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Expanded Follicle-Sulcus-Crack Complex Is an Early Warning Sign of Facial Skin Aging: Improvement by Application of *Galactomyces* Ferment Filtrate-Containing Skin Product

Kukizo Miyamoto[1*], Bandara Dissanayake[2], Shenal Wanigasekara[1], Keisuke Fujii[1], Xianghong Yan[1], Masutaka Furue[3]

[1]Research and Development, Kobe Innovation Center, Procter and Gamble Innovation GK, Kobe, Japan
[2]Department of Research and Development, Beauty Technology Division, P&G Company, Cincinnati, USA
[3]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Email: *miyamoto.ku@pg.com

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Abstract

Background: Wrinkles, pigmented spots, and roughness are representative parameters reflecting facial skin aging. Sulci cutis connecting to follicular orifices frequently form perifollicular cracks, which join together adjacent sulci. This follicle-sulcus-crack complex (FSCC) is exacerbated by dehydration. **Purpose:** Although dehydration is associated with facial skin aging, FSCC's implications in facial skin aging remain unresolved. **Method:** We measured facial skin parameters in 1999 and 2010 in 108 Japanese women, and in 2006 and 2016 in 182 Chinese women. We addressed whether expansion of FSCC is associated with other skin aging parameters. We also examined whether skin moisturizer can reverse the expanded FSCC. **Results:** In both clinical studies, FSCC severity as well as wrinkles, spots, and roughness significantly deteriorated with age. Notably, FSCC significantly increased as early as in subjects in their 20s, whereas wrinkles, spots, and roughness became conspicuous in those in their 40s or older. Moreover, subjects with more severe FSCC in the initial measurement exhibited significantly worse wrinkles, spots, and roughness in the second measurement a decade later. Dehydration was significantly correlated with expanded FSCC. Furthermore, FSCC expansion was reversed after appropriate moisturization by daily application of *Galactomyces* ferment filtrate (GFF)-containing skincare product (SK-II Skin Power Cream) for 4 weeks in 37 women. **Conclusion**: The expanded FSCC is likely to be an early indicator of facial skin aging. Appropriate moisturization may reduce FSCC formation and decelerate facial skin aging.

Keywords

Facial Skin Aging, Follicle-Sulcus-Crack Complex, Dehydration, Hyperpigmented Spot, Wrinkle, *Galactomyces* Ferment Filtrate

1. Introduction

Aging is the natural fate of all living organisms. Facial skin aging is a major concern of humans, especially women. Deterioration of surface topography and of tonal attributes of facial skin are the most prominent visible features associated with skin aging. Topographical and color information of the face can be classified in terms of several specific features, such as wrinkles, hyperpigmented spots, surface roughness, texture, and pores, which have been measured and quantified by a variety of imaging techniques [1] [2] [3] [4] [5]. The intensity and speed of the aging process differ markedly between individuals and ethnicities [5] [6]. Wrinkles are known to increase more rapidly and more conspicuously in Caucasian than in Chinese women. Meanwhile, hyperpigmented spots are more apparent in Chinese than in Caucasian women [6]. Among various skin aging parameters, wrinkles, hyperpigmented spots, and skin roughness are considered to be particularly representative of an older appearance of the female face [5]. Facial skin aging is also associated with dehydration [5] [7].

SK-II Pitera™ contains *Galactomyces* ferment filtrate (GFF), which works as a potent antioxidative agonist for aryl hydrocarbon receptor [8] [9]. GFF is known to increase the expression of filaggrin, caspase-14, and claudin-1, which may facilitate the production of natural moisturizing factors and strengthen the tight junction structure [8] [10] [11]. GFF also inhibits oxidative stress due to proinflammatory cytokines via activation of the antioxidative system [9] [12]. Several clinical studies have revealed that the daily application of Pitera™ indeed increases the hydration of facial skin [7] [13] [14]. It also alleviates mask-induced skin damage [14] and can effectively reverse facial skin aging after twice-daily application for 12 months [7].

In normal healthy skin, thin sulci cutis connect neighboring follicular orifices, which results in the formation of triangular or rectangular skin areas called cristae cutis [15] [16]. The aging process and subsequent dehydration widen the diameter of follicular orifices and the sulci that connect them [15]. In addition, dehydration frequently induces the formation of perifollicular cracks between adjacent sulci [15]. The expanded follicle-sulcus-crack complex (FSCC) reflects a dendritic contour that may be attributable to visible pores, one of the major concerns in facial cosmetics [13]. Although dehydration worsens with facial aging [5] [7], to the best of our knowledge the implications of FSCC for facial aging have not been evaluated.

In this study, we aimed to elucidate the relationship between FSCC and facial aging in two longitudinal studies and assessed the effects of GFF-containing

skincare product (SK-II Skin Power Cream) on FSCC formation in a third study. We found that the increase of FSCC over a decade was significantly correlated with worsening of facial wrinkles, pigmented spots, roughness, and dehydration in both Japanese (N = 108) and Chinese (N = 182) longitudinal studies. FSCC also significantly increased in the subjects as early as the 20s in both studies, whereas the other skin aging parameters increased conspicuously only in those aged in their 40s or older. By applying treatment with GFF-containing skin moisturizer, FCSS intensity was significantly decreased at weeks 2 and 4. These results indicate that FCSS has potential as an early indicator of facial skin aging, which is improved by appropriate cosmetic moisturization.

2. Materials and Methods

2.1. Subjects in Studies 1 and 2

Skin evaluation was performed in 1999 and 2010 (11 years later) on 108 healthy Japanese females in Study 1, and in 2006 and 2016 (10 years later) on 182 Chinese females in Study 2. The included individuals either worked indoors or were housewives.

