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Review Article

Premature hair graying: a multifaceted phenomenon

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Abstract

Premature hair graying (PHG) is the early loss of natural hair color, influenced by genetic, biological, and environmental factors. This review discusses the significant psychological impacts of PHG and explores its underlying mechanisms, related health conditions, and available treatments. The review examines the roles of genetics, oxidative stress, and lifestyle factors such as smoking and diet in premature graying. It also considers associated medical conditions and current and emerging treatment options. This overview aims to improve understanding of PHG and its broader implications.

Introduction

Early graying, also known as premature hair graying (PHG), is defined as the loss of natural hair color before the typical onset of gray hair. Multiple factors impact this occurrence, including intrinsic and extrinsic contributors, medical conditions, and genetic predispositions. Premature graying carries significant psychosocial implications for many individuals. The color of one's hair often serves as a marker of aging and has the potential to influence self-esteem and social interactions.

Despite its widespread occurrence, there remains a notable gap in comprehensive research addressing premature graying, including its underlying pathomechanisms, associated medical comorbidities, and available treatment options. Our review aims to delve into the multifaceted components influencing PHG in the hopes of providing a better understanding of PHG and its broader implications.

Pathomechanism of hair color

Hair color is determined by the type and amount of melanin produced by melanocytes located in the hair follicles.[1] Melanin is the primary pigment responsible for hair color and is subdivided into two forms important in hair color: eumelanin and pheomelanin.[2]

Eumelanin is further divided into two subtypes: brown eumelanin and black eumelanin. Eumelanin is responsible for the dark colors of skin, eyes, and hair. People with brown or black hair have varying amounts of brown and black eumelanin.

Pheomelanin, on the other hand, is responsible for red and yellow hues. This form of melanin pigments the lips and nipples and contributes to hair colors such as red and blonde.

The process of hair pigmentation begins in the hair follicle's melanocytes, where several genetic and biochemical pathways regulate melanin production.[3,4] One key regulatory pathway is the melanogenesis pathway, which involves the enzyme tyrosinase. Tyrosinase catalyzes the conversion of tyrosine to dopaquinone, the initial step in melanin synthesis.[5] From there, eumelanin and pheomelanin are synthesized through different downstream pathways, ultimately resulting in the deposition of these pigments in the hair cortex, providing color to the growing hair shaft.[6]

Evaluation of premature graying

The evaluation of PHG poses a challenge, as there is a lack of standardization and objective tools for the assessment of hair graying. Several grading scales have been proposed, including the graying severity score (GSS), which involves dividing the scalp into five zones, visually identifying regions with the most graying in each zone, then cropping the hairs in a 1 cm^2 section of each region and numerically counting the number of colored vs gray hairs. Each zone is assigned a score based on the percentage of gray hair, and an overall graying score is assigned based on the cumulative assessment of the five regions.[7] Another proposed method of PHG grading is the hair whitening score (HWS), which has been used in two studies and involves visual inspection and categorization of graying into five classes by the percentage of white hair (HWS 1: <25%; HWS 2: 25%–50%; HWS 3: 50%–75%: HWS 4: 75%–100%: HWS 5: 100%).[7] Further development of objective tools of assessment is warranted to evaluate the severity of graying and PHG more comprehensively.

Contribution of intrinsic factors

The mechanisms behind PHG involve a combination of intrinsic and extrinsic factors. Intrinsically, oxidative stress and genetic pathways are pivotal contributors.

Genetic contributors

Recent advancements in genome-wide association studies (GWAS) have shed light on potential genetic pathways implicated in PHG, offering a better understanding of the underlying mechanisms.[8,9] This growing field of research has identified single nucleotide polymorphisms (SNPs) as key players in the genetic landscape of PHG. Notably, SNPs such as rs12203592 within an intron of the IRF4 gene and rs59733750 in KIF1A have been associated with hair graying. For rs12203592, the T allele appears to act in a dominant manner concerning hair graying. For rs59733750, more research is needed to determine the alleles' specific inheritance pattern and dominance.[10–12]

Further exploration into gene expression patterns has demonstrated the intricate involvement of various genes in the development of melanocyte stem cells (MeSCs) and melanocytes, as well as the process of melanogenesis.[13] Remarkably, these studies have revealed a gradual decline in gene expression associated with melanin production as individuals age, particularly in white hair follicles compared to black hair follicles. Among the key genes implicated in this process are tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1), tyrosinase-related protein 2 (TYRP2), microphthalmia-associated transcription factor (MITF), paired box gene 3 (Pax3), SRY-box transcription factor 10 (Sox10), melanocortin 1 receptor (MC1R), tyrosine kinase receptor (c-Kit), Plexin C1 (Plexin C1), Melan-A (Melan-A), premelanosome protein (Pmel17), and the receptor for hepatocyte growth factor (MET).[14–16] Polymorphisms within these gene loci have been intricately linked to the normal variation observed in hair color traits, further underscoring the complex interplay between genetic factors and hair pigmentation.[17] This network of genetic factors underscores both the complexity and broader genetic contribution related to premature graying across populations.

