted that miR-125, miR-145, and miR-203 target TYR, while the majority target other genes, such as MITF. It has also been demonstrated that miR-125b specifically targets SRC homology 3 domain-binding protein 4 (SH3BP4), an MITF-regulated gene that may function via regulating the mTOR signaling pathway or the transport of melanogenic enzymes to melanosomes. DNA hypermethylation of the miR-125b promoter is the cause of the decreased expression of miR-125b, a negative regulator of melanogenesis, in melanocytes (101). The MITF regulators, the SOX family, were impacted by miR-155 and miR-145 (102). MYO5A, a component of the RAB27a/MLPH/MYO5A complex that connects melanosomes to the actin cytoskeleton in human melanocytes, is the

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target of miR-143-5p (9). In alpaca melanocytes, miR-143-5p overexpression results in a reduction in TGF-b-activated kinase 1 (TAK1) expression, which in turn affects melanocyte migration and proliferation as well as MITF downregulation. Thus, miR-143-5p may control many gene targets to modulate melanogenesis (103). Genes associated with the first stage of melanogenesis (SOX9, MITF, TYR, TYRP1) in mouse melanocytes and melanosome transport genes (MYO5A and RAB27A) in human melanocytes were the targets of miR-145 overexpression, which resulted in hypopigmentation (104). In B16-4A5 cells, overexpression of miR-141-3p and miR-200a-3p inhibited MITF expression and TYR activity. The MITF-targeting miRs miR-148a-3p, miR-200a-3p, and miR-141-3p were found to be downregulated in α-MSH-stimulated cells as opposed to untreated cells (105). Among the miRNAs linked to UV irradiation, miR-340 was found to be upregulated in pigmented cells exposed to UVB irradiation. Research has demonstrated that miR-340 increases melanosome transport while markedly suppressing the expression of the RhoA protein. Melanin production and MITF expression are both downregulated by miR-340 (106). Due to the fact that miR-25 targets MITF, overexpression of miR-25 results in melanocyte malfunction, suppression of tyrosinase activity, and a decrease in melanin concentration. Moreover, miR-25 blocked keratinocytes' synthesis and release of SCF and bFGF, which reduced their paracrine influence on melanocyte survival in the face of oxidative stress (107). It has been demonstrated that in human melanoma cell lines, miR-137 regulates MITF. The downregulation of KIT and TYRP2 genes and a decrease in the amount of melanin in mouse skin melanocytes were the results of overexpression of miR-137 (108). miR-21 and miR-206 target is to block the α-MSH signaling pathway by targeting α-MSH and its receptor, MC1R, respectively. The MAPK/ERK pathway, the Wnt pathway, the mTOR pathway, and the SCF/c-Kit pathway are inhibited by miR-137, miR-379, miR-27a-3p, and miR-125b (4).