In Study 1, the age of the subjects ranged from 5 to 65 years old [mean ± standard deviation (SD), 38.1 ± 16.9] in 1999, and from 16 to 76 years old (49.1 ± 16.9) in 2010. The number of subjects by age group in 2010 was as follows: 8 in their teens (18.3 ± 1.1), 15 in their 20s (23.7 ± 1.9), 13 in their 30s (37.3 ± 2.7), 22 in their 40s (44.2 ± 2.7), 23 in their 50s (55.9 ± 2.6), 14 in their 60s (65.4 ± 1.2), and 13 in their 70s (71.1 ± 1.3) in Study 1.

In Study 2, the age of the subjects ranged from 10 to 66 years old (40.4 ± 14.2) in 2006, and from 20 to 76 years old (50.4 ± 14.2) in 2016. The number of subjects by age group in 2010 was as follows: 20 in their 20s (24.9 ± 2.8), 24 in their 30s (34.3 ± 2.1), 38 in their 40s (45.5 ± 3.0), 43 in their 50s (55.1 ± 2.8), 41 in their 60s (62.8 ± 2.5), and 16 in their 70s (71.9 ± 2.1) in Study 2.

The study protocol was approved by the Ethical Committee of Global Product Stewardship in P&G Innovation Godo Kaisya (ethical approval number CT10-016 for Study 1 and CT16-001 for Study 2). Written informed consent was obtained from all subjects prior to enrollment in the study.

2.2. Facial Optical Imaging

The subjects washed their faces using the prescribed cleansing foam and then spent 20 min becoming accustomed to the environment of the measurement room. The examination room was maintained at a constant temperature and humidity (room temperature 20˚C ± 2˚C, relative humidity 50% ± 5%). None of the subjects underwent any type of esthetic treatment such as laser cosmetic procedures during the study period. Each subject's face was photographed using a portable image capture system (Magic Scan) illuminated by a number of 5600-K light-emitting diodes mounted at both left and right sides of the system (**Figure 1**). A high-resolution complementary-symmetry metal-oxide-semiconductor

Figure 1. Magic Scan facial imaging system. Each subject's face was photographed using Magic Scan.

digital camera, capable of generating 1980 (vertical) × 1024 (horizontal) effective picture elements (pixels), was also mounted in the imaging module. A series of deep-learning-based post-calibration algorithms was carried out to ensure the consistent brightness, hue, and saturation after capturing the facial images. This enabled the captured images to be controlled to ensure reproducible collection under the different external optical conditions. A neutral 8.0 gray color board (GretagMacbeth GmbH, Munich, Germany) was used for white balancing of the camera.

2.3. Objective Image Analysis for Wrinkles, Hyperpigmented Spots, Roughness, and Redness

The region of interest (ROI) of the images was from the outer edge of the eye to the cheek, and the following characteristic parameters od aging were extracted by measuring the contrast in the shape and pixels using an image analysis algorithm [5] [7]. Wrinkles were defined as ≥ 5 mm in length, perimeter/length ratio ≤ 2.5, and circularity (perimeter^2/area) ≥ 34. Total wrinkle area fraction was quantified as follows: total wrinkle area (pixels)/ROI (pixels). Pigmented spots were defined as ≥ 5 mm^2 in area, color contrast deltaE ≥ 3 compared with the surrounding skin region, and circularity (perimeter^2/area) ≥ 20. Total pigmented spot area fraction was also quantified as follows: total hyperpigmented area (pixels)/ROI (pixels). As an index of skin surface roughness, total texture area fraction [total texture area (pixels)/ROI (pixels)] was quantified as ≤ 3 mm^2 in area, aspect ratio ranging from 0.5 to 2, and color contrast deltaE ≥ 1.5. Facial skin redness (a-value) was also measured in the ROI. The mean values of the resulting data obtained by these evaluations were analyzed.

2.4. Objective Image Analysis for FSCC

FSCC was defined as a complex area composed of 1) follicular orifices, 2) sulci

cutis connecting to follicular orifices, and 3) at least one perifollicular crack joining up with adjacent sulci. To identify FSCC, a histogram-equalized image was filtered by fast Fourier transformation to remove one or more skin features (e.g., pigmented spots and moles). Then, skin feature segmentation was performed to extract images of follicles with one or more of the following features: threshold follicle area major diameter (200 - 1000 μm), width/length aspect ratio (0.3 - 1), and redness (a-value) contrast of more than 1.5 units compared with the surrounding skin. In the same manner, crack-sulcus images were also extracted with one or more of the following line geometry threshold parameters: line thickness (35 μm to 1 cm), line length (250 μm to 2 cm), and redness (a-value) contrast of more than 1.5 units compared with the surrounding skin. Finally, the follicle image and the crack-sulcus image were overlaid to identify FSCC (**Figure 2**). Total FSCC area fraction was quantified from the obtained overlaid image as follows: total FSCC area (pixels)/ROI (pixels). Skin hydration (water content) was measured using Corneometer1 (Courage + Khazaka Electronic GmbH, Cologne, Germany) [5] [7].

2.5. Subjects and Study Protocol in Study 3

To evaluate whether skin moisturizer can affect FSCC and other facial skin aging parameters, we enrolled 37 Japanese female volunteers aged 22 to 55 (39.6 ± 11.3) years old in Study 3. During Study 3, 0.6 mL of a skin moisturizer containing GFF (SK-II Skin Power Cream) was applied to the face of each subject twice daily, in the morning and in the evening. Skin measurements were performed at the start of the study (baseline), on day 14, and on day 28. The study protocol was approved by the Ethical Committee of Global Product Stewardship in P&G Innovation Godo Kaisya (ethical approval number CT21-010). Written informed consent was obtained from all subjects prior to enrollment in the study.