The significance of genetics in premature graying is highlighted by its familial nature, evident through observed associations between affected family members and an in-depth examination of family history.[18] Insights from kinship studies emphasize the role of genetic predisposition, revealing that as much as 90% of the variability in hair graying can be attributed to genetic factors, as indicated by twin-controlled studies.[19–21] Within the realm of genetic influence, paternal history emerges as influential in comparison to maternal history, adding to our comprehension of the hereditary aspects of premature graying (Table 1).[22]

Endogenous oxidative stress

Endogenous oxidative stress refers to an imbalance within the body caused by the production of reactive oxygen species (ROS).[23] The natural aging process involves a decline in the efficiency of antioxidant systems, leading to an increase in oxidative stress.[24]

During the anagen phase of the hair growth cycle, melanocytes are engaged in melanin production, a process that requires hydroxylation of tyrosine and oxidation of dihydroxyphenylalanine to create melanin.[5] These biochemical reactions generate ROS, which can damage cells if not neutralized.[25] The body's antioxidant defenses weaken with age, reducing their capacity to counteract ROS.[24] This accumulation of ROS can lead to cellular damage within the hair follicle, ultimately affecting melanin production and leading to the graying process.[24,26]

Studies examining melanocytes in graying hair bulbs have found these cells to be highly vacuolated, a typical cellular response to increased oxidative stress.[23] This finding supports the theory that endogenous oxidative stress contributes significantly to the disruption of melanocytes and, consequently, hair pigmentation. A 2015 study conducted in New Delhi compared levels of three oxidative stress parameters: malonaldehyde

Table 1 Intrinsic and extrinsic mechanisms underlying premature hair graying

Factor	Physiologic mechanism	Impact on hair follicle pigmentation	Contributing factors
Intrinsic factors			
Endogenous oxidative stress	Natural aging involves a decline in the efficiency of antioxidant systems, leading to increased oxidative stress	Accumulation of reactive oxygen species leads to cellular damage within hair follicles, impacting melanin production	• Age • UV radiation • Emotional stress • High vacuolation of hair bulb melanocytes in response to oxidative stress
Genetic factors	Variation in the expression of genes involved in the development of melanocytic stem cells and melanocytes	Decreased gene expression associated with melanin production with increased age, particularly in white follicles compared to black follicles	• Age
Extrinsic factors			
Smoking	Smoking produces a large quantity of reactive oxygen species	Pro-oxidant effect of smoking leads to melanocyte damage, resulting in premature damage to hair follicles	High vacuolation of hair bulb melanocytes in response to oxidative stress
Vitamin and mineral deficiencies			
Vitamin B12	Vitamin B12 levels may impair proliferation of cells via impaired DNA synthesis	Vitamin B12 is involved in stabilization of early anagen phase of the hair follicle, fostering pigmentation	• Diet
Iron	Iron is needed by metalloenzymes involved in melanogenesis	Conflicting evidence on association between low iron levels and PHG	Diet
Vitamin D3	Vitamin D3 involved in calcium metabolism, implicated in some steps of melanogenesis	Low vitamin D3 may impair calcium-dependent steps of melanogenesis	• Diet • Climate
Calcium			Diet
Copper	Copper facilitates tyrosine kinase activity essential for the synthesis of eumelanin and phaeomelanin	Low copper levels may result in decreased production of melanin in the hair follicle	Diet

(MDA), whole blood reduced glutathione in erythrocytes (GSH), and ferric reducing antioxidant potential (FRAP) between 52 cases with premature graying and controls. They identified, on average, higher levels of MDA and lower levels of GSH and FRAP in cases compared to controls, all of which align with a higher pro-oxidant and lower antioxidant profile within cases of PHG.[27]

Exogenous oxidative stress can also be driven by external factors that escalate the production of ROS or intensify oxidative stress within the body, primarily Ultraviolet (UV) radiation and emotional stress.[24]

