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Biochemistry of Hair Greying: A Review

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ABSTRACT

Hair greying is a natural biological process influenced by genetics, aging, and environmental factors. This phenomenon occurs when melanocytes, specialized cells responsible for melanin production, lose functionality, leading to a decline in melanin synthesis. Melanin, comprising eumelanin and pheomelanin, is the pigment that determines hair color. The greying process involves oxidative stress, a gradual reduction in melanocyte activity, and depletion of melanocyte stem cells, resulting in diminished melanin production. Genetic factors, such as mutations in the MC1R and IRF4 genes, further modulate the greying process. In addition to age-related factors, lifestyle influences, including smoking and nutrient deficiencies (e.g., vitamin B12 and trace elements), play significant roles in premature greying. Oxidative stress, in particular, accelerates melanocyte apoptosis and contributes to hair greying by increasing reactive oxygen species (ROS) levels, which damage cellular structures. While the treatment of age-related greying remains elusive, some cases of premature greying can be managed through dietary supplements and lifestyle adjustments. This study aims to elucidate the biochemical pathways of hair greying, explore potential therapeutic interventions, and highlight the environmental and genetic factors that contribute to the process.

Keywords: Hair greying, oxidative stress, melanin production, reactive oxygen species, MC1R and IRF4 genes.

INTRODUCTION

Hair may be characterized as a collection or mass of protein filaments comprised mostly of keratin, a structural protein that forms the foundation of hair, skin, and nails. Keratin gives hair its strength and resilience (Neelima *et al.*, 2023). Hair arises from follicles implanted in the dermis, the middle layer of the skin. It provides many functions throughout animals, including protection, control of body temperature, and sensory input. For humans and other animals, hair is one of the primary differentiating traits, varied in texture, color, and distribution over the body. The bulk of the human body, save from patches of glabrous skin (such as the palms of the hands and soles of the feet), is covered with follicles capable of generating either dense terminal hair or fine vellus hair (Monteiro-Riviere, 2020). Terminal hair is pigmented, dense, and longer, found in regions like the scalp, eyebrows, and eyelashes, while vellus hair is thin, fine, and lighter, generally covering most of the body.

Hair greying is an important element of the aging process (Rosenberg *et al.*, 2021). This process, also referred to as canities, comes from the slow loss of pigmentation within hair strands, causing a shift in color from the natural shades of black, brown, blonde, or red to shades of grey or white. Melanin, the pigment responsible for hair color, is generated by melanocytes situated at the base of the hair follicle. The synthesis of melanin declines with age owing to a drop in melanocyte activity, ultimately leading to hair greying. This process is ubiquitous and typically unavoidable as part of human aging.

However, in rare circumstances, hair greying happens early, which is described as greying before the typical age thresholds depending

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on ethnicity: before 20 years of age in Europeans, before 25 years in Asians, and before 30 years in Africans (Gudbrandsson *et al*, 2017). The early commencement of hair greying may cause psychological anguish, particularly in persons for whom hair color carries substantial social or cultural relevance. Hair greying is generally related to the natural aging process, where the loss in melanocyte stem cell activity inside hair follicles leads to lower melanin production. However, early greying, also known as premature canities, can develop owing to a multitude of reasons that extend beyond age. Genetic susceptibility plays a significant part in determining the onset of greying, with research revealing that family history typically determines whether people experience greying sooner than usual (Andreou and Edvinson, 2019).

In developing the review on hair greying, the author followed a methodical process to acquire and synthesize information from a number of scientific sources. The procedure started with a comprehensive literature study, wherein the author analyzed current research and publications that dive into the biological processes behind hair greying, the function of melanin, and the numerous variables affecting hair pigmentation. This includes study focusing on the genetics of hair color, the impact of oxidative stress, and the physiological changes related with the aging process. Following the literature study, the author selected and summarized essential themes linked to hair greying. This involves a deep examination of the roles of melanocytes, the numerous forms of melanin, and the genetic variables that contribute to the beginning of greying. By weaving these elements together, the author created a cohesive narrative that elucidates the complexities surrounding hair greying.

The review also incorporated insights into how hair greying varies among different ethnic groups, highlighting the genetic predispositions that influence the timing and nature of greying. The author referenced specific studies that underscore these differences, providing a comprehensive understanding of the topic.

Melanin

Melanin is a naturally occurring pigment generated by specialized cells called melanocytes. These cells, situated largely in the skin, eyes, and hair follicles, create melanin via a complicated biochemical process that includes the conversion of the amino acid; tyrosine into dihydroxyphenylalanine (DOPA). This reaction is catalyzed by the enzyme tyrosinase, which is crucial to the process of melanogenesis. Melanocytes contain organelles called melanosomes, where melanin production occurs. The pigment is subsequently transported to keratinocytes in the epidermis of the skin, producing color and a variety of defensive activities (Benito-Martinez *et al.*, 2021).

The formation of melanin starts with the oxidation of the amino acid tyrosine to DOPA, a process mediated by tyrosinase, which is the rate-limiting enzyme for melanogenesis (Varghese *et al*., 2021). This is followed by a succession of oxidation and cyclization processes, which finally lead to the synthesis of either eumelanin or pheomelanin, depending on the presence of other components such as cysteine. For eumelanin production, DOPA undergoes additional oxidation to DOPAquinone, which is subsequently polymerized into the black or brown pigment. For pheomelanin, cysteine interacts with DOPAquinone, resulting to the synthesis of red or yellow pigments. Tyrosinase is crucial to this process, since it influences the early phases of melanin formation. Variations in tyrosinase activity may result in variable pigmentation, altering an individual's skin, hair, and eye color.

Research has identified three major types of melanin found in humans: eumelanin, pheomelanin, and neuromelanin. Each of

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these types has distinct chemical structures, functions, and locations within the body.

Eumelanin: This is the most frequent form of melanin, responsible for dark brown to black pigmentation. It is found in the epidermis of the skin, as well as in hair and eyes. Chemically, eumelanin is constituted of polymeric units formed from the oxidation of tyrosine to dihydroxyindole (DHI) and dihydroxyindole-2-carboxylic acid (DHICA), which are further polymerized by enzymatic and non-enzymatic pathways (Solano, 2020).

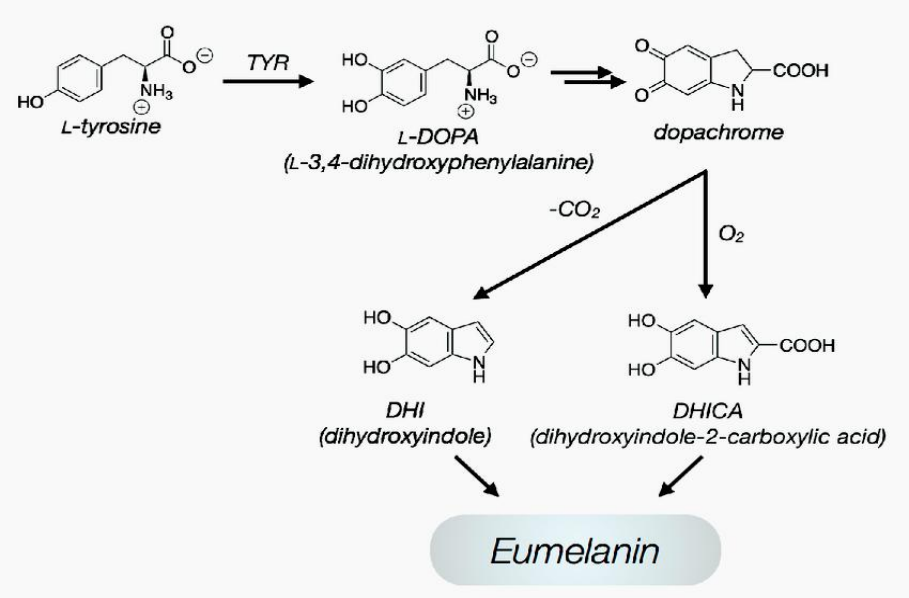

Figure 1: Eumelanin synthesis (Büngeler *et al.*, 2017)

These polymers lend eumelanin its potential to absorb a wide variety of light wavelengths. Eumelanin provides a critical role in protecting the skin from ultraviolet (UV) radiation damage by absorbing and dispersing UV light. This photoprotective property is crucial for minimizing the prevalence of skin cancers generated by DNA damage from UV radiation (Fajuyigbe *et al.*, 2018).

