Expression of Melanocortin-1 Receptor and Serum Melanin in Canities at Young Male students

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Abstract

BACKGROUND: Molecular genetics suggest that hair pigmentation is related to the melanocortin-1 receptor gene. It is a G protein-coupled receptor, which is activated by a number of peptides to stimulate melanogenesis. Melanocortin-1 receptor gene mutation tends to produce functional variability in premature hair graying (PHG) or canities.

AIM: Therefore, the objective of this study was to determine melanocortin-1 receptor expression and asses serum melanin in college students canities at Universitas Sumatera Utara.

METHODS: This study was a cross-sectional design. We recruited 80 subjects equally divided into normal (control) and premature hair graying groups. The sample included males, aged 25 years who had gray hair and had no history of pigmentary disorders of the skin. Expression of melanocortin-1 receptor was detected with conventional PCR and serum melanin was measured with Elisa using Elisa kit melanin for human.

RESULTS: The results showed that the Mean ± SD graying age was 20.28 ± 1.99 years with an age range of 19–24 years and the average age in the control group was 21.25 ± 2.02 years with an age range of 18–24 years. Melanocortin-1 receptor gene expression was shown in the control and PHG groups. Serum melanin levels were decreased significantly (p = 0.0001) in the gray-haired group was 9.27 ± 1.62 µg/dl and the control group was 10.72 ± 1.78 µg/dl.

CONCLUSION: Melanocortin-1 receptor gene plays a role in hair graying at young age and there serum melanin levels were low significantly.

Introduction

Healthy hair is a sign of general well-being and youth. Hair is a great esthetic tool and a means of nonverbal communication. Hair color and style describe a person's physical appearance and can change his body image [1]. Canities (hair graying) has a negative impact on a person, reducing one's self-confidence, because gray hair is a sign of aging [1]. Premature graying of hair (PHG) occurs prematurely, before the age of 20 in Caucasians, 25 in Asians, and 30 in Africans [2].

Gray hair is physiologically associated with a progressive loss of pigment-producing cells. The genetic factor plays a role in hair color variations. Melanocortin-1 receptor (MC1R) interacted with other peptides to modify the penetration of this variant and expressed on the surface of skin and hair melanocytes. Red hair is associated with coding variations in the MC1R45 gene [3]. A previous study showed that loss of MC1R signaling resulted in the inability to produce eumelanin that causes yellow or red pigment [4]. Melanocortin-1 receptor is a G-protein-coupled receptor, binds to other peptides, pro-opiomelanocortin (POMC), α-melanocyte stimulating hormone (α-MSH), and adrenocorticotropic hormone (ACTH), induce a melanogenic cascade that results in the production of dark eumelanin, which is then packaged into vesicles called melanosomes, for transport to epidermal keratinocytes which provide protection against ultraviolet radiation. The migration of melanosomes to keratinocytes in hair follicles also gives the growing hair its color [3].

Variants of the MC1R gene are also associated with an increased risk for the development of cutaneous melanoma [5]. The MC1R gene variant is also associated with phenotypical features such as fair skin and red hair that carry a higher risk for melanoma and non-melanoma skin cancers [6]. Considering this association, the MC1R gene is very important as a susceptibility gene for sunburn, photo-aging, and skin melanoma [7].

Previous studies had suggested the factors associated with gradual loss of pigmentation to include exhaustion of enzyme involved in melanogenesis, impaired DNA synthesis, loos of telomerase, antioxidant mechanism, and anti-apoptotic signals that all may contribute in part to hair graying [8].

Different variants of the MC1R gene can lead to altered ligand binding, altered function, or loss of ligand function. The effect of MC1R on melanogenesis is mediated through activation of adenylate cyclase to

increase cyclical levels of adenosine monophosphate after binding with α-MSH and ACTH. The loss of functional variants may lead to reduced cyclic adenosine monophosphate production after stimulation with α-MSH resulting in increased levels of pheomelanins which are predominantly found in individuals with fair skin and red hair and which may contribute to the increased risk of cancer by generating free radicals by ultraviolet exposure [6], [7]

Based on the data above, many studies on PHG found an associated with genetics, but the study in Indonesia and in North Sumatra in particular did not been find. Therefore, the aim of this study was to provide an overview, of which risk factors are dominant in early graying of hair at a young age, particularly of college students at Universitas Sumatera Utara (USU).