UV radiation has been shown to induce oxidative damage to hair follicles, potentially leading to graying.[28] Experimental studies on mice have elucidated that exposure to UV rays can trigger oxidative stress within hair follicles, resulting in hair graying.[28] The oxidative harm caused by UV radiation can impede melanocytes' ability to produce melanin, thereby expediting the graying process.[28] Importantly, these studies have also underscored the protective role of antioxidants such as superoxide dismutase, implying that enhancing the body's antioxidant capacity could neutralize the impact of exogenous oxidative stress on hair pigmentation.[28]

Emotional stress is another external factor associated with oxidative stress and premature graying.[29] Research reveals a correlation between psychological stress and heightened oxidative stress, implying the influence of emotional factors on PHG (Table 1).[29]

Extrinsic factors contributing to PHG

Smoking

Multiple external factors are potentially implicated in the etiology of PHG. Reports have linked smoking and gray hair in both men and women, as reported by Mosley and Gibbs in 1996.[23,30]

The exact mechanism by which smoking causes premature graying is inadequately understood. Smoking generates a large host of ROS.[31] The pro-oxidant effect of tobacco leads to melanocyte damage, culminating in premature damage to hair follicles.[31] Melanocytes in gray hair bulbs are also reported to be highly vacuolated, a known response to oxidative stress.[23] This nuanced association between smoking and premature graying underscores the multifaceted impact of environmental factors on hair health and pigmentation (Table 1).

Nutrition/vitamin deficiencies

Other extrinsic contributors to premature graying include nutritional and vitamin deficiencies, which have been explored in several studies.

Vitamin B12 and iron emerge as key elements in stabilizing the early anagen phase of the hair follicle and fostering

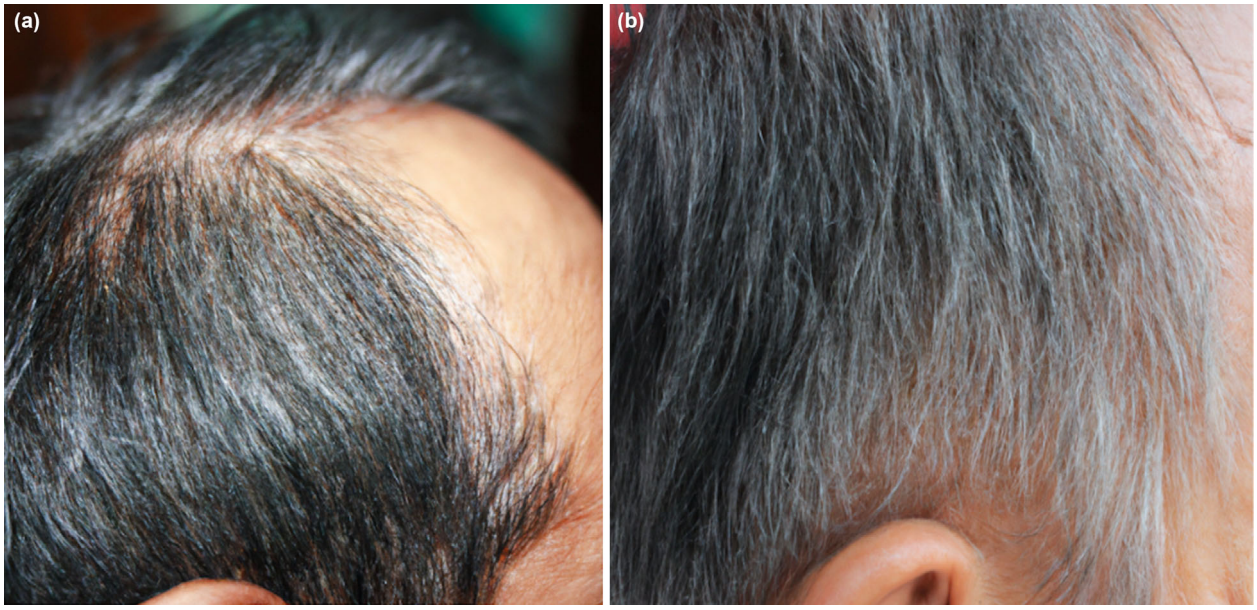

Figure 1 Spatial distribution of graying for men.

pigmentation.[32] A study conducted in North India revealed a significant disparity in serum vitamin B12 levels between individuals with PHG and control subjects, shedding light on the potential role of this vitamin in maintaining hair health.[32]