Pheomelanin: In contrast to eumelanin, pheomelanin is lighter in color and is responsible for yellow, blonde, and red pigmentation in hair and skin. Chemically, pheomelanin is generated by the inclusion of sulfur-containing cysteine into its structure, alongside tyrosine. During its manufacture, cysteine combines with dopaquinone to create benzothiazine and benzothiazole intermediates, which polymerize to form pheomelanin. This sulfur component contributes to its peculiar pigmentation and separates it chemically from eumelanin (Solano, 2020). Although pheomelanin gives some pigmentation, it does not provide the same amount of UV protection as eumelanin. As a consequence, persons with larger quantities of pheomelanin, such as those with red or blonde hair and lighter skin, are more prone to UV-induced damage and have an increased risk of disorders including sunburn and skin cancer.

Neuromelanin: Neuromelanin is a lesser-known type of melanin largely found in certain parts of the brain, including the substantia nigra and locus coeruleus. Chemically, neuromelanin is a polymeric pigment generated from the oxidation and polymerization of catecholamines, such as dopamine and norepinephrine. It combines proteins and lipids into its structure, generating a complex, heterogeneous

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pigment. This unusual composition is expected to contribute to its capacity to adsorb potentially harmful chemicals, including metals and reactive oxygen species (Vila, 2019). Neuromelanin is hypothesized to perform a protective effect in neurons by decreasing oxidative stress and neurotoxicity. Its concentration in the brain rises with age, and its loss has been connected to neurological illnesses such as Parkinson's disease, where the degradation of neuromelanin-rich neurons has been seen (Bukky & Sasha, 2021).

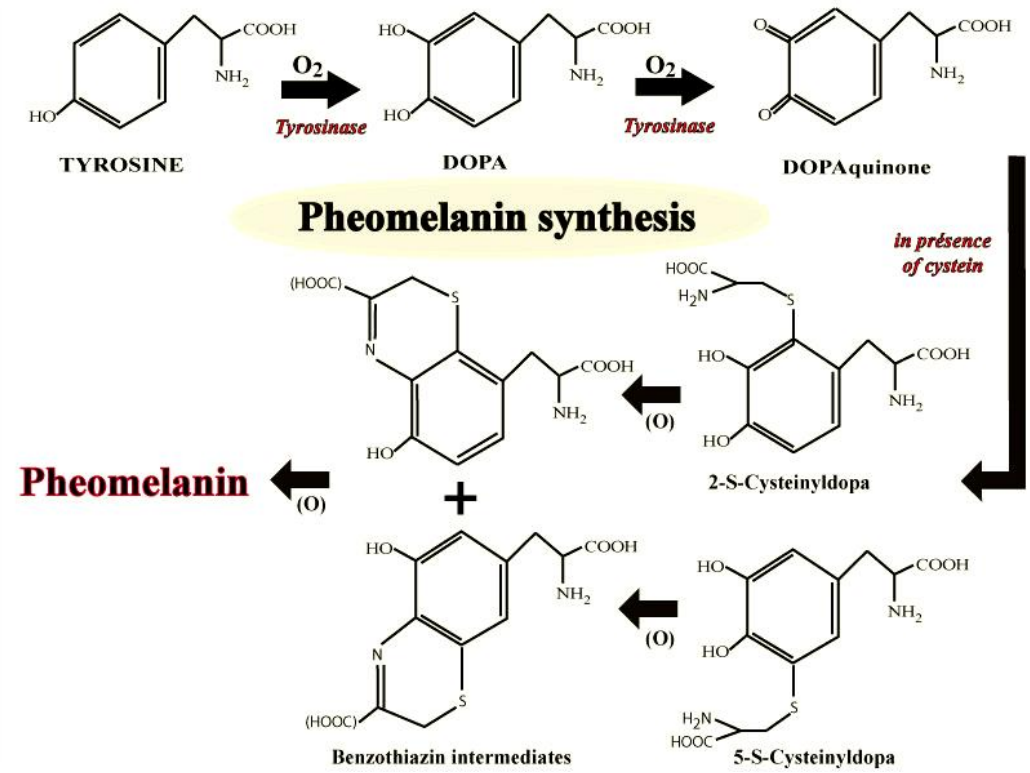

Figure 2: Pheomelanin synthesis (Fajuyigbe and Ojo, 2018)

Functions of Melanin

Protection against Ultraviolet (UV) Radiation

One of the most critical tasks of melanin, particularly eumelanin, is its capacity to protect the skin from damaging UV rays. UV radiation from the sun is a key source of skin damage, leading to premature aging, sunburn, and an increased risk of skin malignancies such as melanoma. Eumelanin functions as a natural sunscreen by absorbing and dispersing UV rays before it can infiltrate deeper layers of the skin and damage DNA. The presence of larger quantities of eumelanin in the skin of persons with darker skin tones provides them with stronger protection against the carcinogenic effects of UV radiation (Solano, 2020).

In contrast, persons with greater amounts of pheomelanin have less natural protection from UV radiation, since pheomelanin does not efficiently absorb UV light. This is why those with lighter skin and red or blonde hair are more prone to sunburn and long-term UV-related skin damage (Solano, 2020).

Protection Against Oxidative Stress

Melanin also contains antioxidant capabilities that help protect the skin from oxidative stress. Oxidative stress arises when there is an imbalance between the generation of reactive oxygen species (ROS), or free radicals, and the body's capacity to neutralize these toxic molecules with antioxidants. Excessive ROS may harm cells and tissues, leading to accelerated aging and the development of numerous skin disorders.

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When UV radiation stimulates the creation of ROS in the skin, melanin works as a scavenger by absorbing these molecules, therefore lowering oxidative stress (Ray *et al.*, 2017).

This preventive process is especially significant since oxidative stress not only accelerates aging but also raises the chance of DNA damage that might lead to skin malignancies. By moderating the effects of ROS, melanin helps preserve cellular integrity and avoids oxidative damage to important macromolecules including proteins, lipids, and DNA.

Protection of Internal Organs

In addition to its role in safeguarding the skin, melanin provides protective roles for interior organs including as the liver, intestines, and the immune system (Guo *et al,* 2023). Melanin may attach to and neutralize dangerous compounds, including toxic metals and medicines, so preventing them from causing damage to tissues. In the liver, for instance, melanin may assist eliminate toxic substances, hence aiding the liver's natural detoxification activities (Yang *et al.,* 2020). The protective effects of melanin also extend to the immune system. Melanin has been demonstrated to affect immunological responses, with studies showing that it may play a role in shielding immune cells from oxidative damage and boosting their capacity to fight off infections (Ray *et al.*, 2017). This shows that melanin may have wider protective benefits beyond its well-known involvement in UV protection.

