INTRODUCTION

Hair graying is considered a prominent sign of aging in humans. Aside from being a major cosmetic concern, the presence of gray hair may also reflect the progression of systemic processes, including development of atherosclerosis, dysregulation of innate immunity, viral infection, and nutritional deficiencies.

Investigating the factors associated with premature hair graying (PHG) is a necessary step toward understanding risk factors for graying as well as the risk for developing systemic disease that PHG may portend. In this study, we investigate a variety of physiological, psychological, and lifestyle factors and their potential associations with PHG.

MATERIALS AND METHODS

We conducted a cross-sectional, case-control survey study using Qualtrics online survey software (Qualtrics LLC, Provo, UT). The study was approved by the Institutional Review Board, and all participants provided consent within.

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ABSTRACT

Background: Canities, or hair graying, is believed to be driven by the cytotoxic effect of reactive oxygen species on follicular melanocytes, thus raising the concern that premature hair graying (PHG) may represent an outward sign of systemic oxidative stress.

Objective: This study aimed to identify the physiological, psychological, and lifestyle factors associated with PHG (defined as graying at age ≤30 years) in men and women.

Materials and Methods: Data from 467 participants (female = 354 and male = 113; age: 18–77 years) were collected and analyzed, including demographic information, medical history, family history, supplement intake, and lifestyle factors.

Results: PHG was found to be significantly associated with a history of PHG in the mother, \( P < 0.001 \), odds ratio (OR) = 3.165; father, \( P < 0.001 \), OR = 5.166; maternal grandparent, \( P = 0.002 \), OR = 2.442; paternal grandparent, \( P = 0.007 \), OR = 2.369; and siblings, \( P < 0.001 \), OR = 3.125. PHG was significantly associated with iron deficiency (\( P = 0.026 \), OR = 1.751) and family history of depression (\( P = 0.012 \), OR = 1.751) and herpes simplex virus infection (\( P = 0.004 \), OR = 0.367) and smoking history (\( P = 0.003 \)) demonstrated significant negative associations. In Caucasians only (n = 306), in addition to these trends, irritable bowel syndrome was also significantly associated with PHG (\( P = 0.010 \), OR = 2.753). In Asians only (n = 75), history of heart disease in a first-degree relative (\( P = 0.038 \)) was significantly associated with PHG.

Limitations: As a survey study, the findings may be subject to recall bias.

Conclusions: Important associations exist between PHG and family history of PHG, psychiatric history, supplement use, and vitamin deficiencies, providing insight into the pathophysiology and potential comorbidities of PHG.

Key words: Canities, gray hair, premature hair graying
the survey. The study was designed to collect participant information including demographics, medical history, family history, and lifestyle factors in order to identify factors with a significant positive or negative association with PHG. Participants were recruited from the local surrounding area through the use of advertisements. Inclusion criteria included age ≥ 18 years, and exclusion criteria included inability to provide consent.

The collected participant information included age, sex, race, height, weight, history of PHG (defined as graying beginning age ≤ 30), severity of graying (0, 1–10, 11–100, and > 100 self-reported gray hairs), presence/absence of hair loss, and difficulty hearing. Participants also provided information concerning lifestyle: alcohol intake, smoking, caffeine intake, exercise, and meat/poultry/fish/egg intake.

Family history of PHG in the mother, father, paternal grandparents, maternal grandparents, and siblings was assessed. Family and personal history of depression, anxiety, and bipolar disorder was collected. Family medical history of cardiovascular disease (CVD) was assessed through the number of first-degree relatives with a history of CVD at any age and the number presenting with CVD at an early age (men < 45 years and women < 55 years). Data collected concerning participant past medical history included cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, and personal history of CVD); nutritional deficiencies (iron, Vitamin B12, folic acid, calcium, and Vitamin D); diseases associated with nutritional deficiencies (iron-deficiency anemia, pernicious anemia, celiac disease, inflammatory bowel disease, irritable bowel syndrome (IBS), and cystic fibrosis); autoimmune diseases (systemic lupus erythematosus, diabetes mellitus type I, vitiligo, hypothyroidism, hyperthyroidism, and rheumatoid arthritis); and viral infections (herpes simplex, hepatitis B and C, human immunodeficiency virus, Epstein–Barr virus, varicella zoster, and influenza). Supplement use was assessed: multivitamins/prenatal vitamins, folic acid, Vitamin B12, biotin, fish oil/omega-3 fatty acids, and calcium/Vitamin D.

