A review of the etiologies, clinical characteristics, and treatment of canities

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Abstract

Hair pigmentation is regulated by follicular melanogenesis, in which the process consists of melanin formation and transfer to keratinocytes in the hair shaft. Human hair follicles contain two types of melanin: the brown-black eumelanin and yellow-red pheomelanin. Eumelanin is commonly present in black and brown hair while pheomelanin is found in auburn and blonde hair. Hair follicle melanogenesis is under cyclical control and is concurrently coupled to hair growth. Many factors including intrinsic and extrinsic factors affect the follicular melanogenesis. Though many studies have been conducted to identify the pathogenesis and regulation of hair pigmentation, the etiology of canities and hair pigmentation is still unclear. The pathogenesis of canities or gray hair is believed to occur either from insufficient melanin formation due to melanocyte degeneration or a defect in melanosomal transfer. Canities is an aging sign which often interferes with one’s socio-cultural adjustment. On the other hand, premature canities correlate with diseases such as osteopenia and cardiovascular disease. Risk factors associated with canities are not only genetic but also external causes. For example, smoking, alcohol consumption, and stress are among the most common factors. Camouflage techniques are still used as the primary treatment of canities. Further treatments for canities are being developed to achieve the true reversal of hair pigmentation.

Literature review search method

This review has focused on the pathology of canities, age-related changes in canities, premature development of canities, and current treatments for canities. The literature review for this study was limited to articles published in the PubMed database. Articles related to the study topic were searched until the end of February 2017 using the search terms “gray hair” or “canities.” A total of 477 articles were identified including clinical trials, reviews, and case reports. Articles published in languages other than English were excluded. However, references cited in articles identified in our search were also obtained for additional data.

Normal hair follicle melanin unit and melanogenesis

The hair follicle is a small organ that consists of several types of cells such as epithelial cells (i.e., endothelium and over seven different keratinocyte lineages), mesenchymal cells (i.e., dermal papilla fibroblasts and connective tissue sheath fibroblasts), neuroectodermal cell populations (i.e., nerves and melanocytes), and transient migratory cells (i.e., immune cells and mast cells). Skin melanocytes are derived from pluripotent neural crest cells. Melanoblasts migrate from the truncal neural crest during weeks 6–8 of embryogenesis. By weeks 12–13, most melanoblasts are present in the epidermis. Hair bud development begins during weeks 9–12, when melanoblasts migrate to hair follicle to become a component of the follicle melanin unit. Finally, at the 18th week of intrauterine life, the first hair called lanugo is present throughout the body with melanocytes in the hair bulb. The color of human hair comes only from melanins in the keratinocytes of the hair, unlike the color of skin, which is derived from a mixture of oxidized/reduced hemoglobin (red/blue), carotenoids (yellow), and melanins (brown) that make the skin appear white, yellow, brown, or black. The difference in hair color is determined by the presence or absence of
melanins. The process of melanin production and transfer to keratinocytes is called melanogenesis. Human hair follicles contain two types of melanin: the brown-black eumelanin and yellow-red pheomelanin. Eumelanin is commonly present in black and brown hair while pheomelanin is found in auburn and blonde hair.1

There is a difference in the ratio between melanocytes and keratinocytes between the follicular unit and the dermis. The follicle melanin unit contains one melanocyte to five keratinocytes in the hair bulb, and one melanocyte to one keratinocyte in the basal layer of the hair bulb matrix. The dermis, on the other hand, has one melanocyte to 36 keratinocytes. Melanogenesis of the hair follicle is greatly influenced by the hair growth cycle, which is a cyclical control, whereas epidermal melanogenesis is a continuous process. There are three phases of hair growth: (i) the anagen phase, which refers to the hair shaft production period; (ii) the catagen phase, which is a regression period driven by apoptosis that occurs when the lower two-thirds of the hair follicle is resorbed; and (iii) the telogen phase, which refers to the resting period of the hair follicle.3

