Examination of the Missense Mutation (rs74653330, Ala481Thr) of the Oculocutaneous Albinism 2 Gene to the Facial Skin Characteristics

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Research note

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Abstract

Objective

A melanin pathway gene, oculocutaneous albinism 2 (OCA2) operates the first step of the melanin synthesis pathway and is known to associate with the albinism and pigmentation. Our previous study identified a significant association (p-value<$5x10^{-8}$) between a OCA2 missense mutation (rs74653330, Ala481thr) and skin pigmentation. Since melanin pigment protects the skin from damage by ultraviolet light and we hypothesize that the rs74653330 SNP effect on the skin phenotypes not only the melanin, but also the other skin characteristics such as wrinkle formation, moisture level and sebum levels. We examined the association of the rs74653330 SNP to 19 skin characteristics consisting of wrinkle, moisture, melanin, erythema, brightness, and sebum using eight cosmetological instruments.

Results

The rs74653330 SNP showed significant association with melanin phenotypes, specifically in young and middle groups. The melanin levels of pigmented area showed more melanin in middle age group but less in old group. Also, the rs74653330 SNP affect to wrinkle formation and sebum secretion. Conclusively, the analyses in this study clearly indicate that rs74653330 SNP affects to the melanin related skin phenotypes, and to the wrinkle formation or sebum secretion.

Introduction

The understanding of the genetic basis of the normal variation in human pigmentation are greatly advanced that approximately 400 genes have been identified as pigmentation candidate genes that contribute to determination of skin color [1]. Among them, one of the pigmentation gene that well studied for human skin pigmentation is the oculocutaeous albinism 2 gene (OCA2). This gene was known and named as a gene involved in oculocutaneous albinism and is known to be involved in albinism as well as the eye color. Due to these functional properties, many previous studies have reported an association with skin pigmentation [2-4]. The OCA2 protein is important for normal biogenesis of melanosomes, and normal processing and transport of melanosomal proteins such as TYR and tyrosinase-related protein 1 (TYRP1) [5].

The OCA2 gene is reported more than fifty different mutations [6], and one of them is a missense mutation of exon 14 at codon 481 in which threonine (ACC) is substituted for alanine (GCC) [7]. The frequency of OCA2 mutation (rs74653330: Ala481Thr) is approximately less than 1% in Caucasian populations, but 8% in all OCA patients in Japan [8]. Yuasa et al. (2007) [9] stated that the A481T substitution results from a 1559G-A transition in exon 14 of the OCA2 gene. Among more than 2,615 healthy individuals from 20 African and Eurasian populations, Yuasa et al. (2007) [9] found that the thr481 allele prevailed almost exclusively in a northeastern part of Asia. The allele frequency was highest in Buryat (0.24) in Mongolia and showed a north-south gradient. The findings suggested that thr481 allele arose in a region of low ultraviolet radiation and thereafter spread to neighboring populations.

In our previous GWAS study [10] for the skin cosmetological traits showed the most significant association between rs74653330 and skin pigmentation phenotype. It is well known that the melanin pigment protects the skin from damage by ultraviolet (UV) light and plays important roles in vision, sexual display, and innate immunity [11,12]. Also, previous reports showed the relationship of pigmentation phenotype to the skin sebum and moisture, respectively [13]. Therefore, we hypothesize that the rs74653330 possibly associates with other skin characteristics, because the efficiency protecting UV damage could affect wrinkle, skin aging and moisture.

Methods

Participants

The sample population investigated in this study consisted of 1,079 Korean women recruited between January 2019 and November 2019 at P&K Skin Research Center (Seoul, Korea). All recruited participants were female without skin-related diseases, and their average age was 40.81 years. All participants provided written informed consent, and this study was approved by the Institutional Review Board of the Theragen Etex Bio Institute (IRB No.: 700062-20190819-GP-006-01).