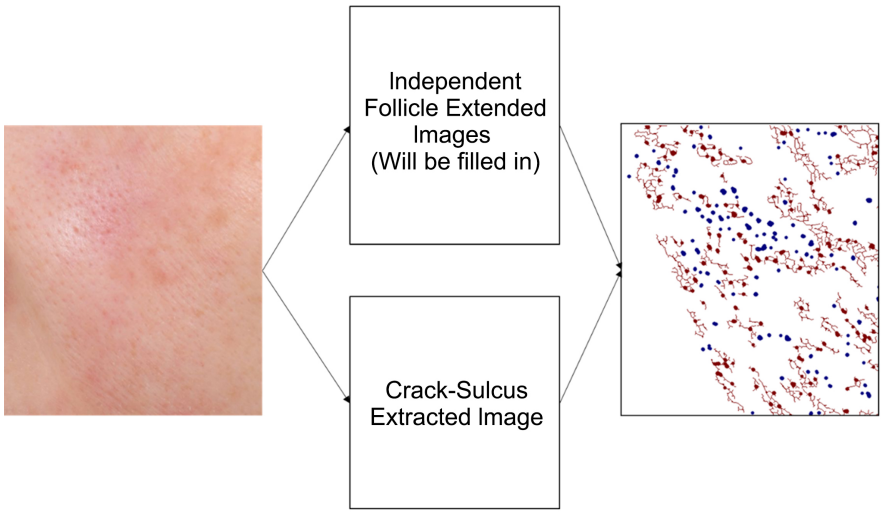

Figure 2. Measurement of FSCC. From an original skin image (left), independent follicle extracted image and crack-sulcus extracted image were obtained. FSCC was defined by the overlay image (right). Blue color: follicular orifices. Red color: FSCC.

2.6. Statistical Analysis

All statistical analyses were performed using JMP® Pro 16.1.0 (SAS Institute Inc., Cary, NC, USA). For each outcome variable, data were analyzed by fitting a linear mixed-effects model with time point as the fixed effect and subject as the random effect to account for within-subject variation. Pearson's correlation coefficients (r) between the following variables were examined: 1) between the changes of four skin optical and physical parameters (image analysis data on wrinkles, pigmented spots, roughness, and hydration) from 1999 to 2019 and the change of FSCC from 1999 to 2010 in Study 1; and 2) between the changes of four skin optical and physical parameters (image analysis data on wrinkles, pigmented spots, roughness, and hydration) from 2006 to 2016 and the change of FSCC from 2006 to 2016 in Study 2. Quantitative comparisons were also performed for the following variables: 1) those skin parameters (image analysis data on FSCC, wrinkles, pigmented spots, roughness, and hydration) in 1999 versus those in 2010 in Study 1; 2) those skin parameters in 2006 versus those in 2016 in Study 2; 3) those skin parameters among the age groups of teens versus 20s, 20s versus 30s, 30s versus 40s, 40s versus 50s, and 50s versus 60s in 1999 in Study 1 and in 2006 in Study 2, using two-way ANOVA. Quantitative comparisons were also carried out for the following variables: 1) four skin optical and physical parameters (image analysis data on wrinkles, pigmented spots, roughness, and hydration) in 2010 between high- and low-FSCC groups in 1999 in Study 1; 2) those four skin parameters (image analysis data on wrinkles, pigmented spots, roughness, and hydration) in 2016 between high- and low-FSCC groups in 2006 in Study 2; and 3) the skin hydration, FSCC, and wrinkles after 2 and 4 weeks of treatment with GFF-containing formula (SK-II Skin Power Cream) versus baseline in Study 3 using two-way ANOVA. A P-value less than 0.05 was considered to reflect statistical significance.

3. Results

We measured six facial skin parameters (FSCC, wrinkles, pigmented spots, roughness, hydration, and redness) in 1999 and 2010 in Study 1 (N = 108, Japanese, Table 1) and in 2006 and 2016 in Study 2 (N = 182, Chinese, Table 2).

In initial measurements (1999) in Study 1, FSCC, wrinkles, pigmented spots, and roughness showed stepwise and significant increases with increasing age (Figure 3).

A significant and stepwise decrease of facial skin hydration was also observed (Figure 3). Notably, a significant increase of FSCC was detected in subjects as young as their 20s compared with that in those aged 10 - 19, whereas increases of wrinkles, pigmented spots, and roughness only became obvious in subjects in their 40s or older (Figure 3). Similar observations were confirmed in the initial measurement (2006) in Study 2 (Figure 4).

Significant increases in FSCC, wrinkles, pigmented spots, and roughness, along with a decrease in hydration, were observed with increasing age in Study 2

(Figure 4). Again, significant expansion of FSCC was detected in subjects in their 20s compared with those aged 10 - 19 in Study 2 (Figure 4). These results suggested that FSCC is a potential parameter representing the early facial aging process that appears in those in their 20s.

Table 1. Chronological measurement of six facial skin parameters in 1999 and 2010 in Study 1 (N = 108 Japanese females).