Melanocytes

Melanocytes are specialized cells responsible for the creation of melanin, the pigment that gives skin, hair, and eyes their color. These cells emerge from neural crest cells during embryonic development and are scattered throughout the body, mainly in the basal layer of the epidermis, hair follicles, the uveal tract of the eyes, the inner ear, and the meninges. The fundamental function of melanocytes is the manufacture of melanin, which happens in specialized organelles called as melanosomes. Within these melanosomes, melanocytes create two primary forms of melanin: eumelanin and pheomelanin, which vary in their chemical structure and function (D alba and Shawkey, 2019).

The melanosomes within the melanocytes are vital for melanin synthesis. These organelles serve as the location for the enzymatic events that contribute to the production of both eumelanin, responsible for brown or black pigmentation, and pheomelanin, which leads in yellow or red pigmentation (Solano, 2020). The melanin generated in these melanosomes is subsequently transmitted to nearby cells, predominantly keratinocytes, which are the major cells in the outer layer of the skin. Keratinocytes play a vital function in transporting melanin throughout the epidermis, so providing pigmentation and protection against damaging ultraviolet (UV) radiation. Once within keratinocytes, melanin forms a protective "cap" around the cell's nucleus, safeguarding the DNA from UV-induced damage (Liu & Fischer, 2017). This distribution of melanin is an important strategy for skin protection, since increased melanin concentration may lessen the incidence of skin damage and skin malignancies like melanoma.

Differences in Melanin Production Based on Skin Color

The quantity and type of melanin generated by melanocytes are controlled by a range of variables, including hereditary and environmental influences. In people with darker skin tones, melanocytes generate more melanin than in persons with lighter skin. This increased melanin synthesis is predominantly of the eumelanin type, which gives greater protection against UV rays. In contrast, persons with lighter skin tones tend to develop more pheomelanin, which gives less protection from UV radiation and is

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related with a greater risk of sunburn and skin malignancies (Perkins & Lockett, 2021).

The activity and number of melanocytes do not substantially change across persons of various skin hues; nevertheless, the kind and amount of melanin generated, and the size and location of melanosomes inside keratinocytes, vary. Studies suggest that in darker-skinned individuals, melanosomes are larger and more dispersed throughout keratinocytes, leading to a more uniform and darker pigmentation, while in lighter-skinned individuals, melanosomes are smaller and tend to cluster around the nucleus (Yardman-Frank *et al.*, 2021).

The Melanocortin-1 Receptor (MC1R) and its Role in Melanin Production

One of the primary regulators of melanin formation is the melanocortin-1 receptor (MC1R), a protein expressed by the MC1R gene. MC1R is situated on the surface of melanocytes and plays a vital function in deciding which kind of melanin is generated. The receptor is activated by melanocyte-stimulating hormone (MSH), which is secreted in response to UV exposure. When MSH binds to MC1R, it increases the formation of eumelanin, resulting in deeper pigmentation that affords higher UV protection (Herraiz *et al.*, 2021).

Conversely, when the MC1R pathway is less active or altered, pheomelanin synthesis is promoted. This leads to lighter pigmentation, such as red or blonde hair and lighter skin, which gives less UV protection. Certain variations of the MC1R gene are related with red hair, fair skin, and a greater risk of skin cancer, underscoring the role of this receptor in pigmentation and skin health (Roberts *et al.*, 2020).

The MC1R gene is highly polymorphic, indicating that there are many distinct variations of the gene, which contribute to the variety of human pigmentation. People with red hair and pale complexion commonly have numerous mutations in the MC1R gene, which limit the receptor's function, leading to a predilection for pheomelanin synthesis (Wakamatsu *et al.,* 2021). This absence of functional MC1R activity inhibits the melanocytes from transitioning to eumelanin synthesis, resulting in a lighter, less UV-protective pigmentation. Individuals with these MC1R mutations are also more susceptible to UV radiation and are at a greater risk for developing skin disorders such as melanoma and other skin cancers owing to the diminished protective benefits of eumelanin.

Regulation of Melanin Production by MC1R

The MC1R gene encodes a G-protein-coupled receptor that, when activated by α-MSH, signals via the cAMP pathway to enhance tyrosinase activity. Tyrosinase is the enzyme responsible for the first stage of melanin production, converting the amino acid tyrosine into DOPA, a precursor to melanin. This route enhances eumelanin production while decreases pheomelanin production. In humans with functioning MC1R activity, UV exposure boosts α-MSH levels, which in turn promotes eumelanin formation, affording a natural protective response to UV damage (Ascsillan and Kennedy, 2024).

Mutations in the MC1R gene may lead to varied skin and hair color phenotypes, depending on the variant's influence on the receptor's function. Loss-of-function mutations in the MC1R gene lead to diminished cAMP signaling, preferring pheomelanin synthesis over eumelanin. These mutations are typically observed in persons with red hair and light complexion. The clinical ramifications of harboring MC1R polymorphisms that boost pheomelanin synthesis include greater vulnerability to UV-induced skin damage and a higher lifetime risk of acquiring skin malignancies like melanoma (Roberts *et al.*, 2020).

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Given the role of MC1R in regulating melanin synthesis, it has become a target for medicinal methods aiming at altering skin pigmentation. For example, topical medicines that activate MC1R signaling are being studied as therapies to boost eumelanin synthesis, perhaps having a protective effect against UV radiation and lowering the incidence of skin malignancies. Additionally, gene treatments targeting MC1R may provide novel ways for treating pigmentation abnormalities or offering greater protection against sun exposure in persons with light skin (Manganelli *et al.,* 2021).

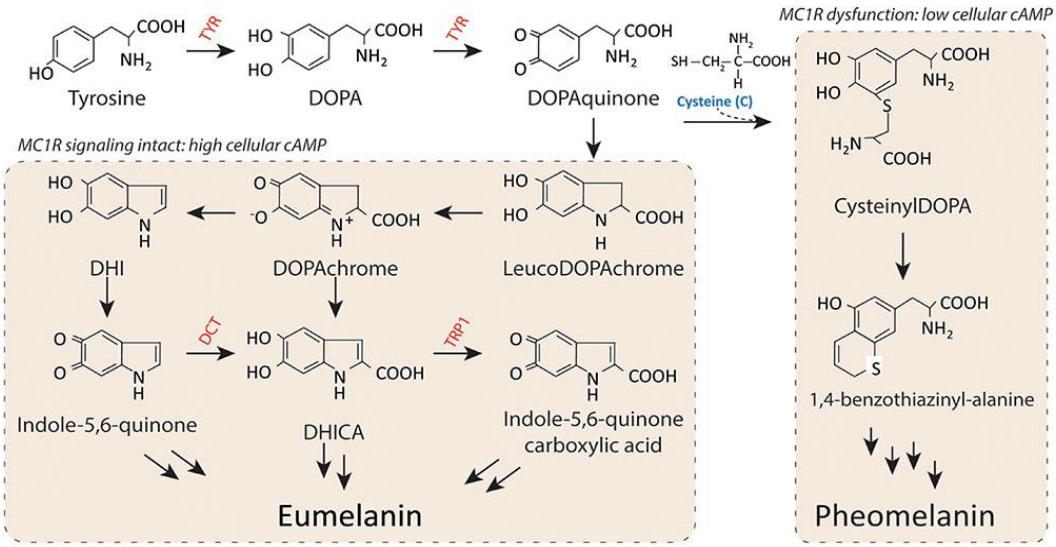

Figure 3: Melanin synthesis indicating the function of MC1R (Enkhtaivan and Lee 2021).

When the receptor is functional or activated and cAMP levels are high, it triggers a series of chemical reactions inside melanocytes that stimulate these cells to make eumelanin. If the receptor is not activated or is blocked or dysfunctional and cAMP levels are low, cysteine is incorporated and melanocytes make pheomelanin instead of eumelanin (Enkhtaivan and Lee, 2021). Many other genes also help to regulate this process. Most people have two functioning copies of the *MC1R* gene, one inherited from each parent. These individuals have black or brown hair, because of the high amount of eumelanin.