Materials and Methods

This study was a cross-sectional design with 80 samples of the college students at the Universitas Sumatera Utara (USU) area such as Faculty of Medicine, Dentistry, Engineering, Public Health, Mathematics and Natural Science, Agriculture, and Politeknik Negeri Medan. The protocol of this study was approved by the Medical Ethics Committee at Universitas Sumatera Utara.

Study subjects

These included forty respondents with PHG and 40 healthy controls with normal hair. The inclusion criteria were male sex, below 25 years old, with gray hair and not have skin pigmentation disorders. Written informed consent was taken from all respondents. The questionnaires including onset, location, and numbers of graying hair were collected. The MC1R expression was detected with PCR and the serum melanin was assessed by Elisa. The data were analyzed with independent *t*-test with *P*< 0.05 was considered significant.

Results

The mean ± SD age of cases was 20.28 ± 1.99 years and the age range was 19–24 years, whereas the control was 21.25 ± 2.02 years and 18–24 years, respectively.

In this study, majority of the gray areas were parietal regions (50%), followed by more than one region, frontal, occipital, and temporal regions which were 17%, 15%, 13%, and 5%, respectively (Figure 1).
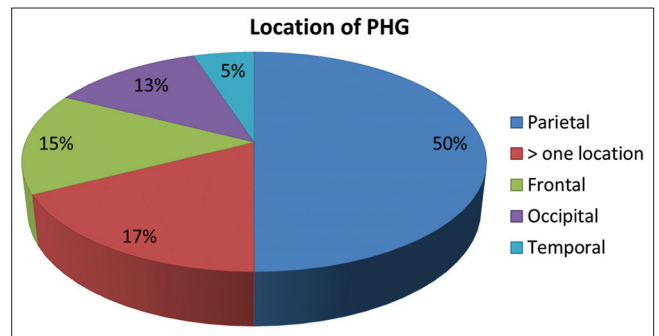

Figure 1: Distribution of PHG areas.

In addition, this study showed that the expression of MC1R gene was positive in control and PHG groups (Figure 2).
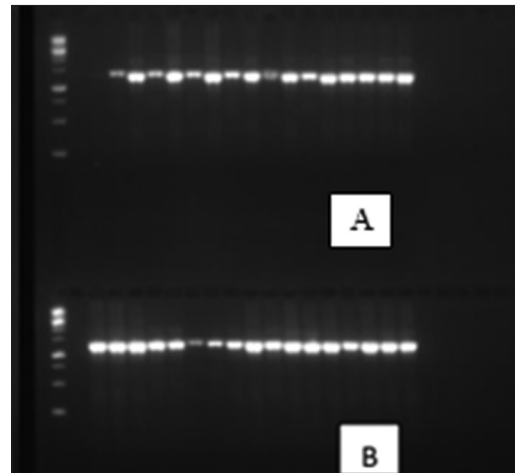

Figure 2: Expression of MC1R in control group (A) and PHG group (B)

Table 1 showed that serum melanin level was significantly lower in PHG (9.27 ± 1.62 ug/dl) than in control group (10.72 ± 1.78 ug/dl) (p = 0.0001).

Table 1: The level of serum melanin in PHG and control groups

Group	Level of serum melanin serum (ug/dl)		p
	Mean and SD	N	
Control	10.72 ± 1.78	40	0.0001
PHG	9.27 ± 1.62	40	

Discussion

Canities (hair graying) is an age-related loss of pigmentation (melanin) from hair. It is one of the most unique traits in humans ranging from black, brown, and blonde to red. It is modulated by genetic, oxidative, senescence-associated, metabolic, and nutritional factors. Human hair color is caused by the melanin pigment produced by melanocytes which are derived from the neural crest. Human hair follicles contain two types of melanin eumelanin and pheomelanin [1].