Similarly, an in-depth investigation emphasized the intricate correlation between PHG and factors such as family history, vitamin B12 deficiency, ferritin deficiency, and hypothyroidism. Highlights from this retrospective review of 71 patients with PHG in India include a statistically significant association with B12 deficiency in the PHG population compared with the control population, along with statistically higher TSH levels.[33]

A further study explored hematological parameters, including hemoglobin, total iron binding capacity, ferritin, iron, vitamin B12, and vitamin D3, in 35 school-aged participants with PHG.[22] This provided evidence underscoring the pertinent role of vitamin D3 deficiency in the manifestation of PHG, with a significantly higher incidence of vitamin D deficiency in the PHG group. The participants' age ranges were between 5 and 18.[22]

A case–control study conducted in New Delhi of 52 individuals with self-reported premature graying also found that average serum levels of Vitamin B12, folic acid, and biotin levels were significantly lower in cases compared to controls.[34] The associations identified in this small study suggest further work may be warranted to more comprehensively evaluate the role of these vitamins in the graying process.

Additionally, an Iranian study delved into the realm of metal ions, particularly serum iron, zinc, and copper, key trace elements that play a role in melanogenesis. Copper, in particular, is crucial for tyrosinase activity, which is pivotal for the creation of hair pigment, including both eumelanin and phaeomelanin.[35] The study examined serum copper, zinc, and iron concentrations in 66 patients with PHG compared with age-matched controls. There was a significantly lower serum copper concentration in the PHG cohort.[35] Notably, serum iron concentration was markedly higher in the PHG group than in the control group.[35] Sonthalia *et al.* also reported this absence of low serum iron levels (Table 1).[33]

Role of ethnicity and gender in premature hair graying

The interplay between ethnicity and gender shapes the landscape of premature graying. Premature graying is delineated by age thresholds, with Whites experiencing premature graying before age 20, Asians before 25, and Blacks before 30.[6,18,32] This demarcation underscores the varied temporal manifestations across diverse ethnic groups. Beyond the temporal differences, certain populations display very low frequency and intensity of hair graying, namely African and Asian population groups. Conversely, the highest intensities of hair graying were found in patients with blonde hair, including those of Polish, Scottish, Russian, and Danish descent.[36] Adding another level of complexity, there are also gender-specific patterns of hair graying. Within the previously described racial variations, hair graying affects both genders equally.[19] However, it exhibits different spatial patterns: men typically initiate graying at the temples and sideburns, while women predominantly undergo this process around the frontal area (Figures 1 and 2).[19,26,36] Regardless of gender, the occipital area of the scalp was the least affected by graying.[36] The slow development of gray hair across the top, sides, and back of the scalp results in diverse gender-specific appearances.

Figure 2 Spatial distribution of graying for women.

The experience and perception of premature graying can differ significantly among various racial groups, influenced by both cultural norms and biological factors. For example, premature graying may be perceived as more unusual in certain populations where it occurs less frequently. The impact of premature graying on self-image and social perception also varies across cultures. For some racial groups, premature graying might be less stigmatized, while for others, it could significantly affect quality of life. For example, studies have demonstrated premature graying results in significant decreases in dermatology life quality index (DLQI) scores in patients of Indian origin.[34,37]

This comprehensive exploration of family, gender, and ethnicity deepens our understanding of the multifaceted factors contributing to premature graying, offering valuable insights into its diverse manifestations across populations (Table 1).

Role of underlying medical pathology contributing to premature hair graying

In contrast to physiologic aging, premature graying may also be influenced by underlying health conditions that disrupt the normal pigmentation process. Autoimmune conditions, such as vitiligo and hypothyroidism, may promote premature graying.[38] Furthermore, certain rare syndromes may influence hair pigmentation, highlighting the complex and multifactorial nature of premature graying.

Among autoimmune conditions, vitiligo contributes significantly to premature graying. The sensitivity of melanocytes to oxidative stress in vitiligo patients provides a unique perspective on how oxidative stress plays a pivotal role in disrupting melanocytes and diminishing pigmentation in hair follicles. Furthermore, the hair bulb often acts as a protected site and an important reservoir for melanocytes that aid in skin repigmentation during vitiligo treatment.[38] The most common repigmentation pattern in vitiligo is the perifollicular type, which results from UVB radiation-induced migration of melanocytes from the hair follicle to the epidermis.[39,40] Leukotrichia, the presence of a localized patch of white hair, is, therefore, a poor prognostic sign in vitiligo patients, and vitiliginous areas with overlying leukotrichia may require more aggressive therapies to achieve successful repigmentation.[38,41]

