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Assessment of scalp hair survivin in patients with premature greying of hair

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Abstract
Healthy hair is a sign of overall health and vitality. Premature graying of hair (PGH) have a unfavourable impact on an individual's self-esteem, as it is frequently perceived as a sign of aging. Hair graying known as achromotrichia or canities, is a natural by-product of aging. On the other hand, the age at which it manifests itself differs among various ethnicities. Uncertainties persist regarding the precise etiopathogenesis of graying. Autosomal dominant primary disease, PGH, is a scenario that may manifest. Progeria and pangeria are types of premature aging disorders that can also result in graying.
The control of cell proliferation and the inhibition of apoptosis have been associated with apoptosis protein family inhibitor and survivin. Survivin protein is a crucial a constituent of chromosomal passenger complex, which is necessary for cell division. Several autoimmune diseases were found to have survivin overexpression, which has important role in survival of auto-reactive T- and B-cell clones.
Aim of this review was to evaluate scalp hair Survivin in patients with premature greying of hair.

Keywords: Survivin, scalp hair, premature greying of hair

Introduction
Hair follicles are distinguished by the same structural components, but their shape and size vary reliant to their site. Melanocytes, which are responsible for pigmentation, are interspersed with proliferating matrix cells in the hair bulb, which generate hair shaft. hair shaft's upgrowth is facilitated by differentiation and upward movement, and Intermediate proteins and filaments comprise its cortex. dermal papilla is situated at the follicle base, regulates matrix cells quantity and therefore hair size [1].

Hair anatomy
The abundance, distribution, width, and length of hair follicles can vary significantly conditional on its nature and site on body. There are 2 primary forms of hair: terminal hair and vellus hair. Hair bulbs are firmly rooted in subcutaneous tissue, and terminal hairs are typically longer and thicker, with diameters of hair shaft exceeding 0.06 mm. Conversely, vellus hairs are composed of filaments that have diameter < 0.03 mm and length only 1–2 mm. The bulbs of these hairs are situated in upper dermis and are typically more hypopigmented than basal hair color. Men are more likely to have terminal body hair, which is why presence of vellus hair is generally more obvious on females and infants [2].

Pigmentation of hair
The pigmentations of human hair, which vary from black to red, blonde and brown, are among the most distinctive features of an individual. Melanocytes are neural crest derivatives responsible for the production of the pigment melanin, which is responsible for the pigmentation of human hair. Human hair follicles contain two forms of melanin: eumelanin and pheomelanin. Hair color variation is primarily dependent on abundance and proportion of black-brown eumelanin and reddish-brown pheomelanin. The pH and cysteine levels of melanosomes have been suggested as factors that may influence the hair phenotype. Tyrosinase activity decreases as pH decreases, leading to an increase in blonde or reddish hair and pheomelanin. The auburn or red color of hair is the result of a mutation in the

melanocortin-1 receptor gene. This mutation is seen usually in individuals of Northern Europe with less sun exposure [3]. Numerous distinctions exist between hair or skin pigmentation. In hair bulb, each melanocyte is related to 5 keratinocytes, thereby forming a "hair follicle-melanin unit." Conversely, each melanocyte in the epidermis is linked to 36 keratinocytes, which collectively form an "epidermal-melanin unit." Melanogenesis in the hair is closely related to hair cycle stages, in contrast to continuous production of pigment in epidermis. Hair is actively pigmented during the anagen phase; however, it is "off" nonexistent during telogen and during catagen phase [4].

Pigmentary units are black, pear-shaped structures that are situated at dermal papilla apex in pigmented hair. In proximal hair bulb, faintly pigmented oligodendritic melanocytes become visible, and unit of pigmentation becomes hazy. melanocytes are fewer and more rounded in gray hair. During anagen, melanocytes amount in hair follicles reduces significantly, resulting in pigment loss, which is caused by autophagolysosomal degeneration. This is considered to be key to the development of graying. Graying is exacerbated by melanin incontinence, which is a consequence of impaired melanosomal convert to cortical keratinocytes or melanocyte degeneration. A rise in dendritic cells within Hair Follicle (HF) is an indicator of degenerative changes. The hair bulb eventually does not contain any melanogenic melanocytes [5, 6].