Melanocytes are present at two sites within the hair follicle. The first site is the anagen hair bulb, where they have melanogenic function. The second site is the outer root sheath (ORS), which is composed of nonmelanized melanocytes. More specifically, these melanocytes are located in the basal layer of the epithelium along the length of the hair follicle. In the anagen phase, melanosomes were produced by melanocytes and transferred to surrounding keratinocytes via dendritic projection.4 Toward the end of the anagen phase, the retraction of hair bulb melanocyte dendrites concurrently occurs with the decrease in three main melanogenic enzyme activities (i.e., tyrosinase, gp75, and dopachrome tautomerase), which begins a shutdown of melanogenesis. In the catagen phase, melanogenically active melanocytes disappear from the follicular epithelium, and a low number of dendritic, nonmelanogenic melanocytes are present. In the telogen phase, sleeping germ cells which act as precursors of melanocytes in the next anagen phase are found. It is thought that melanocytes in the subsequent anagen phase are derived from dedifferentiating nonmelanogenic and TRP-1 expression-lacking melanocytes that survive extensive apoptosis in the catagen phase and subsequently redifferentiate in the anagen phase. It is also believed that redifferentiating melanocytes are derived from a pigmented cell reservoir in the upper-permanent ORS. According to this theory, melanogenic hair bulb melanocytes subsist for only one hair growth cycle and disappear during the catagen phase.1

Transient canities normally occur in every cycle of hair growth. This is due to shutdown of melanogenesis at the end of the anagen phase a few days before discontinuation of keratinocyte proliferation, which causes the proximal ends of the hair to be pigment-free.5

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**Function and biologic value of hair pigmentation**

**Functions/benefits of human pigmented scalp hair**

**Sunblock properties**

Scalp hair provides sun protection for the skin of the scalp.1 Skin problems related to sunlight are normally found in subjects who are bald.5

**Antimicrobial activities**

During melanin synthesis, reactive quinone intermediates are generated, and these intermediates have potent antibacterial properties.3

**Social and sexual communication**

Increasing life expectancy has increased demand for hair colorants (especially to cover gray hair) in order to retain or regain the youthful characteristics associated with nongray pigmented hair. Moreover, hair has been identified as an important component of nonverbal communication, especially for female attractiveness.5

**Thermal insulation and thermal regulation**

Hair acts as insulation that protects the head and scalp from heat. Scalp hair can generate a wind current that can ventilate heat more efficiently than a bald scalp can.1 Lastly, the network of hair fibers increases the effectiveness of sweating, which helps with scalp cooling.5

**The regulation of hair pigmentation**

There is a difference in the regulation of pigmentation between the hair follicle and the dermis.1 Hair pigmentation and hair growth are affected by many factors. These factors are classified into two groups: intrinsic factors and extrinsic factors. Intrinsic factors include race, gender, body distribution, hair cycle-dependent changes, hormone, genetic defects, and age-associated changes. Extrinsic factors include climate, season, infection, toxins, and chemical exposure.

**Extrinsic factors**

**Ultraviolet B**

Unlike ultraviolet B (UVB)-sensitive epidermal melanocytes, melanogenic cells of the anagen hair bulb, which is located within subcutaneous fatty tissues, are not vulnerable to or influenced by UVB.1

**Intrinsic factors**

Although there have been many studies in rodent hair pigmentation, limited information is available regarding the pigmentation...
of human hair. Knowledge emerging from many rodent studies indicates that numerous mutations influence coat color in mice. The intrinsic factors that regulate hair pigmentation involve endocrine, paracrine, and autocrine hormones. Extensive research at the molecular level is also being conducted to identify the pathogenesis of hair graying. The following is a summary of currently known intrinsic factors which influence melanogenesis.