Till today, the pathogenesis of canities remains incompletely understood. A hypothesis that pH and

cysteine level of melanosome play critical roles in determining the course of mixed melanosome leading to dark, light, or red hair phenotype has been proposed causes of diversity of human pigmentation [8]. Few studies had also reported that environmental factors (such as ultraviolet light and climate), smoking, drugs, deficiencies of trace elements, and nutritional deficiencies also play a role in PHG [9], [10], [11].

This study was continued of the previous studied to detect risk factors associated with premature graying, including family history, levels of vitamin D, calcium, vitamin B12, Fe, and trace elements. The mean age of cases was 20.28 ± 1.99 years (mean vs. standard deviation), range was 19–24 years old and the controls were 21.25 ± 2.02 years, and the range was 18–24 years old.

It has been observed that pattern of gray hair depends on age of onset, gender, and smoking habit, with increased chances of having canities in smokers [1]. Jo *et al.* (2012) showed that temporal area is involved in males, while females are the frontal and parietal areas. Onset of graying also affects the area involvement: In early onset, parietal and occipital areas are involved, while in late onset, frontal area is involved [1]. In this study, an analysis of questionnaire responses revealed that majority of the gray areas were parietal region (50%), followed frontal, occipital, and temporal. Daulatabad *et al.* (2016) showed involvement of the frontal more likely than temporal region. Another study had reported that differences in pattern are related with racial variation [13].

In this study, serum melanin concentration was significantly lower in PHG compared with controls (9.27 ± 1.62 vs. 10.72 ± 1.78 ug/Dl, respectively, $p = 0.0001$). Human hair follicles contain two types of melanin as follows: Eumelanin and pheomelanin. The diversity of hair color arises mostly from the quantity and ratio of black-brown eumelanin and reddish-brown pheomelanin. It has been hypothesized that the pH and cysteine level of melanosomes influence the phenotype of hair. As pH reduces, there is a progressive reduction in tyrosinase activity leading to increased pheomelanin and reddish or blonde hair [12]. A mutation in melanocortin-1 receptor (MC1R) gene causes auburn or red color of hair. This mutation is seen usually in individuals of Northern Europe with less sun exposure [12], [13]. A study, in 2012, showed a recessive mutation in tyrosinase-related protein 1 (TYRP1) in people with blonde hair [14].

The graying of hair is usually progressive and permanent, but there are occasional reports of spontaneous repigmentation of gray hair. Environmental factors such as ultraviolet light, climate, smoking, drugs, trace elements, and nutritional deficiencies all play a role in the pathogenesis of canities [14], [15]. Trace element deficiencies lead to a spectrum of the clinical manifestations, especially in skin and hair. Kruglugeret *et al.* (year) hypothesized that iron and vitamin B12 affect hair growth and pigmentation [16], whereas Anggraini *et al.* (year) showed that premature graying is associated with deficiency of vitamin D at young age [17]. Deficiency in trace metal ions may also lead to hypopigmentation. Tyrosinase enzyme in melanocytes requires copper ion to maintain normal color [14].

This study supported a critical role of expression of M1CR gene and decreasing of serum melanin may contribute as risk factors of PHG at young age especially in college students at Universitas Sumatera Utara, Medan.

The limitation of this study was small sample. The different genetic backgrounds affected different consequences for the functioning of the MC1R. In the next study, we will recruit big sample compare male and female at young age.

Conclusion

Expression of MC1R gene and decreasing of serum melanin concentrations may contribute to the risk of premature hair graying of college students.

Acknowledgment

References

1. Kumar AB, Shamim H, Nagaraju U. Premature graying of hair: Review with updates. Int J Trichol. 2018;10(5):198-203. https://doi.org/10.4103/ijt.ijt_47_18
   PMid:30607038

2. Sehrawat M, Sinha AS, Meena N, Sharma PK. Biology of hair pigmentation and its role in premature canities. Pigment Int. 2017;4(1):7-12.