Pigmented hair undergoes terminal differentiation prior to nonpigmented hair. The average diameter, hair growth rate, and Each nonpigmented hair strand has a medulla diameter that exceeds its pigmented counterpart [4]

The melanocytes and progenitor cells of HF are influenced by environmental and genetic factors. This aging process has been linked to a decrease in cell count, telomere shortening, and the involvement of transcription factor. Therefore, these molecular modifications result in structural modification of hair fibers, an extension of the telogen phase of the hair cycle, and a reduction in melanin production [7].

At present, the molecular level is being employed to investigate a diverse array of genes and signaling pathways which affect hair pigmentation. Bone morphogenic protein receptors (Bmpr2) and activins (acvr2a), specifically Bmpr2 and Acvr2a, are recognized to influence hair pigmentation. reduced activity of Bmpr2 and Acvr2 can cause early graying in experimental mice. The Notch signaling pathway influences various biological processes. Notch 1 and Notch 2 signaling pathways were reported to have a role in maintenance of hair pigmentation. A cytokine, stem cell factor (SCF) is involved in a variety of physiological processes, including hematopoiesis. At present, during the anagen phase it has been demonstrated that SCF and its receptor (kit) are involved in melanogenesis [4].

Premature Hair Greying (PHG)

natural hair pigment loss prior to gray hair typical onset is devoted to as early graying, or PHG. Numerous factors influence this phenomenon, such as extrinsic and intrinsic medical, genetic predispositions conditions, and contributors. For a significant number of individuals, premature graying has significant psychosocial implications. Age is frequently indicated by the pigment of one's hair, which has the capacity to impact social interactions and self-esteem. Despite the prevalence of premature graying, there is a significant deficiency in comprehensive research talks its underlying pathogenic mechanisms, related medical comorbidities, and available treatment regimens. In order to improve understanding of PHG and its broader implications, our review aims to investigate the multifaceted components that influence PHG [6].

Epidemiology

It is susceptible to racial variation since canities onset age is more contingent upon individual genotype. The average age of onset for Caucasians is 34 ± 9.6 years. while Negroes experience an average age of 43.9 ± 10.3 years. Graying of hair is noticed in Japanese men between the ages of 30 and 34, and in Japanese women between the ages of 35 and 39. Asians typically begin to gray in their late 30s, while Africans, at the latest, do so in their mid-40s. Caucasians, on the other hand, typically gray in their mid-30s. Before the age of 40-50, it is believed that graying of hair is uncommon in Bantus. Furthermore, early in the 2nd decade or as late as 9th decade, the onset may occur. By the age of 50, 6-23% of individuals have 50% gray hair, according to a recent study. Individuals with dark hair have a more pronounced and noticeable graying process, while fair-haired individuals appear completely gray at an earlier stage. Men and women are equally afflicted [8].

Etiopathogenesis

Normal hair pigmentation

Melanogenesis in melanocytes and the distribution of pigment-containing melanosomes to the connected keratinocytes are the causes of hair color in humans. The synthesis of eumelanin, pheomelanin, and a brown-black pigment, a red-yellow pigment, occurs in a varying proportion during this process. Hair color variety in various ethnicities is contingent upon quantity and proportion of pheomelanin and eumelanin formed. This diversity ranges from black to blonde or red [9].