**Alpha-melanocyte-stimulating hormone**

Alpha-melanocyte-stimulating hormone (α-MSH) can stimulate melanogenesis by removing 6BH4 (Fig. 1), which is an inhibitor of tyrosinase activity. Intramuscular injection of α-MSH in guinea pigs has shown to increase the amount of black hair.6 In humans, injection of α-MSH or [Nle4, D-Phe7]-α-MSH, a potent synthetic analogue, can also increase melanogenesis, especially in sun-exposed areas. However, the hair follicle was not affected.4

**MC1 receptor**

MC1 receptor (MC1-R) is the cognate receptor of α-MSH, which plays a role as a positive regulator of melanogenesis. MC1-R is activated by the binding of proopiomelanocortin-derived ACTH, α-MSH, and β-MSH peptides. A transduction cascade then occurs, which triggers adenylate cyclase activity and results in an increase in production of cyclic adenosine monophosphate. The final effects are increased melanocyte proliferation, melanogenesis, and dendrite formation. Polymorphism of MC1-R gene is related to red hair and fair skin in humans. It is believed that mutation of the MC1-R gene causes white-blond, yellow-blond, and auburn hair colors.1,4,7,8

**Agouti signaling protein**

Agouti signaling protein acts as a negative regulator of melanogenesis, and it is a competitive inhibitor of α-MSH binding to the MC1-R. This results not only in a switch from eumelanin to pheomelanin but also in inhibition of the whole process of melanogenesis.1,8,10

**Pterin 6BH4**

Pterin 6BH4 is a cofactor of phenylalanine hydroxylase (PAH) (Fig. 1), which has functions in the conversion of L-phenylalanine to L-tyrosine. Pterin 6BH4 also directly regulates tyrosinase activity (Fig. 1), the rate-limiting melanogenesis enzyme, via noncompetitive allosteric inhibition. In addition, it was reported that the 6BH4/tyrosinase inhibitor complex can be removed by both UVB/tyrosinase inhibitor complex can be removed by both UVB-generated O2-/H2O2 and α-MSH.4

**c-Kit**

Tyrosine-kinase receptor c-Kit and its ligand, stem cell factor (mast cell growth factor, Steel factor), play essential roles in the maintenance of hair follicle melanogenesis and physiological aging in humans.11 c-Kit and its ligand are also required for melanoblast and melanocyte stem cell maintenance in mice.3,12 Mutations of c-Kit in humans were found to be associated with piebaldism.1

**Endothelin 3 and its receptor B**

Endothelin 3 and its receptor B (Ednrb) are essential for the development of neural crest-derived melanocytes. Only the migration of melanoblasts from the melanoblast staging area requires Ednrb. However, the postmigratory stages, including proliferation, differentiation, and survival, do not need Ednrb. In humans, the Ednrb homozygous mutation is found in Hirschsprung’s disease/Waardenburg syndrome.1

**Bmpr2**

Bmpr2 is a receptor of bone morphogenetic proteins (Bmps), and Acvr2a is a receptor of Bmps and activins. Bmpr2 and Acvr2a are both individually numerous, but the combination of both is essential for many follicular traits. Gray hair with an

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**Figure 1** Intrinsic factors that influence melanogenesis. PAH; phenylalanine hydroxylase, α-MSH; Alpha-melanocyte-stimulating hormone

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abnormal hair shaft and melanosome differentiation was found in mice with reduced Bmpr2/Acvr2a function in melanocytes.\textsuperscript{13}

**BCL-2**

BCL-2 is an anti-apoptotic oncogene that is involved in cell survival. This survival factor is expressed in follicular melanocytes, especially at the outer root sheath. It has been proposed that BCL-2 can regulate the antioxidant function, and this results in the inhibition of cell death caused by reactive oxygen species (ROS).\textsuperscript{1,14} Thus, melanocytes with low BCL-2 expression may be susceptible to apoptosis.