Table 2. Noncoding RNAs involved in melanogenesis

miRNA	Produced by	Model	Target genes	Mechanisms	Melanin content	Ref
I.Produced by melanocytes and directly target the genes of melanogenesis-related proteins						
miR-125b	WM266-4 Human Melanoma cells, MNT1 Human Melanoma Cells	Human	SH3BP4	Decreases levels of the melanogenic enzymes TYR and DCT	↓	(118)
	Melanocytes	Human	MITF,TYR,TYRP1,DCT		↓	(119,120)
miR-155	Melanocytes and Keratinocytes	Human	TYRP1, YWHAE,SDCBP, SOX10	Inhibits melanogenesis genes	↓	(102)
miR-143-5p	Melanocytes	Human/Mouse	Myo5a	Inhibits melanosome transport	↓	(121)
			TAK1	Downregulates MITF	↓	(122)
miR-145	Melanocytes	Human/Mouse	MITF,TYR, TYRP1, MYO5A, SOX9, RAB27A, FSCN1	Inhibits melanosome transport, Inhibits melanogenesis genes	↓	(104)
miR-203	Melanocytes	Human	kif5b	Increases the number of melanosomes Inhibits melanosome transport	↑	(123)
miR-1291	Melanocytes	Human	TYR	Inhibits melanogenesis enzyme	↓	(124)
miR-434	Melanocytes	Human	TYR	Decreases tyrosinase and melanin content	↓	(125)
miR-5110	Melanocytes	Alpaca	MLPH, WNT1	Inhibits WNT signaling and melanin transfer	↓	(125)
II.Produced by melanocytes and target the genes of transcription factors in melanogenesis						
miR-141a-3p	Melanocytes	Mouse	MITF	Inhibits melanogenesis genes	↓	(105)
miR-200a-3p	Melanocytes	Mouse	MITF	Inhibits melanogenesis genes	↓	(105)
miR-340	Melanocytes	Human	MITF	Binds specifically to the 3′-UTR of MITF and downregulates MITF expression and melanin synthesis	↓	(106,126)
			RhoA protein	Upregulated miR-340 was observed in pigmented cells treated with UVB irradiation which represses RhoA protein expression and stimulates melanosome transport	↓	(127)
miR-218	Primary Melanocytes Melanoma Cell Line sG361,WN35,WN39 and MNT1	Human/Mouse	MITF	Decreases melanogenesis	↓	(128)
	Melan-a Cells			Decreases tyrosinase activity, melanin content, Decreases TYR, DCT, TYRP1 mRNA, Decreases melanogenesis	↓	
miR-25	Melanocytes	Human	MITF, TYR, TYRP1	Regulation of TYR, TYRP1 Decreases tyrosinase activity and melanin content	↓	(129)
miR-183	B16 Melanoma Cells	Mouse	MITF	Regulates the MEK/ERK signaling pathway	↓	(130)
miR-148a	Melanocytes	Human	MITF	Inhibits melanogenesis genes	↓	(131)
miR-137	Melanoma cell line, Melanocytes	Human/Mouse	MITF, SOX6, c-kit	Inhibits melanogenesis genes, Inhibits c-Kit Inhibits SCF/c-Kit pathway	↓	(108,132)
miR-145	Melanocytes	Human/Mouse	MITF, TYR, TYRP1, MYO5A, SOX9, RAB27A, FSCN1	Inhibits melanosome transport, Inhibits melanogenesis genes	↓	(104)
miR-21a-5p	Melanocytes	Human/Mouse	SOX5	miR-21a-5p overexpression downregulated the SOX5 target, as well as β-catenin and CDK2 protein expression	↑	(133)
miR-155	Melanocytes and Keratinocytes	Human	TYRP1, YWHAE, SDCBP, SOX10	Inhibits melanogenesis genes	↓	(102)
miR-675	Melanocytes	Human	MITF	miR-675 upregulation decreased TYRP-1 and TYRP-2 expression, whereas its knockdown increased their expression	↓	(118)

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Table2 (Continued)

III.Produced by melanocytes and target the genes of signaling pathways						
miR-21a-5p	Melanocytes	Human/Mouse	SOX5	miR-21a-5p overexpression downregulated the SOX5 target, as well as β-catenin and CDK2 protein expression	↑	(133)
miR-137	Melanoma Cell Line, Melanocytes	Human/Mouse	MITF, SOX6, c-kit	Inhibits melanogenesis genes, Inhibits c-Kit Inhibits SCF/c-Kit pathway	↓	(108,132)
miR-379	Melanocytes	Mouse	IGFTR	Inhibits MAPK/ERK pathway	↓	(134)
miR-27a-3p	Melanocytes	Mouse	WNT3A	Decreases melanin content, increase in beta-catenin	↓	(135)
miR-125b	WM266-4 Human Melanoma cells, MNT1 Human Melanoma Cells	Human	SH3BP4	Decreases levels of the melanogenic enzymes TYR and DCT	↓	(118)
	Melanocytes	Human	MITF,TYR,TYRP1,DCT		↓	(119,120)
miR-206	Pigmented Skin	Koi carp	MC1R	Suppresses MC1R-mediated melanogenesis	↓	(120)
IV.Produced by keratinocytes and affect the secretion of paracrine factors						
miR-488	Keratinocytes	Mouse	POMC	Downregulates ACTH, β-endorphin, MSH-α	↓	(136)
miR-7	Keratinocytes	Human	FGF2	Inhibits paracrine	↓	(137)
V.Produced by keratinocytes and transferred to melanocytes in the form of exosomes						
miR-330-5p	Keratinocytes	Mouse	TYR	Released as exosomes	↓	(138)
miR-200c	Keratinocytes	Human	SOX1	Leading to intranuclear β-catenin upregulation and increased expression of MITF-dependent gene expression as well as melanogenesis	↑	(139)