5 keratinocytes are related to a single melanocyte in the hair bulb. whereas in basal stratum of hair bulb matrix, a single melanocyte is connected to one keratinocyte. This component of HF is melanin. On the other hand, the epidermis displays a 1:36 ratio of keratinocytes to melanocytes. Melanocytes are differentiated from neural crest and migrate to hair follicle. Depending on the compartment in which they are located, they undergo a conversion into either DOPA oxidase-positive cells that express tyrosinase or DOPA oxidase-negative cells. Tyrosinase is expressed by melanocytes in the bulb of anagen hair, and it is subsequently converted to melanin. However, they are not melanized upon reaching outer root membrane of hair follicle. Melanogenic melanocytes are replaced by a melanogenic or non-melanized melanocytes when they are depleted, which function as stem cells [10].

Melanogenesis related to HF is straight correlated with hair growth cycle. During early anagen phase, melanin synthesis commences, reaches its apex, and subsequently ceases as it enters the catagen phase. At telogen phase, there is no synthesis of melanin. As HF transitions from anagen to telogen phase, gp75, three essential enzymes—tyrosinase, and dopachrome tautomerase are employed in the process of melanogenesis. These enzymes also deteriorate. In the anagen phase of the subsequent hair cycle, melanocytes initiate melanogenesis process once more [11].

hair melanin synthesis is also significantly influenced by

neuroendocrine factors. Melanogenesis is regulated and modulated by thyroid hormones, ACTH, and alpha melanocyte-stimulating hormone. Signalling pathways and various genes were founded to impact hair pigmentation at the molecular level. Bmpr2, acvr2a, notch signalling pathway, and SCF (and its receptor kit) receptors was attributed to various functions in hair pigmentation [6].

Pathogenesis of gray hair

The depletion of the regenerative capacity of hair pigment cells is believed to be the cause of physiological or senile canities. After the age of 40–45 years, the regenerative capacity of a hair bulb is lost, resulting in hair graying, after it undergoes an average of 7 ± 15 cycles of melanocyte replenishment from the ORS reservoir. Histologically, At the apex of dermal papilla in pigmented hair, HF pigmentary unit is a pear-shaped structure. conversely, gray hair exhibits a hazy appearance due to reduced oligodendritic melanocytes, which also exhibit a decrease DOPA reaction and a progressive reduction in melanogenic melanocytes [6, 12].

Disrupted transfer of melanosomes from melanocytes and/or early loss of melanogenic melanocytes, which may be caused by a variety of factors, are the most probable causes of PHG. Our hypothesis is that the most critical of these factors is oxidative stress, which is a result of the generation of free radicals. Furthermore, oxidative stress decreases premature apoptosis melanocytes in hair bulb, in addition to promoting differentiation of amelanogenic melanocytes to melanogenic ones, regenerative capacity loss results [11].

Free radical generation may be precipitated by either exogenous or endogenous stress. There are two primary sources of endogenous free radicals: free radicals are released because of increased metabolic activity during the anagen phase and during melanogenesis. In addition to this, free radical theory of graying is influenced by exogenous stress from psychological stress, environmental injury, and smoking [11].

Additionally, the oxidative stress appears to be exacerbated by antioxidant mechanisms dysregulation in hair follicles. The ferric reducing capacity of non-pigmented hair follicles is reduced, and catalase activity is suppressed. association between coronary heart diseases and PHG may be attributed to high oxidative stress present in HF and serum of patients with PHG [6].

Presentation of graying

An optical illusion is responsible for the whiteness of canines. Due to incident light refraction or reflection, faint yellow color of keratin appears white. Melanosomes are sparsely distributed in gray hair, which has a tinge of color. Conversely, Melanosomes and pigmentation are wholly absent in white hair. White hair is exclusively present in the cranium. Hair that is gray is more difficult to manage, harsher, and coarser than hair that is darker. The thickness and growth rate of nonpigmented hair are significantly increase than those of dark hair. The rate of hair growth in graybeards can be up to 4 times greater than that of pigmented hair. Additionally, gray hair is more susceptible to UV radiation damage and is more susceptible to deterioration. As a result of structural changes in the hair fiber, gray hair requires more extensive photoprotection and is probable to retain artificial color. Additionally, laser hair removal of gray and white facial hair is difficult due to melanin chromophore absence [4].