**Age-associated changes in the hair follicle melanin unit**

The mechanisms of skin aging that are also involved in its pigmentation need to be understood to fully understand canities. Chronological aging is related to a $10 \pm 20\%$ reduction in pigment-producing melanocytes for every decade after 30 years of age.\textsuperscript{15} This involves both exposed and unexposed epidermis. Dopa-positive melanocytes are lost in a wide area of the body at approximately in the fifth decade of life. That means that not only the epidermis is involved but also the hair follicles, nevi, and eyes.\textsuperscript{1}

The following two theories for age-associated changes have been proposed.

**Free radical theory of aging**

This is the most popular aging theory, and it can be easily tested in \textit{in vitro} settings. This theory holds that the mechanism of aging is an accumulation of mutations in DNA (nuclear and mitochondrial) that is caused by ROS. Free radicals subsequently induce not only oxidative stress but also antioxidant mechanisms. This theory can explain the aging mechanism for hearing, vision, and the physiologic or pathologic aging of neural cells (e.g., Alzheimer’s disease). Studies have shown that some syndromes (e.g., Down syndrome) have accelerated aging, similar to the model of neuronal cell pathology in Alzheimer’s disease. Down syndrome is associated with an increase in copper-zinc superoxide dismutase that is encoded by chromosome 21. The result is the promotion of $H_2O_2$ formation and the induction of oxidative damage.\textsuperscript{1}

**Mitochondria theory of aging**

This theory emerged in recognition of the fact that mitochondria, which have an energy-generating function, appear to be the primary target for oxidative damage. Owing that mitochondria produces ROS, it can lead to oxidative stress. Age-related mitochondrial DNA deletion also causes mitochondrial degeneration, which can compromise cell survival.\textsuperscript{1}

In conclusion, the basis of age-associated changes in the hair follicular unit includes both the accumulation of oxidative stress and the depletion of antioxidants (e.g., glutathione). The result is cell apoptosis, including the melanocytes involved in melanogenesis.

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**The pathogenesis of canities**

The term “gray hair” is a misnomer. The color of hair that appears to be gray is actually an admixture of the color of the depigmented hair and the color of the pigmented hair. The white color of hair that is perceived by the eyes is an optical effect that results from the reflection of light that masks the pale yellow of the keratin color.\textsuperscript{1} Canities can affect hair follicles in a variety of ways, including gradual loss of pigment over several hair cycles, gradual loss of pigment within a hair cycle, or fully depigmented growth. Every canities-related study has confirmed that pigment loss in gray hair is caused by a decrease in the level of active melanogenic melanocytes in the hair follicles. This results in a reduction in the total number of melanosomes that are generated into keratinocytes in the hair shaft. However, this pigment loss defect can also be caused by a defect in melanosomal transfer. Evidence has been reported that keratin can be absent of melanin, even if it is located near melanocytes that have a moderate number of melanosomes.\textsuperscript{1} Moreover, melanin debris has been identified in both the gray hair bulb and the surrounding dermis. Thus, the pathogenesis of canities can be either an insufficiency of melanin due to melanocyte degeneration or a defect in melanosomal transfer.

**Onset and progress of canities**

The age of onset of canities depends on individual heredity-related factors. Onset usually starts at the fourth decade of life. The average age of onset of gray hair is in the mid-30s among Caucasians, in the late-30s among Asians, and in the mid-40s among Africans. One study reported that 6%–23% of people have 50% of their hair gray by the age of 50.\textsuperscript{16} Gray hair can be easily noticed and is more readily apparent among people with dark hair, but total graying is found earlier among the fair-haired. Graying affects both genders equally.