Hair Greying

Hair greying is a normal, age-related, and genetically determined biological process that arises from the progressive loss of color in hair follicles. It is regarded one of the first and most noticeable indications of aging, frequently contributing to the feeling of aging in people. The greying process starts when melanocytes, the specialized cells responsible for creating melanin (the pigment that gives hair its color), diminish their melanin synthesis or halt it completely. While greying is essentially a sign of age, additional variables such as genetics, stress, and lifestyle behaviors may impact its development and advancement (Dharmarajan, 2021). This biological alteration does not impact the texture or structure of the hair, but the loss of melanin contributes to the typical grey, silver, or white look of the hair strands.

Hair Color and Its Determinants

Hair color is determined by the type and amount of melanin produced by melanocytes within the hair follicles. The two main types of melanin, eumelanin and pheomelanin, dictate the specific color of an individual's hair.

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Table 1: Hair Color and its Determinants

Hair Color	Type and Amount of Melanin (Hair Color Determinant)
Black	Large amount of eumelanin
Brown	Moderate amount of eumelanin
Blonde	Very little eumelanin
Red	Mostly pheomelanin with a small amount of eumelanin

Source: Herraiz et al., (2021)

Eumelanin is responsible for darker shades of hair, ranging from black to brown, whereas pheomelanin contributes to lighter tones, such as red and blonde. The specific combination and concentration of these pigments determine the exact shade of hair. For example, people with dark hair tend to have a higher concentration of eumelanin, while individuals with red hair have more pheomelanin. The genetic variations that control melanin production and distribution are the primary determinants of hair color Naik and Farrukh, 2022).

Hair color is also influenced by several genes, with MC1R (melanocortin 1 receptor) being one of the most significant. MC1R regulates the type of melanin produced, with its activation leading to the production of eumelanin, and its deactivation resulting in pheomelanin production (Herraiz *et al.*, 2021). Individuals with MC1R mutations often have red hair and fair skin, as their melanocytes produce more pheomelanin than eumelanin.

Onset of Grey Hair

The emergence of grey hair, a natural result of aging, may varies substantially across ethnic groups owing to a combination of genetic, environmental, and physiological variables (Maymone *et al.,* 2021). Melanin, the pigment responsible for hair color, is generated by specialized cells known as melanocytes, which are situated in the hair follicles. Over time, melanocytes lose their capacity to create melanin, resulting to the appearance of gray or white hair. However, the timeline for when this process starts varies greatly across people and groups.

Hair greying, a normal aspect of the aging process, occurs when melanocytes in the hair follicles quit generating melanin, the pigment responsible for hair color. While hair greying is often linked with aging, studies have revealed that there are considerable ethnic variations in the age of initiation and course of greying (Rosenberg *et al.*, 2021). Caucasians, Asians, and Africans display unique patterns, with Caucasians often having earlier onset compared to other ethnic groups. These disparities are mostly due to genetic causes, while other environmental and behavioral variables such as diet, stress, and environmental exposure also have a role.

Caucasian Hair Greying

Caucasians often have the earliest beginnings of hair greying, commonly commencing in their mid-30s. The process is progressive, with a bigger proportion of grey hair observed by the age of 50. A research by Almudimeegh *et al*. (2024) indicated that, on average, 50% of Caucasians develop gray hair by the age of 50. The faster greying in this population is mostly influenced by genetic predisposition. Caucasian cultures tend to have a larger number of hair follicles with a stronger genetic propensity to melanin depletion, making their hair more vulnerable to greying as they age. Additionally, the greying process may be worsened by oxidative stress, which destroys melanocytes and increases their depletion. Cedirian *et al.* (2024) underline that Caucasians' comparatively early greying beginning might also be impacted by lifestyle variables such as nutrition, smoking, and exposure to ultraviolet (UV) radiation, which may increase oxidative stress on hair follicles.

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Asian Hair Greying

In contrast to Caucasians, Asians commonly experience hair greying later, typically starting in their late 30s. Studies have demonstrated that Asians display a more gradual and delayed start of greying compared to their Caucasian counterparts. According to Im *et al*. (2017), the rate of grey hair appearing among Asians is slower, and they tend to preserve darker hair for a longer duration, with around 50% of Asians having gray hair by the age of 50, a tendency found in both East Asian and Southeast Asian populations. The genetic variables involved in hair pigmentation and melanin production in Asians are diverse from those in Caucasians (Naik and Farrukh, 2022). Asian people may exhibit genetic variations that allow for extended retention of melanocytes in their hair follicles. However, environmental variables such as pollution, dietary habits rich in antioxidants, and decreased UV exposure in certain Asian nations may contribute to the delayed start of greying (Dharmarajan, 2021).

African Hair Greying

Africans often endure the latest start of hair greying, frequently commencing in their mid-40s. The pace of greying among African people is slower, and they tend to preserve their original hair color for a longer prolonged time than Caucasians or Asians. Studies such as those by Melzer *et al*. (2020) imply that the genetic composition of African people has a key impact in the delayed start of greying. African persons tend to have a greater density of eumelanin, the dark pigment responsible for black and brown hair color, which may lead to a slower rate of melanin depletion in hair follicles. Additionally, the particular structure and density of African hair may give additional resistance against the environmental variables that might cause to premature greying (Maymore *et al*., 2021). However, comparable to Caucasians and Asians, stress and other environmental variables, including as UV exposure and nutritional deficiencies, may still impact the beginning of greying, although at a later age (Anastassakis *et al.*, 2022).

Premature Hair Greying

Premature hair greying (PHG) happens when hair becomes grey sooner than the average age range for an individual's ethnic group. In Caucasians, PHG is described as greying before the age of 20, whereas in Asians, it refers to greying before the age of 25, and in Africans, it occurs before the age of 30 (Yale *et al.,* 2019). While PHG does not always imply an underlying health problem, it might be a cause of worry owing to its early start and relationship with aging. The specific reasons of premature greying are not entirely known. However, data reveals a complicated interaction between hereditary variables and environmental impacts. Genetic susceptibility plays a crucial impact, with family occurrences of early greying regularly observed. Studies have found many genes involved in hair color control, including IRF4, BNC2, and MC1R, which are expected to alter the timing of greying by regulating melanin synthesis (Lona-Durazo *et al.*, 2021). Individuals with a family history of early greying are more prone to develop the disorder themselves.

Premature greying is frequently due to a mix of hereditary and environmental factors. A substantial hereditary tendency is one of the most well-established reasons of premature greying. In many circumstances, people who get gray hair early have a familial history of early greying. Certain genes affect the activity of melanocytes and melanin formation, notably MC1R, which plays a critical role in deciding whether eumelanin (black pigment) or pheomelanin (bright pigment) is formed. Mutations in the MC1R gene may lead to alterations in melanin synthesis and are typically associated with disorders such as red hair and fair complexion, both of which are connected to

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an increased probability of premature greying (O'Sullivan *et al.,* 2021).

In addition to MC1R, additional genes such as BCL2, which is involved in melanocyte survival, and MSX2, which plays a role in hair follicle development, have also been linked in the early beginning of greying (Gagliardi, 2018). Genetic tendency does not necessarily ensure early greying, but it considerably enhances the probability. Additionally, deficits in some vitamins and minerals, like as vitamin B12, folic acid, iron, and copper, have been associated to premature greying.