Beyond vitiligo, autoimmune conditions such as hypothyroidism also play a role in PHG. Several studies have identified an association between autoimmune thyroid disease and premature graying, and repigmentation of gray hair after treatment of the thyroid disorder was achieved using an animal model.[35,42–44] These findings may be explained by hair follicles' ability to transcribe deiodinase genes that convert T4–T3, two hormones that subsequently stimulate intrafollicular melanin synthesis.[45] Hypothyroid patients are also more likely to develop vitamin B12 deficiency, further supporting the multifactorial influences on hair graying.[46]

Progeroid syndromes constitute another notable category that can underlie premature graying. This group of rare genetic disorders is characterized by a defective DNA repair mechanism that renders DNA more susceptible to oxidative damage. This results in clinical features that imitate physiological aging, ranging from osteoporosis and cardiovascular disease to cutaneous manifestations, including early rhytide development and hair graying.[47] Conditions like Werner's syndrome are included in this classification, highlighting the connection between genetic factors, compromised DNA repair mechanisms, and the premature graying of hair.

Though the association between metabolic syndrome and premature graying is not well understood, an association with obesity and coronary artery disease (CAD) has been suggested. In a recent study, male sex, age, family history of PHG, and obesity were all factors significantly associated with premature graying. In assessing metabolic factors, waist circumference, BMI, systolic blood pressure, diastolic blood pressure, and fasting blood sugar were significantly higher in the premature hair-graying group compared to the nonpremature hair-graying group.[48] Additionally, serum HDL cholesterol was significantly lower in the PHG group.[48]

Further studies have suggested a relationship between premature graying and CAD.[49,50] Erdogan *et al.* investigated whether carotid artery intima-media thickness (as a marker of CAD) is correlated with hair graying and found that the severity of PHG is independently related to carotid intima-media thickness.[49] Additionally, in a 12-year study, patients with an initial myocardial infarction (MI) were followed, and a correlation between hair graying and MI was found. MI risk was proportional to the severity of graying.[50]

Treatments

Camouflage

In managing patients with PHG, several cosmetic and camouflaging options should be considered, including wigs, demiwigs, wiglets, toupees, and cascades. However, hairpieces require frequent care and can be costly, especially if natural human hair fibers are used. Hairpieces made of synthetic fibers are less expensive and require less care; however, they can be associated with significant discomfort and often look and feel less natural. Removable hair pieces can also induce traction on remaining hair fibers due to increased tension on the scalp.[51]

Several modalities exist to help conceal gray hairs, including hair-thickening fibers and concealing powders, pigmented concealing powders and sprays, styling products and techniques, and coloring products.[52] Of these, hair-thickening fibers are composed of the same keratin proteins found in natural hair. These fibers carry a static charge that binds to existing hair to camouflage areas of alopecia and gray hairs. Concealing powders form a coat over existing hair, camouflaging gray tones.

Hair colorants are a common option for hair color restoration in patients with PHG.[53] Colorants can be either natural or synthetic and temporary or permanent in terms of stability. Henna, derived from the plant *Lawsonia alba*, is a commonly used natural hair colorant. Although the color is intended to add red highlights, occasionally, it can lead to gray hair appearing orange.

Scalp micropigmentation is a method of semipermanent concealment where tiny, layered dots in different hues of black are tattooed onto the scalp in a stippling pattern, creating the illusion of natural hair follicles and a fuller hairline.[52] Similarly, eyebrow microblading uses a blade to instill pigment into the skin to mimic the appearance of eyebrow hairs.[54] However, adverse effects include bleeding of the pigment and pigment color changes, delayed granulomatous reactions, sarcoid, allergic contact dermatitis (ACD), and preseptal cellulitis.[55–58]

Permanent hair dyes are classified as nonoxidative or oxidative based on their chemical compositions, which carry the risk of damaging the hair shaft.[53] Oxidative dyes are typically permanent or semipermanent and penetrate the hair, while nonoxidative dyes are temporary or semipermanent.[59] Permanent dyes are more commonly associated with adverse effects.