	Age	FSCC	Wrinkles	Pigmented Spots	Roughness	Hydration	Redness
1999	38.059 ± 16.866	44.044 ± 5.433	45.444 ± 6.185	18.120 ± 9.040	25.725 ± 10.556	56.712 ± 7.109	12.551 ± 1.945
2010	49.059 ± 16.866	47.355 ± 5.932	48.501 ± 7.051	31.71 ± 17.183	33.415 ± 16.918	47.755 ± 8.684	12.429 ± 1.535
Δ2010-1999	11.000	3.351 ± 5.268	3.057 ± 6.844	13.59 ± 13.355	7.71 ± 13.338	−8.955 ± 7.774	−0.122 ± 1.501
Sig.	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P = 0.826

Table 2. Chronological measurement of six facial skin parameters in 2006 and 2016 in Study 2 (N=182 Chinese females).

	Age	FSCC	Wrinkles	Pigmented Spots	Roughness	Hydration	Redness
2006	40.346 ± 14.198	45.444 ± 6.185	18.120 ± 9.040	25.689 ± 10.552	26.232 ± 11.411	54.182 ± 11.312	14.652 ± 2.322
2016	50.346 ± 14.198	48.501 ± 6.911	31.713 ± 17.180	33.410 ± 16.918	36.680 ± 18.422	45.628 ± 9.933	15.045 ± 3.186
Δ2016-2006	10.000	3.057 ± 6.918	13.590 ± 15.869	7.71 ± 14.881	10.48 ± 13.520	−10.554 ± 10.635	0.393 ± 2.699
Sig.	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P = 0.045

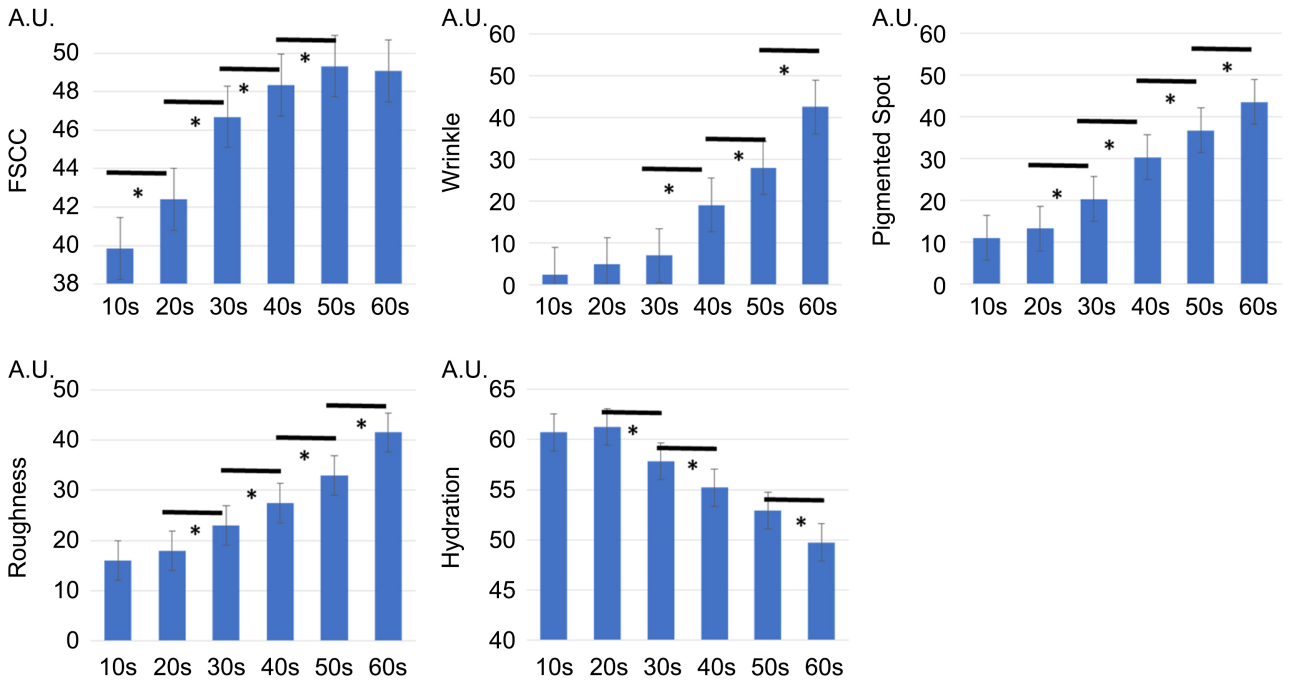

Figure 3. Facial aging parameters in different age groups in 1999 in Study 1. *P < 0.05.