Statistical analysis of the survey results was performed with SPSS-25 software (IBM Corp, Armonk, NY, USA). Participants with a history of PHG were compared against those without PHG. Ordinal variables were each assigned to a numerical scale for data analysis: alcohol intake in standard drinks per week (1 = 0, 2 = 1–3, 3 = 4–7, 4 = 8–10, 5 = 11–14, and 6 = >14 drinks), smoking history (1 = never smoker, 2 = former smoker, and 3 = current smoker), daily caffeine intake (1 = 0, 2 = 1–3, and 3 = >3 drinks), exercise per week (1 = 0, 2 = 1–2, 3 = 3–5, and 4 = >5 times), meat/poultry/fish/egg intake per week (1 = 0, 2 = 1–3, 3 = 4–7, and 4 = >7 times), and difficulty hearing (0 = no difficulty, 1 = difficulty hearing soft sounds, 2 = difficulty hearing conversational speech, and 3 = ability to hear only very loud sounds). Comparisons across ordinal variables were conducted using two-tailed independent t-tests. Discrete variables were compared by the Pearson’s Chi-square test for large cell sizes and Fisher’s exact test when < 20% of cells in the contingency table had an expected value of < 5. P < 0.05 was considered significant for all analyses.

### RESULTS

The survey was completed by 467 participants, 216 with a history of PHG and 251 without. Demographic characteristics were comparable between both the groups [Table 1]. The comparison of participant characteristics between those with and without a history of PHG is summarized in Tables 2-4. Taking all participants into consideration, significant positive associations were observed between personal history of PHG and family history of PHG in the participant’s mother (P < 0.001, odds ratio [OR] = 3.165), father (P < 0.001, OR = 5.166), maternal grandparent (P = 0.002, OR = 2.442), paternal grandparent (P = 0.007, OR = 2.369), and siblings (P < 0.001, OR = 3.125). Family history of depression (P = 0.012, OR = 1.603) and personal history of iron deficiency (P = 0.026, OR = 1.751) were also found to be significantly associated with PHG. Surprisingly, significant negative associations were observed between history of PHG and smoking history (P = 0.004) and herpes simplex virus (HSV) infection (P = 0.004, OR = 0.0367).

### Table 1: Demographic characteristics of study participants

| Demographic characteristics | History of PHG | No history of PHG |
|----------------------------|----------------|------------------|
| Total number of participants | 216            | 251              |
| Age range                   |                |                  |
| 30 and under                | 116            | 103              |
| 32–50                       | 61             | 65               |
| 51–80                       | 39             | 83               |
| Race                        |                |                  |
| Caucasian                   | 140            | 166              |
| Asian                       | 36             | 39               |
| African American            | 18             | 28               |
| Multiracial/other           | 22             | 18               |
| Sex                         |                |                  |
| Female                      | 162            | 192              |
| Male                        | 54             | 59               |

PHG – Premature hair graying
When examining the responses from Caucasian participants only, history of PHG remained significantly positively associated with family history of PHG in each assessed relative, family history of depression ($P = 0.017, OR = 1.734$), and personal history of iron deficiency ($P = 0.038, OR = 1.965$) and significantly negatively associated with smoking history ($P = 0.008$) and HSV infection ($P = 0.027, OR = 0.397$). In addition, history of PHG in Caucasian patients was also significantly positively correlated with IBS ($P = 0.010, OR = 2.753$).

Examining responses from Asian participants only, fewer significant trends were noted. History of PHG was significantly associated with family history of PHG in only the participant’s father ($P = 0.001, OR = 6.084$) and siblings ($P = 0.015, OR = 6.167$). However, in Asian participants, history of PHG
was found to be significantly associated with family history of heart disease in a first-degree relative (P = 0.038). In African American participants, only family history of PHG in the participant's father (P = 0.004, OR = 17.182) was found to be significantly associated with PHG.

Several additional trends were revealed by comparing only data from individuals of the same sex. Among female participants, history of PHG was significantly positively associated with family history of PHG in the participant's mother (P < 0.001, OR = 3.351), father (P < 0.001, OR = 4.741), maternal grandparent (P = 0.039, OR = 1.968), and siblings (P = 0.001, OR = 2.905). History of PHG was also significantly positively correlated with family history of depression (P = 0.002, OR = 1.919) and personal history of iron deficiency (P = 0.033, OR = 1.750). Smoking history (P = 0.015), HSV infection (P = 0.004, OR = 0.331), and fish oil/omega-3 fatty acid supplementation (P = 0.046, OR = 0.489) were significantly negatively correlated with history of PHG. Among male participants, history of PHG was significantly positively correlated with biotin supplementation (P = 0.049) as well as family history of PHG in every relative.

When examining only individuals aged 30 years and under, PHG was significantly positively associated with a family history of PHG in each relative as well as influenza virus infection (P = 0.023, OR = 1.909). Intake of fish oil/omega-3 fatty acids was significantly negatively correlated with PHG (P = 0.008, OR = 0.201).