By the age of 50, 50% of population will have gray hair, according to thumb rule. Nevertheless, more recent research revealed that the percentage of the population that was impacted was significantly lower. Males' temples and sideburns are the first areas to begin graying. It progresses to remainder and vertex of the cranium, ultimately affecting occiput. Graying is initially observed in women at the boundaries of the cranium. Graying progression is influenced by a variety of factors, with genetics being the most significant. Additionally, the rate of graying may differ in various regions of the cranium. Interesting clinical discoveries were disclosed in a study conducted on the Korean populace. Men were more significantly affected than women in the temporal and occipital regions. Additionally, the frontal region of women began to gray, in contrast to the temporal region of males. For individuals who began to gray before the age of 40, the temporal and parietal regions were more significantly affected. More graying was observed in the frontal area among individuals who observed the advent of graying after the age of 40. Interestingly, the rapid progression of graying was not correlated with its early onset. In the fifth decade, graying progressed rapidly, irrespective of the chronological age of onset [4].

Evaluation of premature graying

The absence of standardization and objective instruments for hair graying presents evaluation a challenge in the evaluation of PHG. The graying severity score is one of the numerous grading scales were planned. This approach involves visual identification of regions with the highest degree of graying in each zone, the cropping of hairs in a 1 cm2 section of each region, and numerical recording of the number of colored versus gray hairs. The scalp is alienated to 5 zones. The overall graying score is determined by a cumulative evaluation of the five regions, which is contingent upon gray hair percentage in each zone [13].

Hair whitening score (HWS) is an additional proposed method of PHG grading. It has been implemented in 2 studies and entails visual examination and the classification of greying into 5 categories based on white hair percentage (HWS 5: 100%; HWS 4: 75%–100%; HWS 3: 50%–75%; HWS 2: 25%–50%; HWS 1: <25%). In order to conduct a more thorough evaluation of the severity of graying and PHG, it is imperative to continue the development of objective assessment instruments [13].

Differential diagnosis

Other hypomelanotic hair disorders, some of which are identifiable by their localization, must be distinguished from premature gray hair. White hair may result from albinism. Neurocutaneous disorders, including Chediak–Higashi, Elejalde syndromes, and, Griscelli can result in white hair in minors. Other conditions that can result in gray hair in infancy include Angelman, Prader–Willi, and Cross syndromes. Homocystinuria, histidinemia, phenylketonuria, and oasthouse disease are metabolic syndromes that can result in pale hair. Poliosis is a condition characterized by localized white hair that because vitiligo. In addition to tuberous sclerosis, polio is too observed in Woolf syndrome, Piebaldism, and Waardenburg syndrome. Canities subita is an uncommon disorder in patient experiences hair graying overnight. Vitiligo, alopecia areata, and telogen effluvium,

as well as psychogenic causes, have been linked to Canies subita [4, 14].

Survivin in hair graying

The Inhibitor of Apoptosis (IAP) protein family includes Survivin (SVN), which is a member inhibits apoptosis and promotes cellular proliferation. SVN Overexpression is linked to hyperplasia, malignancies, and autoimmune disease and it can be employed as a biomarker in these conditions.

IAP protein family is known to contain the smallest member, SVN. These proteins are essential for cell mitosis regulation and apoptosis inhibition. The SVN gene, which is situated on human chromosome 17, was cloned by Ambrosini in 1997 [15].

BIRC5, the wild-type human SVN gene, is consist of 4 exons and 3 introns and spans 147 kb. A 16.5-kDa protein containing 142 amino acids is known as human SVN. Two functional domains are present in SVN: A Baculoviral IAP Repeat (BIR) at the N-terminus (100 aa) and an α-helix at the C-terminus (42 aa). In mitosis regulation, both the BIR and α-helical regions are involved. Conversely, the BIR is the sole component of the apoptosis regulation region. SVN is localized in the extracellular matrix, the outer surface of the cell membrane, exosomes, mitochondria, cytoplasm, and nucleus. SVN's various functions are influenced by its subcellular localization, reversible dimerization, and extensive posttranslational modification, which includes phosphorylation ubiquitination and acetylation [16].