MicroRNAs exert their regulatory effects primarily by binding to the 3′ untranslated region (3′ UTR) of target mRNAs, leading to translational repression or mRNA degradation through the RNA-induced silencing complex (RISC). In the context of melanogenesis, many miRNAs directly target master regulators such as MITF or components of melanosome transport and signaling pathways, while others exert indirect effects through intermediate targets. For instance, miR-125b (Commonly referred to as miR-125b-5p) has been experimentally validated to directly target SH3BP4, an MITF-regulated gene that may influence mTOR signaling or the trafficking of melanogenic enzymes to melanosomes. Overexpression of miR-125b results in decreased levels of TYR and DCT, although these are not direct targets; the inhibition appears to occur indirectly via disruption of downstream MITF-dependent networks or related pathways. Additionally, reduced miR-125b expression in pigmented melanocytes is partly attributed to hypermethylation of the MIR125B-1 promoter, which derepresses melanogenesis (109,110). Similar patterns of direct and indirect regulation are observed for other miRNAs listed in Table 1, where mechanisms include suppression of α-MSH/MC1R signaling (e. g., miR-21, miR-206), inhibition of melanosome transport complexes (e. g., miR-143-5p targeting MYO5A or TAK1), or broad pathway modulation (e. g., MAPK/ERK, Wnt, mTOR, SCF/c-Kit by miR-137, miR-379, miR-27a-3p, and miR-125b) (111,112).

Diseases associated with skin pigmentation

Skin pigmentation disorders are significantly influenced by genetic factors that affect melanin production and distribution within the skin. Variations in genetic makeup can lead to differences in pigmentation, affecting how individuals respond to environmental triggers such as UV exposure and hormonal changes. These genetic influences can result in conditions characterized by either excessive or insufficient melanin, often reflecting an interplay between hereditary predispositions and external factors. Understanding the genetic basis of these disorders is crucial for developing targeted therapies and personalized treatment approaches that can improve management strategies and outcomes for affected individuals. By exploring the underlying genetic mechanisms, researchers can gain insights into the complexities of pigmentation regulation and its implications for skin health (Table 3).

Environmental influences on skin color

UV influence on human pigmentation

Upon exposure to ultraviolet (UV) radiation, the skin activates protective mechanisms, enhancing the stratum corneum and melanin production in the epidermis. The stratum corneum, especially thick on the palms and soles, provides resistance to UV damage through keratins and proteins that absorb and scatter UV radiation. UV radiation triggers the synthesis and distribution of melanin from melanocytes to keratinocytes. Keratinocytes respond to UV exposure by increasing mitotic activity and producing factors such as ET-1 and POMC, creating a demand for melanosomes. The mitotic rate of basal keratinocytes rises one day after UV exposure, peaks at two days, and remains elevated for a week. Without further exposure, skin thickness returns to normal within 1-2 months. Post-UV exposure, the epidermal melanin unit shows increased TYR activity, melanosome synthesis, and transfer to keratinocytes to meet the demand from proliferating keratinocytes. UV radiation is classified into three types: UV-A (320-400 nm), UV-B (280-320 nm), and UV-C (200-280 nm). UV-B, absorbed mainly by the epidermis and upper dermis, primarily causes sunburn and stimulates melanin production, forming the basis for tanning. Tanning is characterized by increased melanocyte count, enhanced melanin synthesis, and greater melanocyte dendricity, essential for transferring melanin to keratinocytes (3,113).

Effects of drugs, chemicals, and other factors on human skin pigmentation

Several common pharmaceuticals are known to stimulate hyperpigmentation in human skin. These include antibiotics (Like sulfonamides and tetracyclines), diuretics, nonsteroidal anti-inflammatory drugs, analgesics, and some psychoactive medications. Oral contraceptives can cause skin discoloration, particularly on the cheeks, forehead, and nose, resembling chloasma.