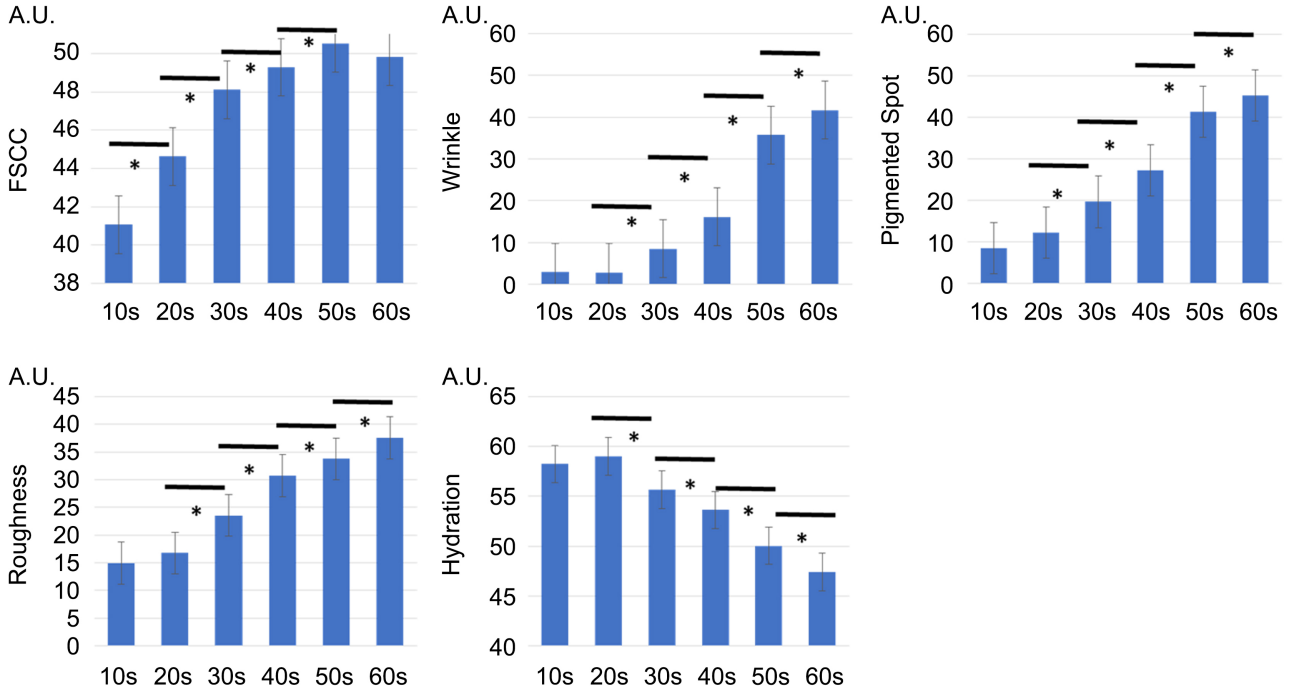

Figure 4. Facial aging parameters in different age groups in 2006 in Study 2. *P < 0.05.

To investigate whether FSCC actually increased with aging in individuals, we conducted a second measurement in 2010 (11 years later) in Study 1 and in 2016 (10 years later) in Study 2. In both studies, a significant increase in FSCC was confirmed with aging (Table 1 and Table 2). Other facial aging parameters, namely, wrinkles, pigmented spots, and roughness, were also significantly aggravated a decade after the initial measurement (Table 1 and Table 2). A significant decrease of facial skin hydration was also found in both Study 1 and Study 2 (Table 1 and Table 2). In contrast, redness was not a suitable marker for facial skin aging because its changes between initial and second measurements were not significant (Table 1) or minimal (Table 2).

We next analyzed whether change of FSCC is correlated with changes of other parameters between initial and second measurements in the individual aging process. Notably, change of FSCC was significantly correlated with changes of wrinkles ($r = 0.385$, $P < 0.05$), pigmented spots ($r = 0.420$, $P < 0.05$), and roughness ($r = 0.393$, $P < 0.05$) in Study 1 (Figure 5). A negative correlation was also observed between change of FSCC and change of hydration ($r = -0.246$, $P < 0.05$) in Study 1 (Figure 5).

Similar results were also evident in Study 2 (Figure 6).

The change of FSCC was significantly correlated with the changes of wrinkles ($r = 0.406$, $P < 0.05$), pigmented spots ($r = 0.429$, $P < 0.05$), and roughness ($r = 0.389$, $P < 0.05$) in Study 2 (Figure 6). The change of FSCC was again negatively correlated with the change of hydration ($r = -0.381$, $P < 0.05$) in Study 2 (Figure 6). These results indicated that FSCC is a crucial parameter for facial aging in concert with wrinkles, pigmented spots, roughness, and dehydration.

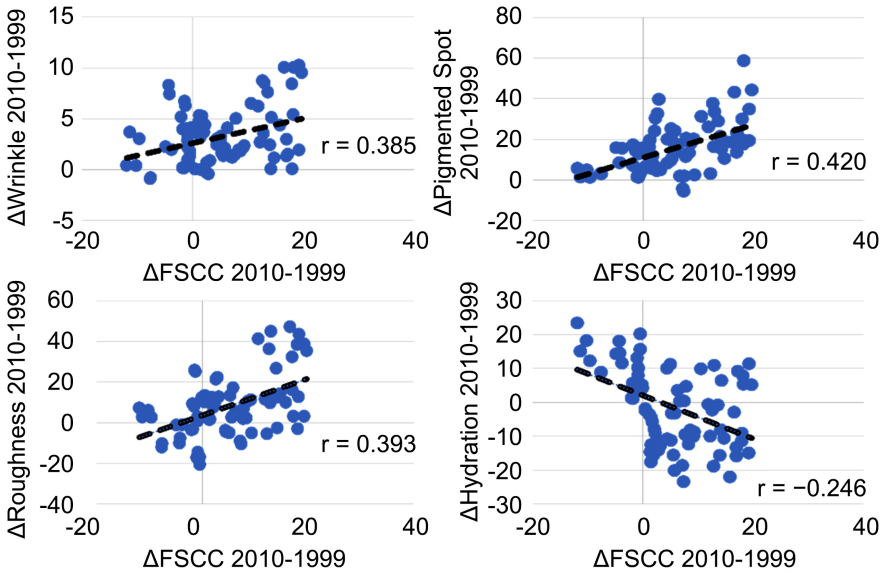

Figure 5. Correlations of change of FSCC with changes of wrinkles, pigmented spots, roughness, and hydration between 2010 and 1999 in Study 1.

