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Review

Interferon Regulatory Factors 4 (IRF4) Gene and Hair Graying

Burçin Aktaş[1], Oytun Erbaş[1,2]

ABSTRACT

Hair graying is known as a natural part of the aging process. This aging process occurs with the graying of half of the hair at the age of 50 on average. There is another process that happens outside this natural process. The graying process that starts under the age of 20 on average is called Premature hair graying (PHG). There are many genetic and environmental factors that affect the graying process. In this review prepared, IRF4 (Interferon regulatory factor 4) gene, which is one of these factors and has many functions in the body, is focused on. In addition, other factors were also mentioned, and many studies carried out for hair repigmentation, which has the characteristics of treatment, were examined, and the obtained findings were shared.

Keywords: Hair graying, interferon regulatory factor 4, repigmentation.

HUMAN PIGMENTATION

Humans are a type of primate that has been covered in many colors as a result of various evolutionary forces throughout history. This type has come up to date with changes in various hair and skin colors.

Pigmentation varies considerably among human populations depending on the amount, the type, and the distribution of melanin.[1] Hair, eye, and skin pigmentation are the most visible examples of human phenotypic variations, with a wide variety in a range subject to significant geographic stratification.[2] While European populations are known to have a wider range of hair and eye color, most other human populations have brown eyes and black hair.

Undoubtedly, the substance that plays the main role in human pigmentation is melanin. Melanin is the main pigment for skin, hair, and eyes, and other chromophores. Melanin consists of a mixture of biopolymers found in the basal layer of the epidermis, the hair bulb, and the iris and is produced by melanocytes, where it is used as the amino acid tyrosine as the major substrate.[1] Pigmentation in human tissue is associated with the number, type and cellular distribution of melanosomes (organelles containing melanin).[2] Depending on the density, chemical and physical properties of melanin pigments, the color of the skin and hair in humans can be determined, while in other mammals, features such as fur color can be determined.[3]

Studies on the molecular genetics of human pigmentation, which have been going on for years, have over time eliminated general questions and reached deep points such as which genes are responsible for this mechanism. Several of the major loci and polymorphisms of genes that cause variations in skin, hair and eye color have been emphasized.[4] Very few genes have been identified in previous studies on pigmentation.

INTERFERON REGULATORY FACTORS 4 (IRF4) GENE

Discovered about 70 years ago, interferon has brought questions such as how it works with itself and how and why they are induced. Interferon

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
[2]Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey

Correspondence: Burçin Aktaş. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.

E-mail: brcnaks@gmail.com

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regulatory factors are the main role in the mechanism of interferon induction.[5]

The IRF is a transcription mediator that plays important roles in antiviral defense, immune response, cell growth regulation and apoptosis. Many varieties of IRF found N-terminal 115 amino acids also carry important homologies. These homologies contain the DNA-binding domain and are characterized by five tryptophan repeats.[5]

IRF4 (6p25p23) encodes the interferon regulatory factor 4, and it is mostly expressed primarily in lymphocytes, macrophages, B cells and DC cells.[6] This protein, which has a weak DNA binding affinity, can strengthen its binding with the help of other transcription factors. It binds to the IgG enhancer by increasing the binding affinity through the heterodimer structure formed with the PU.1 transcription factor and activating expression of the immunoglobulin (Ig) light-chain in B cells.[6-8]

According to the study conducted on IRF4 null mice, it was determined that these mice had deficiency in mature T and B cells. This result indicates that IFR4 plays an important role in the maturation process of T and B cells and the development of CD4 + DC deficient in these mice.[9,10]

In line with all this data, an error in IRF4 expression or its structure will lead to immune deficiency and an inability to produce antibodies.

An intergenic SNP (single-nucleotide polymorphism) close to IRF4 was found associated with human pigmentation and further studies showed that intronic SNP rs12203592 of IRF4 being strongly associated with hair, eye, skin colors.[11] Subsequent studies helped to better understand the role of IRF4 in these regions.