A significant adverse effect to consider with hair dyes is the potential for ACD, manifesting as a facial or scalp eruption or eyelids, forehead, or neck edema.[60] A common sensitizer to consider in hair dyes is p-p-phenylenediamine, or PPD, which has been found to result in a positive patch test in 4.5% of patients tested by one investigative study.[60]

Newer formulations without these contact allergens should be considered for patients with known or suspected ACD to PPD-PPD-containing dyes. In a study investigating the prevalence of cross-reactions to newer dyes containing food, drug and cosmetic dyes (FD&C), drug and cosmetic dyes (D&C), and acid dyes in patients with known allergies to paraphenylenediamine (PPD), direct-to-skin (DTS), and o-nitro-p-phenylenediamine (ONPPD), the new generation of hair dyes did not result in a positive reaction, reaffirming the utio-nitro-p-phenylenediaminelity of these dyes in patients with known allergies to PPD, DTS, or ONPPD (Table S1).[61]

Medical and natural therapies

To date, no known medical therapies can reverse or prevent PHG. Although not formally studied, increasing hair density may help mitigate some of the cosmetic concerns surrounding PHG. Increasing or maintaining pigmented hairs may help to camouflage the appearance of gray hairs. Furthermore, while there are no medical therapies targeted directly at increasing or preserving pigmented hairs, increasing general background hair density, even if gray, may alleviate cosmetic concerns by increasing the thickness and youthful appearance of the hair overall.

Medical therapies targeted at increasing hair density are numerous and include topical and oral formulations. One of the most popular medications is minoxidil, which is FDA-approved for topical use and frequently employed off-label in oral formulations. Minoxidil likely functions at the level of the hair follicle to lengthen the anagen phase of the hair cycle, increase microcirculation to the follicle, stimulate growth, and promote the release of growth factors.[62] Topical minoxidil has demonstrated efficacy and safety, with rare and typically mild side effects, including local irritation, hypertrichosis, and headache.[63,64] When employed at low doses ranging from 0.5 to 5 mg, oral minoxidil has also been shown to be a highly efficacious treatment for increasing hair density and may be easier to comply with than daily topical use.[65,66] It is similarly well tolerated, with the side effects most commonly including hypertrichosis and, more rarely, lightheadedness, fluid retention, tachycardia, headache, periorbital edema, and insomnia.[67]

Beyond minoxidil, other antiandrogen therapies are frequently utilized to increase general hair density. These include finasteride, a 5-alpha-reductase inhibitor that is FDA-approved for treating male pattern hair loss and is used off-label in women, which has demonstrated significant efficacy.[68] Finasteride is generally well-tolerated, with rare side effects including depression, suicidal ideation, erectile dysfunction, decreased libido, and decreased ejaculation.[69] The side effect profiles of dutasteride and finasteride are relatively similar, including mood and sexual side effects. However, the half-life of dutasteride is longer, which may result in longer persistence of side effects after medication discontinuation.[69,70] Lastly, spironolactone is an aldosterone receptor agonist used for many years off-label as an efficacious treatment to increase hair density in women.[71,72] Spironolactone is also typically well tolerated, with the most common side effects including dizziness/headache, increased urination, and menstrual irregularities.[73–75]

In addition to prescription medications used to increase background hair density, there may be a role for other natural

remedies or lifestyle changes in addressing PHG. As previously discussed in this article, certain vitamin deficiencies have been linked to premature graying, although these interventions have not been directly studied, vitamin repletion could address a component of PHG. Specifically, vitamin B12 and vitamin D have been linked to PHG.[31–33,35] vitamin B12 deficiency may be addressed by supplementation or increasing dietary sources, including meat, poultry, fish, shellfish, eggs, and dairy products.[35] Given that the primary source of vitamin D is cutaneous synthesis, which requires exposure to sunlight, supplementation is often key in addressing a deficiency.[47]

Additionally, while these interventions have not been formally evaluated, sun protection may also play a role in preventing UV rays exposure associated with premature graying.[28] Avoiding tanning beds is one essential component of limiting UV exposure. Using hats, sun umbrellas, and parasols, as well as limiting time spent outdoors in direct sunlight, may also help minimize UV exposure on the hair and scalp.[76,77] Notable research has been conducted on how to protect hair strands against photodamage, however, there is a lack of data specifically addressing the photoprotection of the hair-bearing scalp and its impact on PHG.[78] Further research is required in this area to better understand if scalp protection from UV radiation helps to mitigate PHG (Table S1).