Graying usually begins at the temples and then slowly progresses by spreading to the vertex and the remainder of the scalp. The beard and body hair are affected later. Sudden “overnight” graying that results from an acute episode of alopecia areata is called canities subita. However, this type of sudden loss of hair pigmentation resulting from the disease never happens with real canities.\textsuperscript{1}

**Characteristics of gray hair**

Gray hair is coarser, thicker, longer, and less manageable than pigmented hair.\textsuperscript{17–19} Gao \textit{et al.} reported that gray hair is more susceptible to be damaged by UV radiation than dark brown hair, so it requires more UV protection.\textsuperscript{20} Gray hair is also usually hard to stain with artificial hair colorants and hold the color weakly, whether temporary or permanent set. This may be due to changes in the structure of hair fibers. Aging hair may reprogram its structural keratinocyte production, which then increases medullary keratinocyte production rather than cortical keratinocyte production.
This results in enlarged hair fibers with a collapsed medulla, thereby forming a central cavity of gray or white hair. This hair trait may increase insulation to compensate for the sunlight absorption and heat-trapping effects of pigmented hair.1

Premature gray hair/canities

Premature hair graying (PHG) is defined as individuals who begin developing gray hair before the age of 20 among Caucasians, 25 among Asians, and 30 among Africans. Premature canities can appear spontaneously as an autosomal dominant inheritance without any underlying condition(s), or it can be associated with pathologic conditions, including pernicious anemia, hyper/hypothyroidism, osteopenia, and several rare syndromes, like progeria and pangeria.1 To evaluate premature canities, the Graying Severity Score21 has been proposed as a novel, numeric, objective, and reproducible method to assess the level of graying severity.

Several studies have reported data related to the risk factors for PHG. Most of the research has investigated the socio-clinical risk aspects of both intrinsic factors (e.g., family history and age of canities onset) and extrinsic factors. A selection of those studies is given below.

Maternal and paternal PHG22,23
Two cross-sectional studies found family history of PHG as a risk factor for PHG.

Alcohol consumption22
One study found alcohol consumption to be significantly associated with increased incidence of PHG.

Presence of chronic disease22
Subjects with PHG were significantly more likely to have chronic disease than those without PHG.

Educational status22
Educational status was found to be significantly higher in those with PHG than in those without PHG.

Hair loss22
Hair loss was found to be significantly more prevalent among those with PHG than in those that did not have PHG.

Perceived Stress Scale score22
One study in young Turkish adults found that the mean Perceived Stress Scale score was significantly higher in subjects with PHG than in those without PHG.

Smoking23,27
Smoking and the use of other tobacco products (e.g., gutka and straight chewing tobacco) were reported to be associated with PHG.27

Obesity23
Subjects with obese (BMI ≥ 30 kg/m²) or overweight (25 kg/m² ≤ BMI ≤ 30 kg/m²) status were represented in significantly greater proportion in the PHG group than in the non-PHG group.

Oxidative stress28
One previous study reported a rising serum level of malonaldehyde, which is a lipid peroxidation product that is generated by free radical injury in tissues, which suggests a higher level of oxidative stress in patients with premature canities. Moreover, decrease in the whole-blood reduced glutathione (rGSH) (which is used by GSH peroxidase, a selenium-containing enzyme that catalyzes a reduction in H₂O₂ and lipid hydroperoxidases) and a low level of ferric-reducing antioxidant potential are both suggestive of a low antioxidant condition in blood.28

Atopy29
A study conducted in India to investigate for demographic and clinical characteristics related to canities found atopy to be strongly associated with premature canities.

In addition to the risk factors described above, an antioxidant deficiency has been reported in gray hair.30,31 It is still being investigated and debated whether this deficiency can affect mature hair bulb melanocytes and their immature precursor cells in the bulge region. The answer to this question will help to clarify the cause of pigment reversal in the affected gray hair. Canities has also been reported in patients who have received certain drugs (e.g., chloroquine, mephenesin, phenylthiourea, triparanol, fluorobutyrophenone, dixyrazine, the epidermal growth factor receptor inhibitor imatinib, and interferon-alpha) and in individuals who have used certain chemicals (e.g., medicated oils) and certain topically applied agents (e.g., dithranol, chrysarobin, and resorcin).32

Disease-associated canities

Previous studies have attempted to identify association between canities and certain diseases, but these suspected associations remain inconclusive. The following is a list of some of the diseases that have been studied.