No significant associations were observed in our study across any demographic group between history of PHG and obesity, alcohol intake, caffeine intake, difficulty hearing, diet, exercise, hair loss, personal history of mental illness, or autoimmune disease.

**DISCUSSION**

In response to recent studies correlating PHG with a family history of PHG, smoking, obesity, atherosclerosis, defects in innate immunity, viral infection, and nutritional deficiencies, we surveyed 467 individuals on factors that may be associated with PHG.

The strongest associations were observed between personal history and family history of PHG. Family history of PHG in every assessed relative was found to be significantly associated with personal history of PHG. The strongest associations for family history of PHG were observed in the mother, father, and siblings, with slightly weaker,

**Table 4: Environmental and lifestyle factors between those with and without history of premature hair graying**

| Participant characteristics | History of PHG, n (%) | No history of PHG, n (%) | OR (95% CI) | P |
|-----------------------------|------------------------|--------------------------|-------------|---|
| Number of participants      | 216                    | 251                      |             |   |
| Vitamin deficiency          |                        |                          |             |   |
| Iron                        | 44 (20.4)              | 32 (12.7)                | 1.751 (1.065-2.878) | 0.026 |
| Vitamin B12                 | 12 (5.6)               | 8 (3.2)                  | 1.787 (0.717-4.56)  | 0.208 |
| Folic acid                  | 2 (0.9)                | 1 (0.4)                  | 2.336 (0.210-25.946) | 0.598 |
| Calcium/Vitamin D           | 46 (21.3)              | 58 (23.1)                | 0.900 (0.581-1.396) | 0.639 |
| Viral infections            |                        |                          |             |   |
| Herpes simplex              | 11 (5.1)               | 32 (12.7)                | 0.367 (0.180-0.748) | 0.004 |
| Hepatitis B                 | 0 (0.0)                | 1 (0.4)                  | -            | 1.00 |
| Hepatitis C                 | 0 (0.0)                | 1 (0.4)                  | -            | 1.00 |
| HIV                         | 1 (0.5)                | 1 (0.4)                  | 1.163 (0.072-18.702) | 1.000 |
| Epstein-Barr                | 27 (12.5)              | 24 (9.6)                 | 1.351 (0.754-2.420) | 0.310 |
| Varicella-Zoster            | 66 (30.6)              | 90 (35.9)                | 0.787 (0.534-1.160) | 0.226 |
| Influenza                   | 91 (42.1)              | 95 (37.8)                | 1.195 (0.825-1.733) | 0.346 |
| Supplement intake           |                        |                          |             |   |
| Multivitamin/prenatal       | 72 (33.3)              | 89 (35.5)                | 0.910 (0.620-1.335) | 0.630 |
| Folic acid                  | 8 (3.8)                | 5 (2.0)                  | 1.920 (0.639-5.959) | 0.251 |
| Vitamin B12                 | 23 (10.7)              | 33 (13.1)                | 0.791 (0.449-1.395) | 0.418 |
| Biotin                      | 21 (9.7)               | 15 (6.0)                 | 1.694 (0.852-3.375) | 0.130 |
| Fish oil/omega-3            | 18 (8.3)               | 35 (13.9)                | 0.561 (0.308-1.023) | 0.057 |
| Calcium/Vitamin D           | 48 (22.2)              | 73 (29.1)                | 0.697 (0.457-1.062) | 0.092 |

HIV – Human immunodeficiency virus; PHG – Premature hair graying; CI – Confidence interval; OR – Odds ratio
though still significant, associations in maternal and paternal grandparents. This pattern may in part be due to recall bias in participants unable to accurately report their grandparents’ history. When analyzing family history of PHG within each race individually, the number of relatives significantly associated with PHG was highest in Caucasians (n = 306), followed by Asians (n = 75) and African Americans (n = 46). This is likely a product of decreasing sample size across these three groups. The association was found to be strongest in the father (OR = 5.166), followed by the mother (OR = 3.165) and siblings (OR = 3.125). Additional studies would be needed to determine whether the genetic predisposition for PHG is truly stronger for an individual whose father has PHG compared to his/her mother or if external factors such as hair dyeing practices affected participants’ perception and thus reporting of their family history.