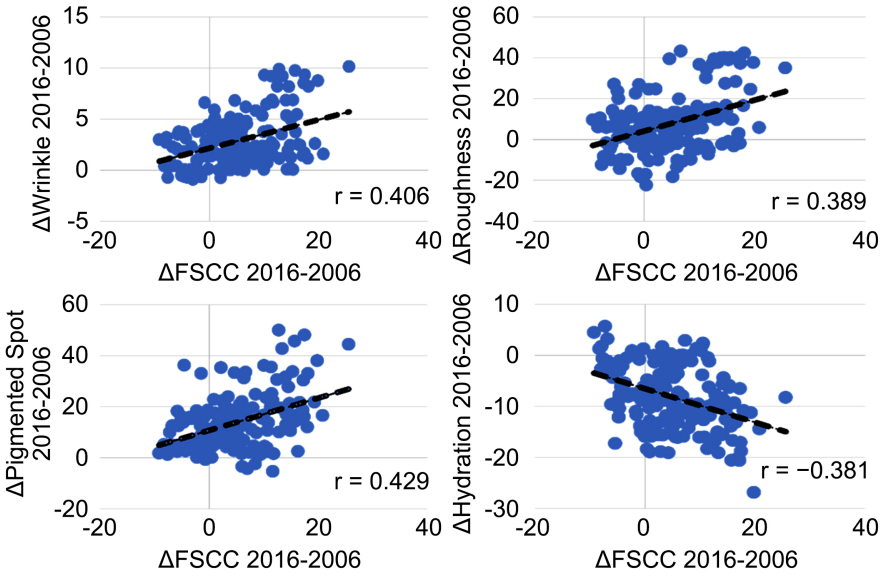

Figure 6. Correlations of change of FSCC with changes of wrinkles, pigmented spots, roughness, and hydration between 2016 and 2006 in Study 2.

We next addressed whether increased FSCC in early life (10 to 39 years old) is predictive of faster facial aging. We focused on the subjects aged 10 to 39 in Study 1 (N = 47) and Study 2 (N = 82). As expected, subjects with high FSCC (above median value) in the initial measurement (1999) showed significant increases in wrinkles, pigmented spots, and roughness in the second measurement (2010) compared with those with low FSCC in 1999 in Study 1 (**Figure 7**). In contrast, the high-FSCC group exhibited significantly decreased hydration compared with the low-FSCC group in Study 1 (**Figure 7**).

Similar results were obtained in Study 2 (**Figure 8**).

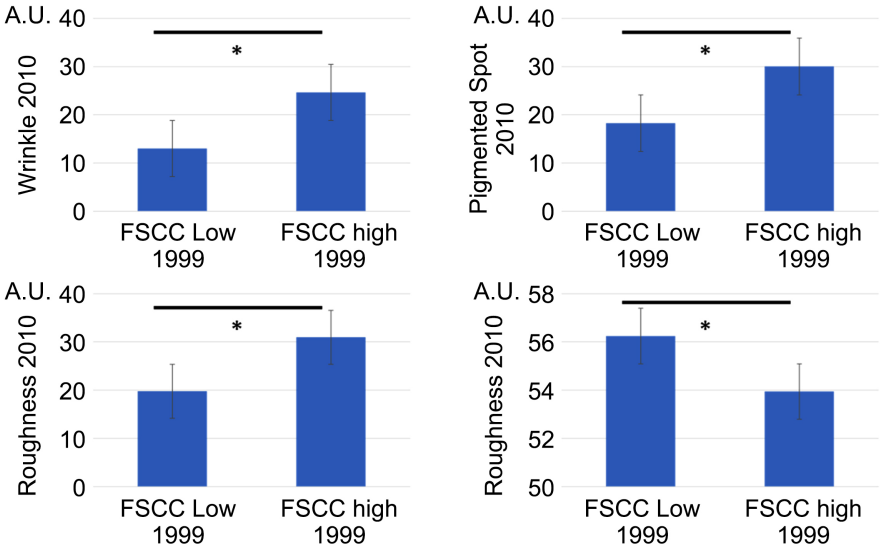

Figure 7. Subjects with high FSCC in 1999 showed significantly worse wrinkles, pigmented spots, roughness, and hydration in 2010 than those with low FSCC in 1999 in Study 1. The median value of FSCC in 1999 was used to divide the high- and low-FSCC groups. Subjects aged 10 to 39 in 1999 in Study 1 were analyzed (N = 47). *P < 0.05.