HAIR GRAYING

Although graying of hair is a part of the natural aging process, worldwide 6–23% of people have 50% gray hair by 50 years of age. The gray process of hair begins in the mid-30s for Caucasians, the late-30s for Asians, and the mid-40s for Africans. Hair graying differs between men and women, with different starting points. Hair whitening in men typically begins at the temples and sideburns, then spreads to the vertex and lastly the occiput. This process, which takes place differently in women than men, develops at the boundaries of the scalp and moves towards the vertex.[12] While the production of melanin, the pigment of the hair shaft, is continuous in the skin, the pigment production in the melanocytes surrounding the hair follicles occurs at intervals determined according to a certain order.[13]

Hair color is caused by the transport of the melanin pigment to hair fiber keratinocytes from hair follicle melanocytes.[14] In the early stages of development, some melanocytes differentiate from melanoblasts that migrate into neural crests into hair follicles, while others do not perform this transformation and act as stem cells in the periodic regeneration of melanocytes.[15] Melanogenesis occurs only in the anagen phase (hair shaft production which occurs 3-5 years period), which is one of the four stages of hair growth.[16] Human hair follicles contain two different types of melanin. One of them is the black-brown pigment eumelanins for black and brown hair, while there are brown hair and the yellow or red pheomelanin in auburn and blonde hair.[17]

Hair color on the scalp tends to darken with advancing age. Because the scalp follicular melanin unit is only a few cycles old, the hair bulb melanocytes reach their highest synthetic capacity in youth. An average scalp hair follicle has a reservoir of 7±15 cycles, and this reservoir corresponds to a period of approximately 45 years. In this process that occurs due to aging, exhaustion of regenerative capacity of hair pigmentation begins. Under normal conditions, the process of graying in the hair around this age will thus begin.[18]

Various factors can play a role in the whitening process. One of the main problems that are often common in these processes is oxidative stress. In the event that occurs in the hair follicle stem cells niche, oxidative stress is accelerated by depletion of the B-cell lymphoma 2 gene (BCL-2). This increased oxidative stress leads to selective apoptosis and diminution of melanocyte stem cells, reducing the formation of new anagen follicles. Normally, melanotic bulbar melanocytes express a high proportion of BCL-2, which allows them to be protected from attacks of reactive oxygen species (ROS). However, with the effect of aging, the expression of BCL-2 and similar proteins decreases and the cell cannot defend itself. This kills the cells, and they cannot contribute to further pigmentation.[19]

In fact, the white of the hair shaft is an optical illusion. Keratin with pale yellow appears white to the eye due to reflection or refraction of

light.[17] Gray hair has a color with sparsely distributed melanosomes, while white hair is completely devoid of melanosomes and color. Interestingly, gray hair is more sensitive to weather conditions and more sensitive to UV rays.[20] In this case, gray hair requires more protection and care.

PREMATURE HAIR GRAYING

In addition to hair graying due to aging, earlier hair graying can be seen as a result of some factors. Hair graying begins before the age of 20 years in Caucasians, before the age of 25 years in Asians, and before the age of 30 years in Africans is called Premature hair graying (PHG).[17,21] To date, etiopathogenesis of graying is not clearly understood. PHG disease can occur autosomal dominantly. Graying can also occur as a result of premature aging disorders such as progeria and pangeria. It has also been reported to be associated with autoimmune diseases.[22,23] The most researched topic on this subject is undoubtedly the role of reactive oxygen species (ROS) on graying. Therefore, an active melanogenesis during the anagen phase in the hair follicle, hydroxylation of tyrosine and oxidation of dihydroxyphenylalanine to melanin causing enormous accumulative oxidative stress. As a result of an error on the antioxidant, melanocytes can be damaged and cause a decrease in pigmentation. As a result of the studies conducted by Wood et al.[24] the theory that prooxidants, a chemical that causes oxidative stress by producing reactive oxygen species or inhibiting antioxidant systems, play a role in graying hair. In addition, oxidative stress can be caused by UV rays, pollution or emotional factors.

As a result of experiments conducted on young adults who are genetically predisposed to the disease in Turkey in 2016; This disease has been found to be closely related to oxidative stress such as emotional stress, alcohol consumption, and chronic diseases.[25] In this case, PHG is likely to be encountered in conditions and diseases where hair follicles are less resistant to oxidative stress (such as Progeroid syndromes).