Structure, domains and key partners

Survivin is a small protein with multifunctional domains, weighing 16.5 kDa and containing 142 Amino Acids (aa) (please refer to the poster). This identifies survivin as an IAP. A Zn2+ finger that is generated by C84, C60, C57, and H77 is responsible for the integrity of the globular baculovirus IAP repeat BIR domain (aa 20–90) that comprises the N-terminal two-thirds of survivin. In the C-terminal third, there is an extended α-helix (98–142). The central linker region (aa 90–102) of survivin crystallizes as a homodimer, with the assistance of N-terminal residues L6 and W10. The two monomers interact through this region [17].

The C-terminus of survivin forms a triple helical bundle with inner centromere protein and N-termini of borealin, and it also interacts with its mitotic companion borealin using the same interface. These proteins, in conjunction with aurora-B kinase, form a critical mitotic complex, CPC. Survivin's stability and its involvement in apoptosis subcellular localization, inhibition, and pro-oncogenic signaling, and its functions, are also influenced by its numerous non-mitotic partners [18].

There are numerous post-translational modifications that survivin undergoes, like phosphorylation by polo-like kinase (Plk1) and Protein Kinase A (PKA) as well as casein kinase II (CKII), aurora-B kinase and cyclin-dependent kinase 1 (Cdk1). It is also acetylated and ubiquitinated [19].

Survivin expression in the hair follicle

PKA and Plk1 phosphorylate survivin, among other post-translational modifications, including Cdk1, CKII, and aurora-B kinase. Also, it undergoes acetylation and ubiquitination. During anagen, which lasts several years on the scalp, there is active proliferation of matrix keratinocytes and melanocytes, leading to hair shaft production and pigmentation. In catagen, the follicle undergoes controlled apoptosis, regresses, and melanin production ceases. Telogen is a resting phase where the follicle remains inactive for a few months, followed by exogen, where the old hair is shed. This cycle is regulated by complex signaling pathways (e.g., Wnt, TGF-β, Shh) and anti-apoptotic proteins like survivin, which supports cell survival during anagen. Survivin has been shown to be most actively expressed during the anagen phase, where there is high mitotic activity and metabolic demand [20, 21].

Key sites of survivin expression within the follicle include [20]

- Hair matrix keratinocytes, which are essential for shaft formation
- Outer root sheath cells, especially in bulge area
- HF melanocytes, which reside near the dermal papilla and are responsible for melanin synthesis

So, by modulating apoptosis and supporting cell proliferation, survivin ensures the survival of critical cell populations required for both hair shaft production and pigmentation.

Survivin and hair pigmentation mechanisms

Hair color is determined by the type and quantity of melanin produced by melanocytes in hair follicles. One of principal pigment responsible for hair color is melanin, which is further divided into two forms that are crucial to hair color: pheomelanin and eumelanin. Black eumelanin and brown eumelanin and are the 2 subtypes of eumelanin. The dark pigments of hair, eyes, and skin are attributed to eumelanin. Individuals with black or brown hair possess varying quantities of brown and black eumelanin. Conversely, pheomelanin is accountable for yellow and red tints. This type of melanin is responsible for nipples and lips pigmentation, as well as the development of hair hues like blonde and red [13].

Melanin production is regulated by a variety of genetic and biochemical pathways in the melanocytes of hair follicle, which is wher process of hair pigmentation commences. 3, 4 melanogenesis pathway is a critical regulatory pathway, which includes enzyme tyrosinase. Initial phase in the synthesis of melanin is conversion of tyrosine to dopaquinone, which is catalyzed by tyrosinase.5 From there, deposition of pheomelanin and eumelanin in hair cortex, which provides color to growing hair shaft, is result of synthesis of these pigments through distinct downstream pathways. Both melanocytes and their stem cells are vulnerable to oxidative damage and intrinsic aging [13].