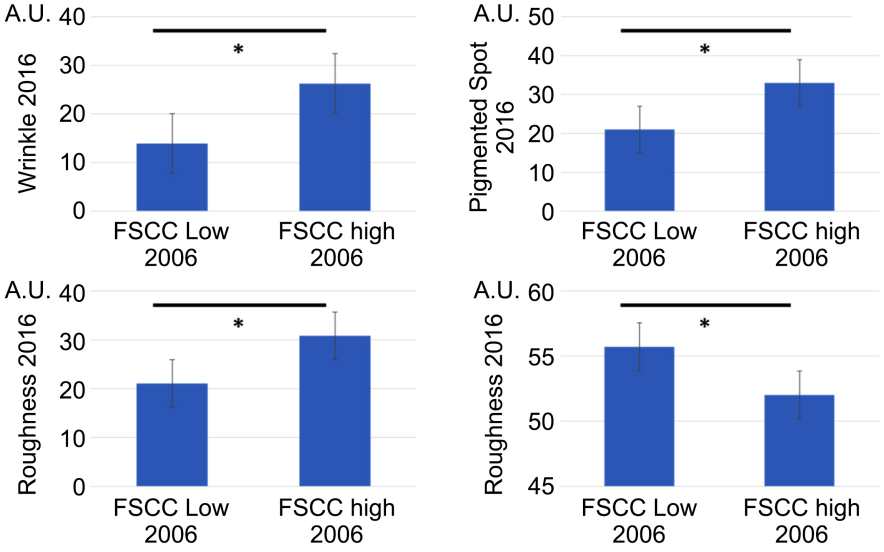

Figure 8. Subjects with high FSCC in 2006 showed significantly worse wrinkles, pigmented spots, roughness, and hydration in 2016 than those with low FSCC in 2006 in Study 2. The median value of FSCC in 2006 was used to divide the high- and low-FSCC groups. Subjects aged 10 to 39 in 2006 in Study 2 were analyzed (N = 82). *P < 0.05.

Subjects with high FSCC (above the median value) in the initial measurement (2006) also showed significant increases in wrinkles, pigmented spots, and roughness in the second measurement (2016) compared with those with low FSCC in 2006 in Study 2 (**Figure 8**). Again, the high-FSCC group exhibited significantly decreased hydration compared with the low-FSCC group in Study 2 (**Figure 8**). These results reinforced the possibility that FSCC could be useful as a warning sign of facial skin aging in young people aged under 40.

As the change of FSCC was significantly correlated with the change of dehydration, we next examined whether appropriate moisturization with a GFF-containing skincare product can decrease FSCC in Study 3. Thirty-seven females applied the GFF-containing skincare moisturizer twice daily for 4 weeks, on whom skin measurements were conducted before application (baseline), and after 2 and 4 weeks of application (Table 3). Application of the GFF-containing skincare product significantly improved skin hydration (Table 3, Figure 9).

Notably, FSCC values were significantly decreased after 2 weeks and more clearly after 4 weeks of application, in association with a significant reduction of wrinkles (Table 3, Figure 9). Clinical images of two representative cases are presented in Figure 10.

We also addressed the relationship between change of hydration and change of FSCC in Study 3. As shown in Figure 11, the change in hydration (4 weeks - baseline) by the GFF-containing skincare product was significantly negatively correlated with the change in FSCC (4 weeks - baseline) ($r = -0.379$, $P < 0.05$). These results further support the existence of a crucial correlation between dehydration and dilated FSCC.

Table 3. Skin aging parameters before and after treatment with GFF-containing skin moisturizer (N = 37).

	Hydration	FSCC	Wrinkles
Baseline	39.714 ± 12.154	41.4345 ± 6.197	23.018 ± 8.330
Week 2	48.291 ± 9.814 (P<0.05)	39.344 ± 8.265 (P<0.05)	18.751 ± 7.599 (P<0.05)
Week 4	49.672 ± 10.088 (P<0.05)	36.213 ± 5.214 (P<0.05)	17.816 ± 6.027 (P<0.05)

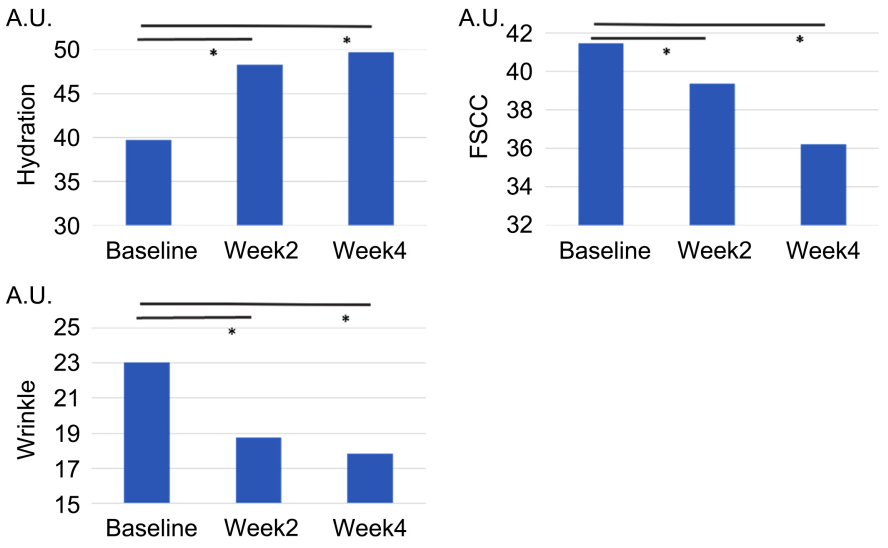

Figure 9. Application of GFF-containing skincare product and skin parameters (N = 37). Significant improvements in hydration, FSCC, and wrinkles were observed. *P < 0.05.

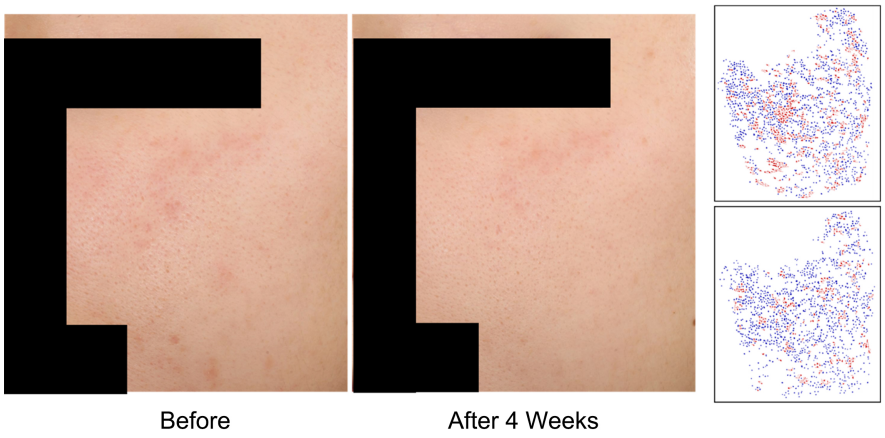

Figure 10. Clinical images of case 1 in Study 3. FSCC as depicted by a red line was markedly decreased by 4 weeks of application of GFF-containing skin moisturizer (SK-II Skin Power Cream).