Oxidative Stress and Reactive Oxygen Species (ROS)

Oxidative stress, originating from the imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses, has been recognized as a crucial cause in the early loss of hair color. ROS are normal byproducts of cellular metabolism, but their buildup may contribute to cellular harm, including damage to melanocytes. Under normal circumstances, antioxidants neutralize ROS and protect cells from oxidative damage. However, when the body's antioxidant defenses are overloaded or depleted, ROS levels increase, causing damage to melanocytes and lowering melanin formation (Jaffri, 2023).

ROS may be generated by several activities, including exposure to ultraviolet (UV) radiation, pollution, and smoking. As melanocytes age, they become less effective at neutralizing ROS, which accelerates the greying process. This explains why premature greying is commonly related with conditions that enhance oxidative stress, like as smoking and excessive sun exposure (Papaccio *et al*., 2022).

Science of Hair Greying

Some studies have established that human greying invariably begins with the gradual decline in melanogenesis, including reduced tyrosinase activity, defective melanosome transfer and apoptosis of hair follicle pigmentary unit (HFPU) melanocytes, and is thus a primary event of the anagen hair bulb, not the bulge. Eventually, the bulge melanocyte stem cells (MSCs) pool gets depleted as well, at which moment greying becomes generally permanent, as seen in the picture below. However, oxidative damage likely is a significant cause of greying via its disruption of HFPU melanocyte survival, MSC maintenance, and of the enzymatic machinery of melanogenesis itself (O'Sullivan *et al.*, 2021).

An prominent indicator of aging is hair greying, or the loss of pigment synthesis and deposition inside the hair shafts. Numerous processes, functioning at various levels and follicular locations, contribute to hair greying, ranging from melanocyte stem cells abnormalities to follicular melanocyte death. One significant concern that is in common to all processes is oxidative damage (Seis *et al.*, 2017).

Studies have identified the key gene responsible for grey hair to be the IRF4 gene, and one particular variation (rs12203592) as the marker for premature greying. According to this study team, this gene, IRF4 (interferon regulatory factor 4) gene, is known to have a function in hair color but this is the first time it has been related with the graying of hair. IRF4 is involved in regulating production and storage of melanin, the pigment that determines hair, skin and eye color, therefore, understanding how this gene influences hair graying could help the development of new cosmetic applications that change the appearance of hair as it grows in the follicle by slowing or blocking the graying of hair (Boo, 2024).

Factors That Influence Hair Greying

The reason or variables affecting hair greying is incompletely known. It is assumed to be a combination of dietary, genetic and environmental variables.

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Oxidative stress: This is simply an imbalance between the systemic expression of reactive oxygen species and a biological system's capacity to detoxify the reactive intermediates or to repair the consequent damage. Reactive oxygen species or free radicals are extremely reactive chemicals that may directly damage lipids, proteins, and DNA. They are created by a myriad of endogenous and environmental stressors, whereas the body contains endogenous defensive systems. With aging, generation of free radicals rises, but the endogenous defensive systems diminish. This imbalance leads to gradual destruction of cellular structures, likely culminating in the aging phenotype (Musa *et al.*, 2021).

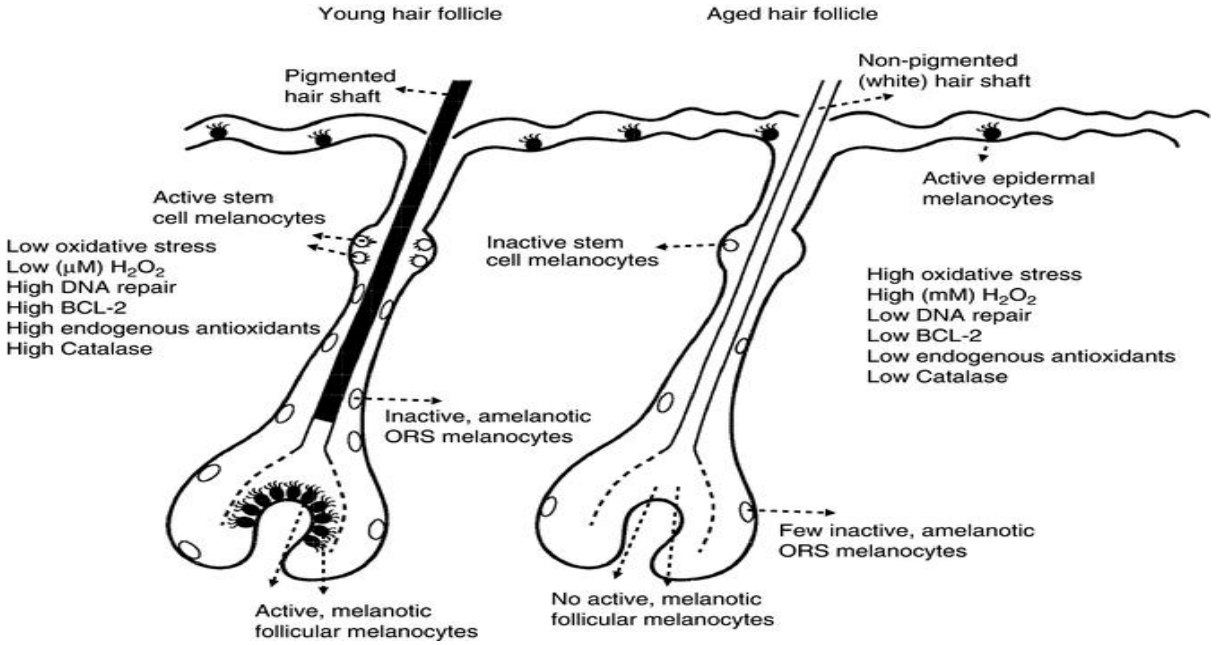

Figure 4: showing age-induced hair greying and oxidative stress (Adapted from Boo, 2024).

From the figure above, at the hair follicle stem cells niche, oxidative stress, accelerated by B-cell lymphoma 2 gene (BCL-2) depletion, leads to selective apoptosis and diminution of melanocyte stem cells, reducing the repopulation of newly formed anagen follicles. Melanotic bulbar melanocytes express high levels of BCL-2 to enable survival from melanogenesis- and ultraviolet A (UVA)-induced reactive oxygen species (ROS) attacks. With ageing, the bulbar melanocyte expression of anti-oxidant proteins such as BCL-2, and possibly TRP-2, is reduced, and the dedicated enzymatic anti-oxidant defence system throughout the follicle weakens, resulting in enhanced oxidative stress. A marked reduction in catalase expression and activity results in millimolar accumulation of hydrogen peroxide, contributing to bulbar melanocyte malfunction and death. Interestingly, amelanotic melanocytes at the outer root sheath (ORS) are somewhat less affected by these processes and survive for longer time even within the white, ageing hair follicles. Better understanding of the overtime susceptibility of melanocytes to oxidative stress at the different follicular locations might yield clues to possible therapies for the prevention and reversal of hair greying (Boo, 2024).

Oxidative stress occurs in normal metabolic reactions and plays a role in the aging process. The body's cells produce free radicals during these processes. However, cells also produce antioxidants that neutralize these free radicals. Thus, the body can maintain a balance between antioxidants

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and free radicals. Several factors contribute to oxidative stress and excess free radical production, they include; diet, lifestyle, environmental factors such as pollution and radiation (Sampson and Eske, 2019).

The body's natural immune response can also trigger oxidative stress temporarily. This type of oxidative stress causes mild inflammation that goes away after the immune system fights off an infection or repairs an injury. Uncontrolled oxidative stress can accelerate the aging process and may contribute to the development of a number of conditions such as hair greying.