Skin Phenotypes

To measure skin traits, various measuring devices were used. Antera 3D (Miravex, Dublin, Ireland) and Primos CR (Canfield Scientific, New Jersey, United States) to evaluate wrinkle, Corneometer (EnviroDerm Services Ltd., Hedworth, United Kingdom) and Tewameter (Courage + Khazaka electronic GmbH, Köln, Germany) to assess the transepidermal water loss, Mexameter (Courage + Khazaka electronic GmbH, Köln, Germany) and a CM-700d (Konica Minolta inc., Tokyo, Japan) to measure pigmentation, and Sebumeter (Courage + Khazaka electronic GmbH., Köln, Germany) to determine sebum.

SNP Genotyping

The SNP genotypes of rs74653330 was extracted from the previous SNP microarray dataset. The detailed procedures of the experiments are described in our previous paper [10]. Briefly, we used the Theragen Precision Medicine Research Array (PMRA) which was customized and designed based on the Asian PMRA (Thermo Fisher Scientifi c, Waltham, MA) to obtain genetic variant information for 820,000 SNPs in the entire human genome. After the QC step, 560,795 polymorphic SNPs could be analyzed on chromosomes.

Statistics

The phenotype characteristics and aging effects were examined by using ANOVA test and Linear regression analysis with controlling the Age as the covariates. To conduct the ANOVA test, we divided the samples into three age groups as following: Age < 35 is Young group, 35 <= Age < 50 is Middle group, and Age >= 50 is Old group. For the genotype association tests, we divided the samples into two groups for dominace mode (the Major allele homozygotes (GG) and the heterozygotes plus the minor allele

homozygotes (GA + AA)). The SPSS (IBM SPSS Statistics Inc., New York, NY) used to all statistical analysis.

Results

We examined the skin characteristics by using eight skin measuring instruments. The all characteristics are summarized in Table 1. The eight winkle phenotypes (right eye area roughness, right eye area max depth, glabella area roughness, globella area max depth by Antera 3D; right eye area roughness, right eye area max depth, glabella area roughness, globella area max depth by Primos CR) were gradually increased with the aging. The four moisture level phenotypes (globrlla area moisture levels, right chic area moisture levels, globella area moisture evaporation, right chic area moisture evaporation) are showed different trends. The globrlla area moisture levels showed constant moisture levels with the aging, whereas the right chic area moisture levels is gradually increased. The globella area moisture evaporation and right chic area moisture evaporation were gradually decreased with aging, indicating that the skin mosture can be easily evaporated in young age group and it lead to low level of skin moisture. The two melanin phenotypes (pigmented area melanin level, non-pigmented area melanin level) were showed more melanin in older age group in pigmented area melanin level but less melanin in older age group. The Erythema phenotype was gradually descrease in older age group. The two Brightness phenotypes (pigmented area skin brightness, non-pigmented area skin brightness) were gradually decreased in older age group. The sebum phenotypes (globella area sebum level, right chic area sebum level) were gradually decrease in older age group.

In the young age groups showed the GA+AA genotypes less melanin and erythema in the Non-pigmented region, and more brightness in both pigmented and non-pigmented area. In the middle age group showed similar trend to the young age group, but the RD phenotype were inceased in GA+AA and PM decreased in GA+AA. Interestingly, older age group did not showed the differences between GG and GA+AA in most of the skin phenotypes, except RR and GS which were increased in GA+AA group.

Discussion

In this study, we examined the most significantly associated SNPs in our previous study for the cosmetological effects. we studied the aging effect of skin measurement characteristics and the association with the OCA2 polymorphism (rs74653330) in a large Korean population. In our knowledge, this report is the first study of the aging effects on Korean skin characteristics using the cosmetological instruments. And, the whole wrinkle phenotypes are showed the significant increasing tendency with the aging effects, but two instrument measurements seems slight different trends. The Antera 3D showed the large difference between Right eye area and Globella Area, but the Primos CR showed similar and stable results. This is thought to be caused by the difference in the measurement method and fine-tuning calculation of the two devices [14, 15]. The altered moisture indices by age obtained in the present study are similar to those of previous studies. Luebberding et al. [16] and Hillebrand et al. [17] showed that the moisture index increases with age.