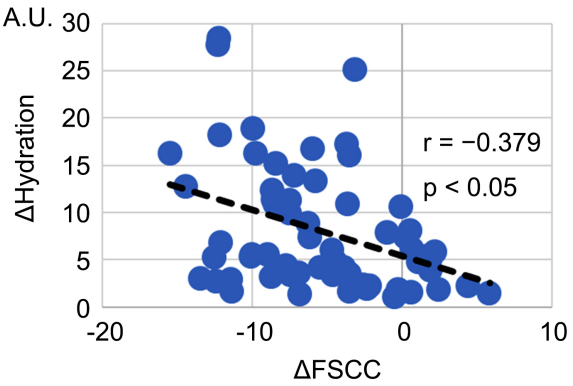

Figure 11. Negative correlation between change of skin hydration (4 weeks - baseline) and change of FSCC (4 weeks - baseline) during Study 3.

4. Discussion

Facial skin aging is an important psychosomatic concern. Physiological or chronological aging starts just after birth and is accelerated by various external stresses such as ultraviolet radiation, environmental pollutants, and mechanical stress [17] [18]. Over the course of natural aging, facial skin gradually acquires signs of aging including wrinkles, pigmented spots, roughness, and decreased elasticity due to dermal collagen damage, skin barrier dysfunction, melanin metabolism and so on [5] [19] [20] [21] [22]. Although these parameters well represent facial skin aging, they become conspicuous only in those aged 40 or above [5] [17]-[22].

In the present study, we conducted two longitudinal studies enrolling Japanese and Chinese volunteers. In both studies, we found that the expansion of FSCC was a valuable marker of facial skin aging. Change of FSCC was significantly correlated with changes of wrinkles, pigmented spots, and roughness. High degree of FSCC accelerated those skin aging parameters in next decade about 1.6 times higher than low degree of FSCC. Notably, the findings showed

that expansion of FSCC could become evident at an age as young as the 20s.

Dehydration was significantly associated with enlarged FSCC in the present study. Therefore, we examined whether the daily application of a GFF-containing skincare product for 4 weeks could reduce the FSCC values. The FSCC intensity was significantly reduced even after 2 weeks of application of the GFF-containing skincare product. The reduction of FSCC was significantly correlated with the recovery from dehydration. Maintaining lower FSCC by GFF-containing skincare product may sustain skin youth (ageless condition).

The face is a unique part of the human body rich in hair follicles. Follicular orifices are packed with cornified and sebaceous debris containing various microbial organisms, which are potential natural sources of subclinical inflammation. Follicular orifices and connecting sulcus structures are also known to be susceptible to dehydration [15]. Dehydration widens orifices and sulci and induces perifollicular cracks, which eventually result in FSCC formation. Expanded orifices and sulci may harbor more microorganisms, which may facilitate inflammaging [23] [24] [25]. Skin care with appropriate moisturization is currently not typically performed by young people aged 10 - 19. Therefore, this age group can readily suffer from facial dehydration, which would facilitate the formation of FSCC.

A potent moisturizing effect of GFF-containing skincare product was proven in previous clinical studies [7] [13] [14]. In the present study, this product also significantly improved facial dehydration after as little as 2 weeks of its application. GFF is known to activate aryl hydrocarbon receptor and upregulate the expression of skin barrier-related proteins [8] [9] [10] [11]. It also activates the cellular antioxidative system and alleviates oxidative stress [9] [12]. In addition, GFF increases the production of interleukin-37, which inhibits the expression of proinflammatory cytokines in keratinocytes [26]. These various beneficial properties of GFF may facilitate its moisturizing and anti-inflammaging effects [25] [27].

Limitations of this study include a lack of understanding of the precise mechanisms by which the expansion of FSCC occurs. Further longitudinal prospective placebo-controlled study is necessary to elucidate whether the GFF-containing skincare product is capable of decelerating the long-term aging process.

In conclusion, the expansion of FSCC is a potential indicator of facial skin aging for individuals in their 20s. The GFF-containing skincare product can reverse the dilation of FSCC upon its application for 2 or 4 weeks. Continuous application of GFF-containing skincare products by those in their 20s onwards may contribute to maintaining a youthful facial appearance.

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Conflicts of Interest

Masutaka Furue is a consultant of P&G Innovation GK. The other authors are employees of P&G Innovation GK.

Author Contributions

Conceptualization and clinical investigation were performed by K.M., B.D., S.W., and K.F., K.M., X.Y., and M.F. wrote the first draft of the manuscript, while all authors revised it. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

This study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by P&G Ethics Committee. Data acquisition and analysis were performed in compliance with protocols approved by the Ethical Committee of Global Product Stewardship in P&G Innovation Godo Kaisya (ethical approval numbers CT10-016, CT16-001, and CT21-010). Written informed consent was obtained from all participants prior to inclusion in the study.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this paper are available on request from the corresponding author. The data are not publicly available because of privacy restrictions.

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