Osteopenia and osteoporosis
One study reported that risk of developing osteopenia in individuals with premature canities is four times higher than in individuals without canities.33 A subsequent study found that individuals whose hair turned gray before their 20s had a lower bone mineral density than those whose hair turned gray later.34 A few studies reported that hair graying before the age of 40 is a predictor of low bone mineral density and osteopenia.33,34 Canities were also found to have a significant association with familial osteoporosis.1

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Cardiovascular disease
The association between premature canities and early onset of cardiovascular disease has not been clearly explained. However, some studies have reported PHG as a risk factor for coronary artery disease (CAD). One study observed that young CAD patients who were heavy smokers developed gray hair; therefore, the authors suggested that there may be a higher risk of CAD among chronic smokers who prematurely develop gray hair compared to normal population. However, another study found no evidence supporting PHG as a risk factor for CAD.

HIV infection, cystic fibrosis, and Hodgkin’s lymphoma
Premature graying has been reported in patients with HIV infection, cystic fibrosis, and Hodgkin’s lymphoma.

Reversal of canities
There are some melanocytes that remain in ORS of gray hair. However, those melanocytes are negative for dopa and most other melanocyte-specific markers. Even though the process is not fully understood, melanocytes can repigment the epidermis (e.g., after wounding). However, this repigmentation process does not occur in the hair bulb. This may be due to a lack of some inductive microenvironment that is necessary for bulbar pigmentation. Acceptance of this hypothesis compels us to explore ways to induce these ORS melanocytes in order to reverse canities.

There have been reports of hair repigmentation in the following conditions and settings.

After radiation or inflammatory events
Scalp hair repigmentation has been reported after radiation therapy for cancer or after inflammatory events (e.g., erythrodermic eczema and erosive candidiasis of the scalp). This is probable from radiation/cytokine-induced activation of ORS melanocytes.

Drugs

P-aminobenzoic acid
Although the mechanism is unclear, large doses of p-aminobenzoic acid administration have been reported to induce transient hair darkening.

Latanoprost
Latanoprost is a prostaglandin F2α (PGF2α) eye drop. Gray hair repigmentation has been reported after prolonged use (~3 years). Repigmentation started from the proximal portion of the hair and then increased over the entire length of the hair. Prostaglandins are one of the most potent stimulators of melanocyte growth and melanogenesis.

Other drugs
Defibrotide, cyclosporine, corticosteroid, etretinate, L-thyroxine, verapamil, tamoxifen, levodopa, cisplatin, acitretin, triiodothyronine, and lenalidomide have been reported as being associated with incidental findings of hair darkening. However, it could not be confirmed whether the pigmentation continued after drug withdrawal, as most of the cases continued their treatment with the suspected drug(s).

Treatment of canities
Despite advancements in our collective knowledge about canities (even at the molecular level), the treatment of canities remains limited and inadequate. No permanent gray hair reversal treatment is approved. Nutritional supplements that contain vitamins and minerals, such as biotin, calcium pantothenate, zinc, copper, and selenium have also been prescribed, but the level of scientific evidence regarding their efficacy in the published literature is low.

The most common treatment is the use of hair colorants to conceal the gray hair. Various hair colors can be chosen according to individual decency. Many factors involve in the consideration such as age of onset and the psychosocial impact of having gray hair (especially relative to how career opportunities will be affected). In addition to concealing gray hair, hair dye may also protect against photodamage from the sun.

Depending on the extent of hair graying, other treatment options can be considered. Plugging out of gray hair may be reasonable if <10% of the hair is gray. Coloring only the gray hair may also be considered in the early stages of gray hair, in cases where it is confined to the temples in men and to the perimeter in women.

Prevention of canities
To date, only a few studies have investigated the prevention of canities. One study evaluated the use of APHG-1001, a compound found in an extract from Pueraria lobata, on gray hair. They found that APHG-1001 can prevent the formation of new gray hair, and it has no remarkable side effects. Additional research in novel prevention and treatment agents, techniques, and modalities are validated.

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