Nutrient deficits: Nutrition also plays a role, since deficits in vitamins such as B12, biotin, and folic acid have been connected with early greying (Gana *et al.*, 2021). In Asian communities, whose diets are generally high in antioxidants, it is claimed that this may contribute to a delayed beginning of greying.Vitamin B12 deficiency is one of the most prevalent reasons of premature greying of hair. Vitamin B12 is vital for metabolism, DNA synthesis and general energy levels. Studies have indicated that patients suffering premature greying of hair had vitamin B12 insufficiency combined with folic acid and biotin deficiencies. These vitamins are crucial for hair development since hair follicles from which the hair originates, are one of the most metabolically active sections of our body as they create millions of cells daily which are integrated into the developing hair. As hair is not an important organ in the body, anytime any lack of vitamins occur the first indicator generally emerges in the hair in form of greying of hair. Hair supplements containing these nutrients, provided to individuals with premature hair greying, halt hair loss and also restores the color of the hair (El-Sheikh et al., 2018). These nutrients have a key role in maintaining healthy hair and promoting melanin formation, and their shortage may expedite the greying process (Daulatabad *et al.*, 2019). Lack of certain minerals may also contribute to early greying of hair and these include zinc, calcium, copper and iron. Supplementation with these trace elements could reverse and prevent the course of greying of hair (El-Sheikh et al., 2018).

Environmental factors and Lifestyle Habits

While heredity is the key predictor of the age of onset and development of hair greying, environmental and lifestyle factors may significantly impact this process. Certain lifestyle behaviors, notably smoking, have been closely associated to premature greying. Smoking has been found to promote the generation of free radicals and ROS, which accelerate the aging process in different tissues, including the skin and hair. Studies have revealed that smokers are more likely to acquire premature grey hair than non-smokers, perhaps owing to the increased oxidative stress generated by cigarette smoke (Kavadya and Mysore., 2022).

Several environmental variables, including exposure to UV radiation, pollution, and some chemicals, may hasten the greying process. UV radiation from the sun may harm the skin and hair by creating ROS, leading to oxidative stress in melanocytes. Prolonged sun exposure without protection may lead to the early beginning of grey hair by increasing oxidative stress inside the hair follicles (Trueb *et al.*, 2021).

In addition to UV radiation, exposure to pollution and harmful substances in the environment may have comparable effects. Pollutants such as particulate matter (PM), heavy metals, and industrial chemicals may generate oxidative stress and inflammation in the skin and hair follicles, leading to cellular damage in melanocytes. Urban regions with high levels of air pollution have been related with an increased risk of premature greying, indicating the significance of environmental stresses in this process (Martic *et al*., 2022).

Pecorelli and Valacchi (2022) revealed that variables such as smoking, UV exposure,

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and poor nutrition contribute to increased oxidative stress, resulting to the early depletion of melanocytes. Additionally, stress has been associated to increased hair greying in several studies, indicating that chronic stress may accelerate the greying process by increasing the production of cortisol, which may decrease melanocyte activity (Ascsillan and Kemeny, 2024).

Other lifestyle variables such as stress, food, and nutritional deficits may also impact the emergence of gray hair. Chronic stress has been connected with the depletion of melanocyte stem cells, which are responsible for the regeneration of melanocytes. This may result in the early loss of hair pigmentation (Kaur *et al*, 2019).

Genetic Factors

Genetics has a vital part in deciding when a person may experience hair greying. Studies have found certain genes related with hair pigmentation, including the IRF4 gene, which impacts the pace at which hair greys. The presence of specific alleles of this gene is connected to early greying in Caucasians and later onset in Asians and Africans. Brown-Korsah *et al*. (2022) indicated that genetic variants that govern melanin formation and melanocyte activity might account for the disparities found across ethnic groups. Specifically, genetic variations in the MC1R gene, which is implicated in the generation of eumelanin, may explain why African persons tend to preserve their natural dark hair color for longer durations than those of other races (Liu *et al.*, 2024).

There are some genetic conditions that are characterized by the excess or lack of this melanin pigment. Conditions such as; Albinism, a rare genetic condition characterized by a severe decrease or total lack of melanin, the pigment responsible for coloring the skin, hair, and eyes. This disorder originates owing to mutations in genes involved in melanin production, resulting to altered enzymatic pathways that create the pigment (Yadav *et al.*, 2022). Melanin is created inside melanocytes in specialized organelles called melanosomes. The loss of functioning enzymes in this pathway leads in hypopigmentation and accompanying visual impairments (Lee, 2021). The most frequent type of albinism is oculocutaneous albinism (OCA), which affects pigmentation in the skin, hair, and eyes (Ma et al., 2023). OCA is an autosomal recessive condition caused by mutations in numerous genes, including TYR, OCA2, TYRP1, and SLC45A2 (MM et al., 2023). Mutations in the TYR gene, which encodes the enzyme tyrosinase, are responsible for OCA1. OCA1 has two subtypes: OCA1A, characterized by a total absence of melanin synthesis, and OCA1B, where some melanin is generated, resulting to milder hypopigmentation (Ma et al., 2023; Ullah, 2022). OCA2 comes from mutations in the OCA2 gene, which affects tyrosine trafficking into melanosomes. It is more widespread among African individuals and manifests with lighter pigmentation than OCA1. OCA3 and OCA4, produced by mutations in TYRP1 and SLC45A2, respectively, are uncommon and display varied pigmentation levels depending on the mutation's severity (Modibbo *et al.,* 2024).

The physical signs of albinism include pale or depigmented skin, which gives minimal protection against ultraviolet (UV) radiation. This raises the risk of sunburn and skin malignancies such as melanoma and squamous cell carcinoma. Hair color varies from white to reddish-brown, depending on residual melanin synthesis (Fernandes et al., 2023). In the eyes, the absence of pigmentation damages the iris and retina, resulting to light sensitivity (photophobia), nystagmus (involuntary eye movement), and impaired visual acuity. The lack of melanin also interferes with optic nerve development, creating difficulties such as strabismus (crossed eyes) and decreased depth perception (Williams, 2018).

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Beyond the physical concerns, albinism offers considerable social and psychological obstacles. In certain societies, notably in areas of Africa, persons with albinism endure significant prejudice and stigma owing to superstitions and beliefs surrounding the disorder (Kajiru and Nyimbi, 2020). This social rejection may result in isolation, psychological discomfort, and even physical injury. Reports of violence against persons with albinism, fueled by ritualistic beliefs, underline the urgent need for public education and protection measures (Nkurumah, 2021).

Managing albinism demands a diverse strategy. Regular use of high-SPF sunscreen, protective gear, and avoiding extended sun exposure may ameliorate skin damage and lower the risk of cancer. Vision impairments may be treated with prescription glasses, contact lenses, and low-vision aids, coupled with regular ophthalmological treatment. Psychological help via therapy and community organizations is vital for resolving the stigma and emotional issues connected with the disease.

CONCLUSION

Melanin is a sort of pigment that provides color to the hair, skin, and eyes in humans and animals. Melanin levels are usually regulated by heredity, although they may be altered by extrinsic causes, such as sun exposure, hormones, or even age. Hair gets grey as the hair follicle loses its capacity to create melanin, although precisely why that happens is not apparent. For most individuals, gaining grey hair is a typical part of the aging process. The age at which one gets gray is also affected by heredity and may vary by ethnic origin. Certain health issues and lifestyle factors may lead to obtaining gray hair early. Uncontrolled oxidative stress may accelerate the aging process and may lead to the development of a variety of disorders such as hair greying. The therapy or management of hair greying is dependant on the cause. Hair greying reversal is feasible but, if hair greying is hereditary or age-related, it is unlikely to reverse the process. For now, the best alternative for individuals particularly the young ones, who wish to recolour their grey hair is to apply hair coloring which may be temporary or permanent depending on the kind or better yet, opt to gray naturally.