The health of mitochondria is maintained, and any damaged components are eliminated through the continuous fusion and fission of these highly dynamic organelles, such as mitochondrial (mt)DNA-harbouring Reactive Oxygen Species (ROS)-induced lesions, survivin is believed to protect melanocytes from apoptosis induced by Reactive Oxygen Species (ROS). In addition to metabolism, there is mounting evidence that survivin regulates mitochondrial dynamics; however, the precise mechanism by which this is accomplished remains unclear. Play a crucial role in the coordination of melanocyte and keratinocyte interaction during the anagen phase, which is essential for synchronized melanin transfer, and contribute to the self-renewal and maintenance of melanocyte stem cells [17, 22, 23].

The downregulation or loss of survivin in this

microenvironment could result in Melanocyte depletion, premature differentiation or apoptosis of melanocyte stem cells, and impaired pigmentation, leading to early hair greying. This suggests a direct link between survivin expression and hair pigmentation, where decreased survivin levels may act as a trigger for premature greying [24].

The role of melanocyte stem cells in greying

The primary cause of human hair greying is not injury to bulge MSCs, as has been a frequently repeated misconception since the groundbreaking discovery of bulge MSCs and their relationship to hair greying. The greying of human scalp HFs is initiated by the highly differentiated melanocytes of the HFPU during a single anagen phase, as previously reported. The view discusses the scalp HFPU must be continuously replenished from the bulge MSC reservoir to sustain a single anagen VI phase in human HFs is not supported by any evidence. consequently, it seems that the latter is self-maintained [11].

Nevertheless, Conclusion: The simultaneous, independent accumulation of (eventually irreversible) MSC damage in bulge stem cell niche over time is not precluded by fact that greying is continuously consequence of significant HFPU dysfunction in the anagen hair matrix, which is situated far from the bulge and independent of MSC activities. In addition, the incapacity to produce melanin is a direct consequence of the depletion of an HF's melanocyte stem/progenitor pools. However, this occurs only after the HFPU has ceased to function during catagen. Consequently, comprehensive coverage is necessary due to the irreparable injury to MSCs that results in their loss during human HF ageing, which is a significant factor in the long-term irreversible greying of human hair [11].

The influence of oxidative stress on the process of greying: Within tyrosine hydroxylation, melanocytes, and DOPA-to-melanin oxidation in the melanogenesis pathway led to high levels of ROS release, which are overseen by an effective local antioxidant system. Catalase, methionine sulfoxide reductase A and B (MSRA/MSRB), nuclear factor erythroid 2-related factor 2, Bcl-2, intrafollicular melatonin production and tyrosinase-related protein-2are examples of this system. Even though its antioxidant activity is restricted to the melanosome, eumelanin also effectively scavenges ROS. Therefore, it has been suggested that melanocyte injury during aging is caused by impaired over-accumulation and antioxidant systems of ROS. External stimuli, such as smoking, oxidizing agents, inflammation, and Ultraviolet (UV), as well subsidise to redox balance loss [25, 26].

Thus, the role of Survivin has been largely overlooked in PHG until recently. Given its anti-apoptotic and cell cycle regulatory functions, Survivin may be a critical survival factor for follicular melanocytes. A decrease in Survivin expression could Lower the threshold for oxidative damage, accelerate melanocyte death or stem cell depletion, and result in impaired hair pigmentation. This raises hypothesis reduced Survivin expression in the hair follicles of PHG patients may play a causative or contributory role in the premature loss of hair pigmentation.

Conclusion

The current study concluded that Survivin could play an important role as a predictor in discrimination between cases with gray hair and healthy controls with at cutoff value >217.11 with 85% sensitivity, with 65% specificity. Moreover, Survivin had in premature greying of hair identification among cases with premature greying of hair either appeared or not at cutoff >250.67 and 91.67% sensitivity, and 75% specificity.

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