Emerging therapies

Various emerging therapies could be promising alternative treatment options for premature graying. Cases of gray hair repigmentation have been reported with the use of therapeutic monoclonal antibodies, tyrosine kinase inhibitors, immunomodulatory drugs, cyclosporine A, and even attempts at modulating MeSC motility.[79,80]

First, there are numerous reports of hair repigmentation in association with monoclonal antibody therapies, including anti-programmed cell death-1 (PD-1)/PD-L1 antibodies, dupilumab, adalimumab, secukinumab, and ustekinumab.[79] Anti-PD-1/PD-L1 antibodies are a class of immune checkpoint inhibitors that prevent T cell inactivation and restore the immune response to cancer cells. In a series of 14 patients undergoing anti-PD1/anti-PD-L1 therapy for lung cancer, these patients experienced hair repigmentation.[81] Similarly, there was a report of full body hair repigmentation in a patient with colorectal cancer and Hodgkin lymphoma who underwent treatment with an anti-PD-1 antibody.[82] While the mechanism is not fully understood, PD-1/PD-L1 immunotherapy and the subsequent cytotoxic tumor destruction are thought to induce a proinflammatory state that could stimulate melanocyte activity.[76,79]

Dupilumab is a monoclonal antibody against the IL-4 receptor, effectively reducing the T helper 2 cell response.[79] Hair repigmentation was reported in one atopic dermatitis patient treated with this medication.[82] IL-4 suppresses the expression of various melanogenesis-related genes. Therefore, the antibody against IL-4 can help promote the restoration of hair pigmentation.[79] Furthermore, adalimumab is a tumor necrosis factor (TNF) inhibitor, and a rheumatoid arthritis patient on this medication demonstrated hair repigmentation.[83] TNF inhibits melanogenesis and melanocyte viability via multiple pathways. Some *in vitro* studies have shown that TNF-α may reduce melanocyte-stimulating hormone receptor binding activity, MC1R expression, or melanosomal protein gp87 expression, all of which promote melanogenesis.

Additionally, secukinumab is a human monoclonal antibody against IL-17A; IL-17 suppresses melanogenesis through both ROS-dependent melanocyte apoptosis and increased production of melanogenesis inhibitors.[84] Interestingly, hair repigmentation was seen in a patient with plaque psoriasis who was being treated with secukinumab. Speckled lentigines emerged in healed psoriatic plaques after treatment with secukinumab, further highlighting its role in the promotion of melanogenesis.[85] Finally, ustekinumab, an antiinterleukin IL-12/23 p40 monoclonal antibody, was shown to induce hair repigmentation in a psoriasis vulgaris patient.[86] This was thought to occur via suppression of inhibitors of melanogenesis (IL-17 and TNF-a) that depend on IL-23 upstream.

Even though tyrosine kinase inhibitors are commonly associated with the cutaneous side effects of skin and hair depigmentation, there have been rare cases of hair repigmentation. While the exact mechanism is not completely understood, tyrosine kinase inhibitors' role in hair repigmentation may be explained by their ability to enhance melanogenesis.[79] In a retrospective study of 133 CML patients treated with imatinib, there were 9 cases of hair repigmentation.[87] Imatinib exerts this effect through inhibition of Bcr-Abl, PDGF-receptor, and c-KIT. Repigmentation effects have also been reported in a CML patient treated with nilotinib, a tyrosine kinase inhibitor that has been shown to promote melanogenesis *in vitro*.[88] In knock-out mouse melanoma cells, nilotinib was found to upregulate MITF (melanocyte-inducing transcription factor) and its downstream genes via activation of the cAMP/PKA/CREB pathway and decreased phosphorylation of AKT.[89]

Similarly, dasatinib was found to promote melanogenesis in normal human melanocytes via ERK/CREB/MITF signaling.[90] Finally, several cases of hair repigmentation were reported after treatment with sorafenib and erlotinib for lung adenocarcinoma.[91,92] Sorafenib inhibits Raf1, VEGF-receptors, and PDGF-receptors, among other targets. It also enhances MITF expression and melanogenesis in mouse melanoma cells by suppressing the AKT and ERK pathways and activating B-catenin. These studies highlight the potential of tyrosine kinase inhibitors to be tools in repigmentation efforts.

Immunomodulatory drugs are another important emerging therapy. There are two reported cases of multiple myeloma patients who experienced hair repigmentation after treatment with lenalidomide or thalidomide, two immunomodulators approved for hematological malignancies and autoimmune conditions.[93,94] The effects of immunomodulators on hair