3. Trüeb RM. Pharmacological interventions in aging hair. Clin Interv Aging. 2006;1(2):121-9. https://doi.org/10.2147/ciia.2006.1.2.121
   PMid:18044109

4. Naieni FF, Ebrahimi B, Vakilian HR, Shahmoradi Z. Serum iron, zinc, and copper concentration in premature graying of hair. Biol Trace Elem Res. 2012;146(1):30-4. https://doi.org/10.1007/s12011-011-9223-6

PMid:21979243

5. Palmer JS, Duffy DL, Box NF. Melanocortin-1 receptor polymorphisms and risk of melanoma: Is the association explained solely by pigmentation phenotype? Am J Hum Genet. 2000;66(1):176-86. https://doi.org/10.1086/302711

PMid:10631149

6. Bastiaens MT, Ter Huurne JA, Kielich C, Gruis NA, Westendorp RG, Vermeer BJ, *et al.* Melanocortin-1 receptor gene variants determine the risk of non-melanoma skin cancer independent of fair skin type and red hair. Am J Hum Genet. 2001;68(4):884-94. https://doi.org/10.1086/319500

PMid:11254446

7. Healy E, Flannagan N, Ray A. Melanocortin-1-receptor gene and sun sensitivity in individuals without red hair. Lancet. 2000;355(9209):1072-3. https://doi.org/10.1016/S0140-6736(00)02042-0

PMid:10744096

8. Chakrabarty S, Krishnappa PG, Gowda DG, Hiremath J. Factors associated with premature hair graying in a young Indian population. Int J Trichol. 2016;8(1):11-4. https://doi.org/10.4103/0974-7753.179384

PMid:27127369

9. Bhat RM, Sharma R, Pinto AC, Dandekeri S, Martis J. Epidemiological and investigative study of premature graying of hair in higher secondary and pre-university School children. Int J Trichol. 2013;5(1):17-21. https://doi.org/10.4103/0974-7753.114706

PMid:23960391

10. Jo SJ, Paik SH, Cho JW, Lee JH, Cho S, Kim KH, *et al.* Hair graying pattern depends on gender, onset age and smoking. Acta Derm Venereol. 2012;92(2):160-1. https://doi.org/10.2340/00015555-1181

PMid:22113716

11. Daulatabad D, Singal A, Grover C, Chhillar N. Profile of Indian patients with premature canities Indian J Dermatol Venereol Leprol. 2016;82(2):169-72. https://doi.org/10.4103/0378-6323.168911

PMid:26585843

12. Ito S, Wakamatsu K. Diversity of human hair pigmentation as studied by chemical analysis of eumelanin and pheomelanin. J Eur Acad Dermatol Venereol. 2011;25(12):1369-80.

PMid:22077870

13. Ancans J, Tobin DJ, Hoogduijn MJ, Smit NP, Wakamatsu K, Thody AJ, *et al.* Melanosomal pH controls rate of melanogenesis, eumelanin/phaeomelanin ratio and melanosome maturation in melanocytes and melanoma cells. Exp Cell Res. 2001;268(1):26-35. https://doi.org/10.1006/excr.2001.5251

PMid:11461115

14. Kenny EE, Timpson NJ, Sikora M, Yee MC, Moreno-Estrada A, Eng C, *et al.* Melanesian blond hair is caused by an amino acid change in TYRP1. Science. 2012;336(6081):554. https://doi.org/10.1126/science.1217849

PMid:22556244

15. Bhat YJ, Hassan I, Sajad P, Malik R, Majid S, Mubashir S, *et al.* Serum iron, ferritin and calcium levels in premature canities. Hair Ther Transplant. 2013;6:142.

16. Krugluger W, Stiefsohn K, Laciak K. Vitamin B12 activates want pathway in human hair follicle by induction of b catenin and inhibition of glycogen synthase kinase 3 transcription. J Cosmet Dermatol Sci Appl. 2011;1:25-9.

17. Anggraini DR, Feriyawati L, Hidayat. Serum ferritin and Vitamin D levels in premature hair graying of college student at the Universitas Sumatera Utara area. IOP Conf Ser Earth Environ Sci. 2019;305:1-5.