Microscopic analysis shows increased melanogenesis and hypertrophied melanocytes. Antiepileptic drugs, especially hydantoins, can lead to brownish discoloration of the face and neck, similar to pregnancy-related chloasma. Females, particularly Caucasians, are more frequently affected. Chloroquine, which binds to melanin, has also been linked to skin hyperpigmentation, with melanin found in the dermis of treated patients. Levodopa, used for Parkinson's disease, may enhance melanin production during treatment. Heavy metals, such as arsenic, bismuth, gold, and silver, can induce hyperpigmentation by deactivating sulfhydryl compounds that inhibit TYR activity, thus stimulating melanogenesis. Mercury may inactivate TYR by replacing essential copper in the enzyme. Certain chemotherapy agents, including cyclophosphamide, 5-fluorouracil, and doxorubicin, are also associated with hyperpigmentation, though their mechanisms remain unclear, possibly involving direct toxicity or melanocyte stimulation (7,114).

Hormonal influence on human skin pigmentation

Skin pigmentation is influenced not only by genetics and UV exposure but also by hormones. The skin contains estrogen and progesterone receptors, with more estrogen receptors present in the dermis and epidermis. Fluctuations in these systemic hormones during the menstrual cycle can affect skin characteristics, including pigmentation,

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leading to catamenial hyperpigmentation in some cases. Melanocyte-stimulating hormone (MSH), produced by the skin, pituitary, and hypothalamus, is a key regulator of pigmentation, with UV exposure enhancing its production. High MSH levels typically increase melanin, though receptor variations can affect tanning ability, especially in fair-skinned individuals. MSH deficiency leads to reduced pigmentation and UV protection. While classical estrogen (ER) and progesterone (PR) receptors may not always be detectable in melanocytes, these cells respond to these hormones via membrane-bound GPER and PAQR7 receptors. These receptors influence cAMP signaling, the same pathway used by α-MSH to regulate pigmentation, suggesting a potential counterbalancing effect between estrogen and progesterone. Estrogen can also modulate progesterone receptor expression, and vice versa, indicating a complex hormonal interplay. Estrogen, progesterone, and α-MSH converge on the adenylate cyclase pathway to reciprocally control melanin synthesis. The involvement of GPER and PAQR7, both GPCRs like the α-MSH receptor MC1R, highlights the significant role of GPCR signaling in mediating the effects of sex hormones on skin pigmentation.

Post-inflammatory Hyperpigmentation of the Skin

Post-inflammatory hyperpigmentation (PIH) is a temporary skin discoloration following injury or inflammation, more common in darker skin types. It results from overproduction and irregular distribution of melanin in the epidermis and/or dermis. Epidermal inflammation stimulates melanocytes to produce more melanin, transferring it to keratinocytes (Epidermal melanosis). Damage to the basal layer releases melanin, trapped by macrophages in the dermis (Dermal melanosis). PIH can be triggered by acne, eczema, trauma, infections, allergies, drug reactions, and even dermatological procedures or electromagnetic devices. Severity often correlates with the depth of injury, particularly when the epidermal basal layer is disrupted. PIH is a common cause of dyspigmentation, alongside melasma and age spots. It presents as localized or widespread patches of excess pigment, with color varying from dark brown (Epidermal) to gray-blue (Dermal), depending on melanin depth. Cellularly, PIH involves increased melanin production and abnormal distribution. Inflammation in the epidermis, particularly involving arachidonic acid and its metabolites, plays a key role in triggering this process.