Table 2 Overview of emerging therapies for premature hair graying

Medication	Mechanism of action	Hypothesized mechanism behind effect(s) of on hair follicle pigmentation
Immune checkpoint inhibitors (anti-PD-1, anti-PD-L1)	Inhibition of T cell inactivation, restoring immune response against cancer cells	Induction of a proinflammatory state that could stimulate melanocyte activity
Dupilumab	Monoclonal antibody against IL-4 receptor that reduces T helper 2 cell response	IL-4 pathway increases expression of genes that inhibit melanogenesis
Adalimumab	Monoclonal antibody against tumor necrosis factor (TNF-alpha)	TNF-alpha inhibits melanogenesis and melanocyte viability via multiple pathways including reduced melanocyte-stimulating hormone receptor binding activity, MCIR expression, or melanosomal protein gp87 expression
Secukizumab	Monoclonal antibody against IL-17A	IL-17 suppresses melanogenesis through ROS-dependent melanocyte apoptosis and increased production of melanogenesis inhibitors
Ustekinumab	Monoclonal antibody against IL-12/23 p40	Suppression of inhibitors of melanogenesis that depend on IL-23 upstream, such as IL-17 and TNF-alpha, may promote hair repigmentation
Tyrosine kinase inhibitors	Inhibition of tyrosine kinases implicated various pathways involved in carcinogenesis	Promotion of melanogenesis via upregulation of transcription factors
Lenalidomide and thalidomide	Immunomodulatory agents	Reduction in TNF-alpha production and IL-6 secretion promotes melanogenesis and repigmentation
Cyclosporine A	Selective inhibition of helper T cells	Downregulation of Wnt ligand and activation of Wnt/B-catenin pathway melanocytes may promote hair regimentation
Melanocyte stem cell modulators	Restoration of melanocyte stem cell motility or physically moving melanocyte stem cells back to their germ compartment	Local environment cues in germ compartment promote melanocyte stem cell pigment production

repigmentation can be explained primarily by their inhibition of melanogenic inhibitors. Lenalidomide and thalidomide have been shown to reduce TNF-a production and decrease secretion of IL-6. Many immunomodulatory drugs also inhibit TGF-B, reduce plasma levels of IL-1 and IL-1B, and prevent activation of NF-kB.[79] These molecular effects are critical because TNF-a, IL-6, TGF-B, and IL-1B—all inhibited by immunomodulators—are melanogenesis inhibitors. Meanwhile, IL-10—which is induced by immunomodulators—is known to activate the STAT-3 and PI3K/AKT/NF-kB pathways that protect melanocytes.

Cyclosporine A, a medication that selectively inhibits helper T cells, has been shown to facilitate hair repigmentation in psoriasis patients.[95,96] Interestingly, hypertrichosis has been identified as the most common adverse effect of cyclosporine A.[97] This medication downregulates an inhibitor of the Wnt ligand, thereby activating the Wnt/B-catenin pathway in hair follicles to promote hair growth. Cyclosporine A's ability to promote melanogenesis and hair repigmentation may be explained by its activation of the WNT pathway in melanocytes.[79]

Finally, Sun et al. have been working to understand the migration of McSCs and the signals that allow for the regeneration of melanocyte progeny, which is required for the pigmentation process.[80] Studies have shown that McSCs are mobile cells that can translocate between the hair follicle stem cell and transit-amplifying compartment and respond to local environmental cues for subsequent differentiation. During aging, there is an accumulation of stranded McSCs that are not involved in the regeneration of melanocyte progeny, leading to hair graying.[80] By harnessing the dedifferentiation capability of McSCs and modulating McSC motility, there may be a new approach to the prevention of PHG. Ongoing research is necessary to explore and harness the repigmentation abilities of the emerging therapies discussed above while minimizing potential side effects (Table 2).

Conclusion

In conclusion, this review comprehensively highlights the intricate facets of PHG, exploring its pathomechanisms, underlying contributors, and associated medical, genetic, and environmental factors. PHG represents a complex condition driven by a variety of factors. The pathomechanisms, ranging from oxidative stress to genetic predispositions, underscore the intricate biology behind hair pigmentation. Additionally, extrinsic factors such as smoking, nutritional deficiencies, and UV radiation contribute to the acceleration of graying, demonstrating that environmental influences are also highly significant.

Furthermore, this review explores various cosmetic and medical interventions for individuals facing premature graying. Treatment modalities such as hairpieces, concealment techniques, colorants, and medical treatments offer a spectrum of options tailored to individual preferences and circumstances.

Understanding the broader implications of premature graying, considering familial, gender, and ethnic factors, adds depth to our comprehension of this phenomenon. The association with autoimmune conditions, metabolic diseases, and obesity highlights the need for a holistic approach to address both cosmetic concerns and potential underlying health issues.

Despite the progress in understanding and treating PHG, significant gaps remain in comprehending its full spectrum. Continued research is essential to unravel the remaining uncertainties of premature graying. This will ultimately lead to more effective preventive strategies, targeted treatments, and improved quality of life for those affected by this condition.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Overview of camouflaging strategies and treatments for premature hair graying.