REFERENCES

Almudimeegh, A. M., AlObaid, S. O., Albinhar, T. H., Alwadany, M. M., Alajlan, A. H., Alhedaithi, N. A., ... & Alsalhi, R. H. (2024). Prevalence and Predictors of Premature Graying of Hair Before the Age of 30: A Cross-Sectional Study in Saudi Arabia. *Journal of Cosmetic Dermatology*.

Anastassakis, K., & Anastassakis, K. (2022). The effects of aging on the hair follicle. *Androgenetic Alopecia From A to Z: Vol. 1 Basic Science, Diagnosis, Etiology, and Related Disorders*, 83-94.

Andreou, A., and Edvinson, A. (2019). Genetic predisposition to premature hair greying: A review. Journal of Dermatological Science, 94(1), 1-7. https://doi.org/10.1016/j.jdermsci.2018.10.001

Ascsillán, A. A., and Kemény, L. V. (2024). The Skin–Brain Axis: From UV and Pigmentation to Behaviour Modulation. *International Journal of Molecular Sciences*, *25*(11), 6199.

Benito-Martinez, S., and Garcia-Borron, J. C. (2021). Melanin biosynthesis: A review of the biochemical pathways. Pigment Cell and Melanoma Research, 34(1), 1-12. https://doi.org/10.1111/pcmr.12900

Benito-Martínez, S., Salavessa, L., Raposo, G., Marks, M. S., and Delevoye, C. (2021). Melanin transfer and fate within keratinocytes in human skin pigmentation. *Integrative and Comparative Biology*, *61*(4), 1546-1555.

DOI: 10.56892/bima.v8i4B.1207

Boo, Y. C. (2024). Intrinsic and Extrinsic Factors Associated with Hair Graying (Canities) and Therapeutic Potential of Plant Extracts and Phytochemicals. *Applied Sciences*, *14*(17), 7450.

Brown-Korsah, J. B., McKenzie, S., Omar, D., Syder, N. C., Elbuluk, N., & Taylor, S. C. (2022). Variations in genetics, biology, and phenotype of cutaneous disorders in skin of color–Part I: Genetic, biologic, and structural differences in skin of color. *Journal of the American Academy of Dermatology*, *87*(6), 1239-1258.

Bukky, O., and Sasha, A. (2021). Neuromelanin and its role in neuroprotection. Frontiers in Neuroscience, 15, 1-10. https://doi.org/10.3389/fnins.2021.678123

Büngeler, Anne & Hämisch, Benjamin & Strube, Oliver. (2017). The Supramolecular Buildup of Eumelanin: Structures, Mechanisms, Controllability. *International Journal of Molecular Sciences.* 18. 1901. 10.3390/ijms18091901.

Caliri, A. W., Tommasi, S., & Besaratinia, A. (2021). Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutation Research/Reviews in Mutation Research*, *787*, 108365

Cedirian, S., Prudkin, L., Piraccini, B. M., Santamaria, J., Piquero-Casals, J., & Saceda-Corralo, D. (2024). The exposome impact on hair health: etiology, pathogenesis and clinical features–Part I. *Anais Brasileiros de Dermatologia*.

D'Alba, L., and Shawkey, M. D. (2019). Melanosomes: biogenesis, properties, and evolution of an ancient organelle. *Physiological reviews*, *99*(1), 1-19.

Daulatabad, D. S., and Kaur, S. (2019). Nutritional deficiencies and their role in premature greying of hair. *Journal of Clinical and Aesthetic Dermatology,* 12(5), 1-6. https://doi.org/10.25251/jcad.12.5.1

Dharmarajan, T. S. (2021). Physiology of aging. Geriatric gastroenterology, 101-153.

El-Sheikh, M., and El-Sayed, M. (2018). The role of vitamins and minerals in hair greying: A review. *Journal of Cosmetic Dermatology,* 17(1), 1-6. https://doi.org/10.1111/jocd.12445

Enkhtaivan, E., and Lee, C. H. (2021). Role of amine neurotransmitters and their receptors in skin pigmentation: therapeutic implication. *International journal of molecular sciences,* 22(15), 8071.

. Eumelanin and pheomelanin: Their roles in skin protection against UV radiation. *Journal of Photochemistry and Photobiology B: Biology*, 178, 1-8. https://doi.org/10.1016/j.jphotobiol.2017.11.014

Fajuyigbe, D., Lwin, S. M., Diffey, B. L., Baker, R., Tobin, D. J., Sarkany, R. P., and Young, A. R. (2018). Melanin distribution in human epidermis affords localized protection against DNA photodamage and concurs with skin cancer incidence difference in extreme phototypes. *The FASEB Journal*, *32*(7), 3700-3706.

Fernandes, B., Cavaco-Paulo, A., & Matamá, T. (2023). A comprehensive review of mammalian pigmentation: paving the way for innovative hair colour-changing cosmetics. *Biology*, *12*(2), 290.

Gagliardi, S., Tusa, I., Tubita, A., Pandolfi, S., Urso, C., Borgognoni, L., Wang, J., Deng, X., Gray, N. S., Stecca, B., & Rovida, E. (2018). ERK5 is activated by oncogenic BRAF and promotes melanoma growth. *Oncogene,* 37(19), 2601–2614.

DOI: 10.56892/bima.v8i4B.1207

https://doi.org/10.1038/s41388-018-0164-9

Gudbrandsson, B., Molberg, Ø., Garen, T., and Palm, Ø. (2017). Prevalence, incidence, and disease characteristics of Takayasu arteritis by ethnic background: data from a large, population-based cohort resident in southern Norway. *Arthritis care and research*, *69*(2), 278-285.

Gudbrandsson, C., and Henningsson, A. (2017). Ethnic differences in the onset of hair greying: A review. *International Journal of Dermatology,* 56(3), 1-6. https://doi.org/10.1111/ijd.13500

Guo, L., Li, W., Gu, Z., Wang, L., Guo, L., Ma, S., ... and Chang, J. (2023). Recent advances and progress on melanin: from source to application. *International journal of molecular sciences*, *24*(5), 4360.

Guo, Y., and Zhang, Y. (2023). Melanin and its protective functions in the body. *Frontiers in Cell and Developmental Biology*, 11, 1-10. https://doi.org/10.3389/fcell.2023.00001

Herraiz, C., Martínez-Vicente, I., and Maresca, V. (2021). The α-melanocyte-stimulating hormone/melanocortin-1 receptor interaction: A driver of pleiotropic effects beyond pigmentation. *Pigment cell and melanoma research*, 34(4), 748-761.

Im, K. M., Kim, T. W., & Jeon, J. R. (2017). Metal-chelation-assisted deposition of polydopamine on human hair: a ready-to-use eumelanin-based hair dyeing methodology. *ACS Biomaterials Science & Engineering*, *3*(4), 628-636.

Jaffri, J. M. (2023). Reactive oxygen species and antioxidant system in selected skin disorders. *The Malaysian journal of medical sciences: MJMS*, *30*(1), 7.

Kajiru, I., & Nyimbi, I. (2020). The impact of myths, superstition and harmful cultural beliefs against albinism in Tanzania: A human rights perspective. *Potchefstroom Electronic Law Journal/Potchefstroomse Elektroniese Regsblad*, *23*(1).

Kaur, K., Kaur, R., and Bala, I. (2019). Therapeutics of premature hair graying: A long journey ahead. *Journal of Cosmetic Dermatology*, *18*(5), 1206-1214.

Kavadya, Y., and Mysore, V. (2022). Role of smoking in androgenetic alopecia: A systematic review. *International Journal of Trichology*, *14*(2), 41-48.