A study conducted by Andrew et al.[26] revealed an important link between Alzheimer's disease (AD) and premature graying of hair. According to this research, it has been revealed that the stress level increases as a side effect of the increased SNS (sympathetic nervous system) signals in Alzheimer's patients and thus causes the hair to turn gray. In their experiments on animals, norepinephrine (NE) SNS signals were blocked, and thus the animals preserves hair coloration.

In addition to these reasons, factors such as B12 deficiency, some chemotherapeutic drugs, cholesterol, imbalanced and malnutrition or smoking are thought to cause PHG.[27-30]

Various studies have been carried out in order to determine the mechanism of graying of hair and its main causes. One of these is the study directed by Han J. et al.[31] in 2008 to determine the hair color gene. As a result of this study, which was conducted with 10,000 Americans and Australians, it was determined that IRF4 and SLC24A4 were highly associated with hair color.

In another study conducted in 2016, the IRF4 gene, which plays an active role in the graying of the hair, was determined. In this study conducted by Adhikari et al.[15] the IRF4 gene, which was previously associated with blonde or lighter-colored hair, was first associated with graying of hair with this study. They found this gene by studying the scalps and facial hair of 6,630 volunteers in Brazil, Colombia, Chile, Mexico and Peru. In this study, the researchers took pictures of the volunteers and asked about their natural hair color. These researchers then took samples from volunteers with a mixture of European, Native American and African ancestry and performed genetic analyses called genome-wide association scans (GWAS) that look for common variants, and matched them with appearance.

In this study, where they obtained 10 new variants, only IRF4 was associated with gray hair color. Others were associated with information such as unibrow, balding, eyebrow thickness and hair structure. Adhikari et al.[15] state in this study that the IRF4 gene constitutes about 30% of gray hair and the rest is caused by environmental factors.

TREATMENTS FOR HAIR GRAYING

The natural whitening of the hair occurs due to complex regulation of melanogenesis. Until today, various studies have been done for hair repigmentation, but no definitive solution has been revealed. So far, 27 studies have been discussing medication-induced gray hair repigmentation, including 6 articles on gray hair repigmentation as a primary objective, notably with psoralen treatment or vitamin supplementation, and 21 reports on medication-induced gray hair repigmentation. The drugs used in drug therapy have a working principle

that focuses on the use of anti-inflammatory medications (thalidomide, lenalidomide, adalimumab, acitretin, etretinate, prednisone, cyclosporin, cisplatinum, interferon-α, and psoralen), stimulators of melanogenesis (erlotinib, imatinib, latanoprost, tamoxifen, and levodopa) and various vitamin medications (calcium pantothenate and para-amino benzoic acid [PABA]).[12,32]

In a study conducted on PHG cases, it was observed that it induces gray hair repigmentation directly using Psoralen plus UVA light (PUVA). Explaining how this idea was born, the author stated that it was the result of observing the effect of PUVA used for psoriasis patients. Pavithran,[33] reported that after 13 months of treatment, 46% of PHG patients gained hair repigmentation during the 8-month follow-up period without any recurrence.

Five drugs documented to induce melanogenesis have been proven in various studies. Imatinib, a chemotherapy drug and used in patients with chronic myeloid leukemia, during the treatment process 7% of 133 patients were reported to experience repigmentation of gray hair 2-14 months.[34] Another tyrosine kinase inhibitor, erlotinib, has been reported to cause hair repigmentation in 2 different patients with metastatic lung adenocarcinoma.[35,36]

In another case, scalp hair repigmentation was observed 2.5 years after starting tamoxifen therapy for breast cancer.[37]

Conclusion

Gray hair is an indicator of a natural aging process. Although all the factors affecting this process are not known precisely, many studies have shed light on the unknown for many years. As a result of these studies, the effect of genetic factors was investigated and the IRF4 gene, whose effect on graying was 30%, was determined. It is expected that the function of this gene, which has quite a variety of functions, will be better understood in future studies. In addition, there are other factors that affect the formation of gray hair-such as environmental factors. The repigmentation process in the natural graying of the hair has not been enlightened yet, and various studies have been carried out for PHG, which occurs outside the natural graying process. Various drug treatments have been applied as low-quality evidence from these studies. Although positive results have been obtained as a result of these studies, more studies are needed. It is thought that these studies will shed light on future studies. In addition, these studies will speed up the studies focused on the graying process and the treatment of this process.

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