A prior survey study of factors associated with hair graying in Korean men found that family history of PHG, smoking, and obesity was significantly associated with PHG. While our results for family history of PHG closely aligned with this study’s results, we found a negative association between smoking history and PHG. This discrepancy is likely due to the manner in which smoking history was evaluated. We investigated chronological smoking history (never, former, and current smokers), while the prior study investigated quantity of smoking (smokers classified as those with ≥5 pack-years) without regard to status as former or current smokers. When we excluded participants who identified as former smokers, we found no association between PHG and current smoking (P = 0.070). While obesity (body mass index [BMI] >30 kg/m²) was more prevalent among those with PHG (16.7%) than those without (14.7%) in our study population, we found no significant association between obesity and PHG. Our study population had a substantially higher proportion of obese individuals than the prior study population, which found 8.6% of those with PHG and 4.9% of those without PHG to be obese. The average weight of individuals in Korea is markedly lower than that of individuals in the United States. Moreover, the prior study only sampled men conscripted for military service who were likely in good physical condition, suggesting that additional factors beyond BMI may be at play in these individuals.

Despite the common societal perception that emotional stress can cause hair to turn gray, no link has been identified to date between stress, mental illness, and PHG. It has been speculated that, in individuals who have already begun to gray, hair regrowth following stress-induced telogen effluvium may create the illusion of rapid graying following stress. Interestingly, our survey found that family history, but not personal history, of depression was significantly associated with PHG. While we surveyed participants about their personal history of hair loss, we did not examine family history of hair loss, which could be a potential confounding variable. We also found that, in Caucasian participants, IBS, a syndrome strongly linked to depression and anxiety, was significantly associated with PHG. Individuals with IBS to whom the fermentable oligo-, di-, and mono-saccharides and polyols diet has been recommended may also be at risk for reduced intake of iron, folate, calcium, Vitamins B and D, fiber, zinc, and natural antioxidants. Prior studies have found associations between PHG and deficiencies in Vitamin B12, folate, and biotin. Iron may modulate the activity of tyrosinase, an important enzyme regulating production of pigment molecules eumelanin and pheomelanin. We found a significant association between iron deficiency and PHG, thus providing further evidence that micronutrient deficiencies may have a role in the development of PHG.

PHG has also been associated with coronary artery disease and carotid atherosclerosis raising the question of whether PHG may be an outward sign of systemic aging processes. We found personal history of PHG to be significantly associated with family history of heart disease in a first-degree relative in Asian participants only. The prevalence of coronary heart disease (CHD) in Asians (3.7%) is substantially lower than any other ethnic group in America (African Americans, 6.3%; Caucasians, 6.1%; and Hispanics, 5.4%). This suggests that there may be genetic factors related to both PHG and cardiovascular risk that are only apparent in populations with low baseline CHD risk.

When examining results of female participants only and of participants aged ≤30 years only, fish oil/omega-3 fatty acid supplementation, which has well-documented cardioprotective effects, was significantly negatively associated with PHG. Additional studies would be required to establish whether fish oil/omega-3 fatty acid supplementation has a protective effect against PHG as well. In male participants only, intake of biotin supplements demonstrated a significant positive association with PHG (P = 0.049) but not hair loss (P = 0.144). While some evidence exists for the role of biotin in hair loss, no studies have demonstrated the utility of biotin supplementation for gray hair calling into question the manner in which biotin supplementation is marketed to patients.

We also discovered a striking negative association between HSV-1 or HSV-2 infection and PHG. This association was...
observed when examining results from all participants and when examining results from only the Caucasian cohort \((n = 306)\). A genome-wide association study has identified a single-nucleotide polymorphism (SNP) rs12203592 in intron 4 of the interferon regulatory factor 4 (IRF4) gene that displays a significant association with gray hair.[18] In individuals of European ancestry, this SNP has been associated with hair, skin, and eye color as well as tanning ability.[19] IRF4, detected in normal melanocytes, has also been shown to negatively regulate toll-like receptor signaling involved in the activation of innate and adaptive immune responses.[20] Further studies would be needed to determine whether this SNP in Caucasians may have a role in the immune response to viral infections such as HSV.

As a survey study, our results may be subject to recall bias in our participants’ responses. While we attempted to study a wide variety of factors, there may be additional confounding variables that have not yet been identified. Future survey studies could elicit further information including quantitative smoking history, family history of hair loss, and hair color at birth that may shed light on some of our more surprising results. To remove the possibility of recall bias in some of our measures, future studies could include biometric examination of participants, serum levels of micronutrients, and viral serology or polymerase chain reaction.

CONCLUSION

Our survey study identified a number of factors positively associated with PHG, including family history of PHG, family history of depression, and iron deficiency, while history of HSV infection was found to be negatively associated with PHG. We did not identify any significant associations between history of PHG and obesity, alcohol intake, caffeine intake, difficulty hearing, diet, exercise, hair loss, personal history of mental illness, or autoimmune disease. This study supports that PHG is highly hereditary. While the mechanisms behind the other identified associations remain as of yet unclear, these associations are interesting clues that can lead to further understanding of the relationship between PHG and systemic health and disease through future study.

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Conflicts of interest

There are no conflicts of interest.

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