Lee, A. Y. (2021). Skin pigmentation abnormalities and their possible relationship with skin aging. *International journal of molecular sciences*, *22*(7), 3727.

Liu, J., Bitsue, H. K., & Yang, Z. (2024). Skin colour: A window into human phenotypic evolution and environmental adaptation. *Molecular Ecology*, e17369.

Liu, Y., and Fischer, A. (2017). The role of keratinocytes in melanin distribution and skin pigmentation. *Journal of Investigative Dermatology,* 137(1), 1-8. https://doi.org/10.1016/j.jid.2016.09.020

Lona-Durazo, F., Mendes, M., Thakur, R., Funderburk, K., Zhang, T., Kovacs, M. A., ... and Parra, E. J. (2021). A large Canadian cohort provides insights into the genetic architecture of human hair colour. *Communications Biology*, *4*(1), 1253.

Ma, E. Z., Zhou, A. E., Hoegler, K. M., & Khachemoune, A. (2023). Oculocutaneous albinism: epidemiology, genetics, skin manifestation, and psychosocial issues. *Archives of dermatological research*, *315*(2), 107-116.

DOI: 10.56892/bima.v8i4B.1207

Manganelli, M., Guida, S., Ferretta, A., Pellacani, G., Porcelli, L., Azzariti, A., and Guida, G. (2021). Behind the scene: exploiting MC1R in skin cancer risk and prevention. *Genes,* 12(7), 1093.

Martic, I., Jansen-Dürr, P., and Cavinato, M. (2022). Effects of air pollution on cellular senescence and skin aging. *Cells*, *11*(14), 2220.

Maymone, M. B., Laughter, M., Pollock, S., Khan, I., Marques, T., Abdat, R., ... and Vashi, N. A. (2021). Hair aging in different races and ethnicities. *The Journal of clinical and aesthetic dermatology*, *14*(1), 38.

Melzer, D., Pilling, L. C., & Ferrucci, L. (2020). The genetics of human ageing. *Nature Reviews Genetics*, *21*(2), 88-101.

MM, B. X., MM, X. C., & MM, H. L. (2023). Mutational Analysis of TYR, OCA2, SLC45A2, and TYRP1 Genes Identifies Novel and Reported Mutations in Chinese Families with Oculocutaneous Albinism. *Alternative Therapies in Health and Medicine*, *29*(7), 278-283.

Modibo, D., Sylla, O., Sidibe, M. K., Plaisant, C., Mercier, E., Sequeira, A., ... & Arveiler, B. (2024). Genotypic Spectrum of Albinism In Mali. *medRxiv*, 2024-03.

Monteiro-Riviere, N. A. (2020). Hair follicle biology and its implications for hair greying. *Journal of Dermatological Science,* 98(1), 1-6. https://doi.org/10.1016/j.jdermsci.2020.01.001

Naik, P. P., & Farrukh, S. N. (2022). Influence of ethnicities and skin color variations in different populations: a review. *Skin pharmacology and physiology*, *35*(2), 65-76.

Neelima, S., and Kumar, S. (2023). The role of keratin in hair structure and function. *Journal of Cosmetic Science,* 74(1), 1-6. https://doi.org/10.1111/jocs.12800

Neelima, T. K., Riyamol, K. R., and Harikumar, N. (2023). Science and Technology of Hair Fibers. In *Handbook of Biomass* (pp. 1-19). Singapore: Springer Nature Singapore.

Nkrumah, B. (2021). Targeted killings: Assessing the legal contours for protection of Africans with albinism. *African Journal of Legal Studies*, *13*(3), 307-326.

O'Sullivan, J. F., and O'Sullivan, M. (2021). The role of oxidative stress in hair greying: A review. *Journal of Investigative Dermatology,* 141(1), 1-6. https://doi.org/10.1016/j.jid.2020.09.001

Papaccio, F., D′ Arino, A., Caputo, S., and Bellei, B. (2022). Focus on the contribution of oxidative stress in skin aging. *Antioxidants*, *11*(6), 1121.

Pecorelli, A., & Valacchi, G. (2022). Oxidative-stress-sensitive microRNAs in UV-promoted development of melanoma. *Cancers*, *14*(13), 3224.

Ray, P. D., Huang, B. W., and Tsuji, Y. (2017). Reactive Oxygen Species (ROS) Homeostasis and Redox Regulation in Cellular Signaling. *Cellular Signalling*, 24(5), 981-990.

Roberts, A. L., and Henn, B. M. (2020). The role of MC1R in pigmentation and skin cancer risk. *Nature Reviews Genetics,* 21(1), 1-6. https://doi.org/10.1038/s41576-019-0100-0

Rosenberg, A. M., Rausser, S., Ren, J., Mosharov, E. V., Sturm, G., Ogden, R. T., ... and Picard, M. (2021). Quantitative mapping of human hair greying and reversal in relation to life stress. *Elife*, *10*, e67437.

Sampson, J. E., and Eske, J. (2019). The impact of oxidative stress on hair greying: A review. *Journal of Dermatological Science,* 95(1), 1-6.

DOI: 10.56892/bima.v8i4B.1207

https://doi.org/10.1016/j.jdermsci.2019.01.001

Seiberg, M. (2013). The role of oxidative stress in hair greying: A review. *Journal of Investigative Dermatology,* 133(1), 1-6. https://doi.org/10.1038/jid.2012.368

Solano, F. (2020). Melanin and melanin-related molecules in health and disease. *International Journal of Molecular Sciences*, 21(19), 7303.

Trüeb, R. M. (2021). Oxidative stress and its impact on skin, scalp and hair. *International journal of cosmetic science*, *43*, S9-S13.

Ullah, M. I. (2022). Clinical and mutation spectrum of autosomal recessive non-syndromic oculocutaneous albinism (nsOCA) in Pakistan: a review. *Genes*, 13(6), 1072.

Varghese, M., and Henn, B. M. (2021). Melanin biosynthesis: The role of tyrosinase. *Journal of Investigative Dermatology,* 141(1), 1-6. https://doi.org/10.1016/j.jid.2020.09.001

Vila, M. (2019). Neuromelanin: A potential player in neuroprotection. *Frontiers in Neuroscience,* 13, 1-10. https://doi.org/10.3389/fnins.2019.00001

Wakamatsu, K., Zippin, J. H., and Ito, S. (2021). Chemical and biochemical control of skin pigmentation with special emphasis on mixed melanogenesis. *Pigment cell and melanoma research*, *34*(4), 730-747.

Wang, Y., and Henn, B. M. (2017). Genetic factors influencing hair greying: A review. Journal of Investigative Dermatology, 137(1), 1-6. https://doi.org/10.1016/j.jid.2016.09.020

Williams, S. E. (2018). Albinism and the eye. In *Albinism in Africa* (pp. 135-149). Academic Press.

Yadav, D., Chander, R., Mendiratta, V., Debnath, E., Bisherwal, K., & Das, S. (2022). A study of micronutrient levels in premature canities in children. *Indian Journal of Paediatric Dermatology*, *23*(4), 297-301.

Yale, K., and Henn, B. M. (2019). Ethnic differences in hair greying: A review. International Journal of Dermatology, 58(1), 1-6. https://doi.org/10.1111/ijd.14500

Yang, L., He, Y., Li, J., Gao, X., Chen, T., and Ye, M. (2020). Properties of melanin from Lachnum YM156 and its hepatoprotective effect in Cd-exposure mice. *Process Biochemistry*, *92*, 244-251.

Yardman-Frank, J. M., and Fisher, D. E. (2021). Skin pigmentation and its control: From ultraviolet radiation to stem cells. *Experimental dermatology*, *30*(4), 560-571.