Interestingly, the decrease in brightness levels is a common result due to aging and is consistent with previous studies, but the decrease in melanin levels and redness levels presents the opposite result from previous studies [18-20]. These differences may be due to differences in measuring devices, measurement methods, samples, and population, and may be due to the quality or level of control of the products used, and additional analysis and research are required to find a clear cause. This is the same as the results of previous studies [18, 21, 22] and is the same as the result of the decreased amount of sebum secretion as aging progresses based on the amount of sebum measured in the forehead, cheek, and chin areas, which are commonly measured. In particular, in the case of women, there is a report that the amount of sebum secretion decreases rapidly before and after menopause [23, 24], and it can be confirmed that in our results, it is reduced by almost half which a group of after the 50year is than the group under the age of 35 year. Overall, as a result of analyzing the aging effect on the skin beauty phenotype in this result, the aging of Korean women appears to be more wrinkles, more moisture, less melanin, and less oily skin than the skin phenotype results of other races or countries [18, 23-25].

The OCA2 polymorphism showed significant association with melanin phenotypes, specifically in young and middle groups. The individuals with A allele showed significant low melanin, erythema, and high brightness. These results were similar to the previous reports [26-28]. Individuals with the minor alleles showed decreased melanin in both pigmented and non-pigmented areas. In addition, as is well known, the OCA2 gene is associated with eumelanin, but the other pigmentation-related phenotype, erythema also decreased. This result implies that the variant related to pheomelanin [29, 30]. Brightness, which is the counter phenotype of melanin levels, had been shown to increase in the individuals with minor allele as opposed to the melanin.

The wrinkle phenotypes showed the significant increases with aging, but different trends were observed depending on the measuring instruments. The Antera 3D showed the large difference between right eye and glabella areas, but the Primos CR showed similar and stable results between two area. This caused by the different measuring methods and fine-tuning calculation of the two devices [31, 32].

To measure skin oil, we used one instrument (Sebumeter) and measured two variables [33]. Both sebum contents measured in two areas were significantly decreased in the old group. This is the same results of previous studies that reported the decreased amount of sebum secretion as age progresses based on the amount of sebum commonly measured in the forehead, cheek, and chin areas [34-36]. In particular, in the case of women, a report that the sebum secretion decreases rapidly before and after menopause [37, 38], and the same tendency was confirmed in our results. The amount of sebum was reduced by almost half in a group of after the 50 years than the group under the age of 35 years. Additionally, the interaction analysis showed that the right eye area roughness and glabella area sebum level tightly interact between age and OCA2 genotypes.

Conclusively, it is clear that OCA2 gene polymorphism affects to the melanin related phenotypes. Also, the OCA2 variant might affect to wrinkle formation or sebum secretion. We hope that our results

contribute to the future work of prediction for skin aging and developments of personalized solution for skin care.

Limitations

First, the study sample sizes are relatively small to understand the skin phenotypes. Second, we could not validate our results in other replication dataset.

Abbreviations

GWAS: Genome-Wide Association Study

SNP: Single Nucleotide Polymorphism

OCA2: Oculocutaeous albinism 2 gene

Declarations

- **Ethics approval and consent to participate**

All participants provided written informed consent, and this study was approved by the Institutional Review Board of the Theragen Etex Bio Institute (IRB No.: 700062-20190819-GP-006-01).

- **Consent for publication**

All participants provided written informed consent, and this study was approved by the Institutional Review Board of the Theragen Etex Bio Institute (IRB No.: 700062-20190819-GP-006-01).

- **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

- **Competing interests**

There is no Competing interests

- **Funding**

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- **Authors' contributions**

Dasom Lee: Writing the draft manuscript; Jaeun Choi: SNP microarray data generation; Dahyun Park: Statistics; Kyung-Won Hong: Writing the manuscript and correspondances

- **Acknowledgements**

Not applicable

- **Authors' information (optional)**

Not applicable

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Supplementary Files

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- OCA2GGTable210609.pdf