Table 3. Overview of skin pigmentation disorders

Disorder	Description	Prevalence	Key features	Genetic cause	Reference
Oculocutaneous Albinism (OCA1 and OCA2)	Group of hereditary conditions characterized by absence or insufficiency of melanin.	OCA1: ~1 in 40,000; OCA2: 1 in 10,000 to 1 in 36,000	Light blue eyes, hypopigmentation, visual acuity issues, nystagmus, pale skin, light hair.	TYR gene (OCA1), OCA2 gene (OCA2)	(140)
Hermansky-Pudlak Syndrome (HPS)	Rare hereditary condition causing albinism, hemorrhage, and ceroid accumulation.	1 in 500,000 to 1 in 1,000,000	Albinism, quick bruising, potential pulmonary and gastrointestinal disorders.	HPS1, HPS3-10 genes	(141)
Chediak-Higashi Syndrome (CHS)	Autosomal recessive syndrome with immune deficiency and albinism.	Estimated <1 in 1,000,000	Pale skin, light hair, vision impairments, nystagmus, photophobia.	LYST gene mutations	(142)
Waardenburg Syndrome	Hereditary disorder with auditory impairment and pigmentation alterations.	~1 in 40,000	Widely spaced eyes, heterochromia, white forelock, congenital deafness.	PAX3, MITF, EDN3, SOX10 genes	(143)
Noonan Syndrome with Multiple Lentigines (NSML)	Rare multisystemic disorder affecting skin, heart, and hearing.	Less than 200 individuals	Brown pigmented spots, cardiac abnormalities, ocular issues.	PTPN11 gene	(144)
Neurofibromatosis Type 1 (NF1)	Condition causing skin patches, neurofibromas, and skeletal dysplasias.	~1 in 2,500	Flat brown patches, neurofibromas, Lisch nodules.	NF1 gene mutations	(145)
Tuberous Sclerosis	Neurocutaneous disease with noncancerous tumors in various organs.	1 in 6,000 to 12,000 live births	Seizures, intellectual disabilities, adenoma sebaceum.	TSC1, TSC2 genes	(146)
Xeroderma Pigmentosum (XP)	Condition characterized by hypersensitivity to UV radiation.	~1 in 1,000,000	Severe sunburn, skin pigmentation changes, increased cancer risk.	XPA to XPG DNA repair genes	(147)
Peutz-Jeghers Syndrome (PJS)	Disorder with gastrointestinal polyps and hyperpigmented macules.	1 in 50,000 to 200,000 live births	Polyps in GI tract, hyperpigmented macules.	STK11 (LKB1) gene mutations	(148)
Fanconi Anemia (FA)	Genetic disorder with developmental delays and bone marrow failure.	~1 in 181 among Ashkenazi Jews	Developmental delays, morphological abnormalities, anemia.	Mutations in 16 different genes	(149)
Dyskeratosis Congenita (DC)	Condition with atypical skin pigmentation and nail dystrophy.	Very rare	Lacy pigmentation, premature graying, oral leukoplakia.	Mutations in telomere maintenance genes	(150)
Charcot-Marie-Tooth Disease (CMT)	Inherited condition affecting peripheral nerves.	~1 in 2,500	Muscular weakness, foot deformities, skin pigmentation changes.	Mutations in PMP22, GJB1 genes	(151)
Hypomelanosis of Ito (HI)	Neurocutaneous disorder with hypopigmented lesions.	1 in 8,000 pediatric outpatients	Whorled and streaked skin lesions.	Chromosomal mosaicism	(152)
Incontinentia Pigmenti (IP)	X-linked dominant genetic disorder.	Rare	Skin lesions, dental abnormalities, hair loss.	IKBKG/NEMO gene mutations	(153)

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Conclusion

This study underscored the intricate regulation of human skin pigmentation. It reviewed the molecular basis of melanocyte biology and how different genes orchestrate melanogenesis and pigmentation. The identification of new genes and mutations in pigmentation-related genes has enhanced our understanding of the genetic basis of pigmentation disorders. Further studies are required to investigate new roles of genes in skin pigmentation, e. g., the CALR gene (115-117). These findings would contribute to a deeper understanding of the molecular mechanisms governing skin pigmentation, offering potential avenues for therapeutic intervention in pigmentation-related diseases.

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Ethical Statement

All sources used are properly disclosed, and all authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

Conflicts of Interest

There are no conflicts of interest to disclose.

Author Contributions

Idea: Morteza Oladnabi; Data Collection or Processing: Fatemeh Vaghefi, Farzaneh Motallebi; Writing-Review & Editing: Teymoor Khosravi, Fatemeh Vaghefi, Farzaneh Motallebi; Figure design: Zainab M. Al Sudani, Mohaddeseh Mohsenipour; Supervision: Arian Rahimzadeh, Mohaddeseh Mohsenipour. All authors reviewed the results and approved the final version of the manuscript.

Data Availability Statement

The raw data supporting the findings presented in this manuscript will be made available to qualified researchers upon contacting the corresponding author.

Use of Artificial Intelligence

The authors declare that no artificial intelligence (AI) tools or AI-assisted technologies were used in the preparation, writing, analysis, or editing of this manuscript.

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