Journal of Clinical & Experimental Dermatology Research

Garoia et al., J Clin Exp Dermatol Res 2018, 9:6
DOI: 10.4172/2155-9554.1000472

Research Article Open Access

Genetic Signature of Skin Aging: A Pilot Study

Flavio Garoia[1], Ester Del Duca[2*], Raffaella Cascella[3], Emiliano Giardina[3], Ugo Bottoni[4], and Steven Paul Nisticò[4]

[1]*Genetic Unit, MDM Group, Bologna, Italy*

[2]*Department of System Medicine, Unit of Dermatology, University of Tor Vergata, Rome, Italy*

[3]*Department of Biomedicine and Prevention, Laboratory of Medical Genetics, University of Tor Vergata, Rome, Italy*

[4]*Department of Health Science, University of Catanzaro, Italy*

[*]**Corresponding author:** Ester Del Duca, Department of System Medicine, Unit of Dermatology, University of Tor Vergata, Rome, Italy 00133, Rome, Italy, Tel: 320 3163921; Fax: 3203163921, E-mail: ester.delduca@gmail.com

Received date: September 20, 2018; **Accepted date:** October 02, 2018; **Published date:** October 10, 2018

Abstract

Genetic risk assessment is becoming an important component of clinical decision-making. Recent research has focused attention on the single nucleotide polymorphisms (SNPs) involved in the aging process. The aging process is a complex interaction of genetic and environmental factors. To evaluate the contribution of individual genetic variability to skin aging we combine the relatively small effects of individual genes in a multi locus genetic risk score (GRS). This study aims to evaluate whether the genetic risk score may be linked to the evolution of skin properties and provide personalized skin care and anti-age treatments.

A GRS was calculated using an additive model, based on the genotype analysis of 8 selected SNPs potentially associated with skin aging. One hundred patients were genotyped, tested for skin properties (elasticity, stratum corneum thickness, H2O content) and subjected to a questionnaire to evaluate sun exposure. ANCOVA analysis was performed to evaluate qualitative and quantitative explanatory variables. Once all the variables were taken in account, we found a significant correlation between GRS and elasticity and the thickness of the stratum corneum (SCT) suggesting that the combination of genetic signature, environmental and lifestyle information may provide a useful tool for personalized and more effective anti-aging therapies.

Keywords: Genetic risk score; Aging skin; Stratum corneum; SNPs; Skin elasticity

Introduction

The increasing knowledge of the genetic bases of several common multifactorial diseases paves the way to personalized medicine that means preventive and therapeutic interventions that are tailored to individuals on the basis of their genetic profiles. Despite the controversial predictive value of genetic testing in multifactorial diseases, an increasing number of companies are offering personalized lifestyle and health recommendations on the basis of individual genetic traits. These commercial developments are attracting increasing interest from consumers and health care professionals, asking for a solid evidence base for genomics applications. One of the major challenges in the next years will be to investigate the translation of this emerging genomic knowledge into medical care.

The aging process, as well as multifactorial diseases, depends on a complex crosstalk between intrinsic (genetic and hormonal) and extrinsic (nutrition, lifestyle etc.) factors. Skin changes are the most visible signs of senescence process, and a field of increasing interest in a society that places more and more interest in appearance and beauty. The interaction between intrinsic and extrinsic factors induces changes in biochemical properties that cause skin decay. Significant structural alteration that cause this process are loss of elasticity due to the degeneration of extracellular matrix and changes in skin water content, thinning of epidermal layer and thickening of the stratum corneum due to the increase of terminal differentiation of keratinocytes [1,2].

Studies on twins show that the genetic component of skin deterioration process accounts for about 60% [3]. Among non-genetic factors, sun exposure is the environmental factors of major importance for premature skin wrinkling or facial aging [4]. On the other hand gender and ethnicity are additional factors to take in account to evaluate the variables that influences skin aging [5,6]. Sun exposure interacts with skin properties modifications increasing oxidative stress processes [7]. A major consequence of oxidative stress is the damage to nucleic acid bases, lipids, and proteins, which can severely compromise cell health and viability. In model systems, this process has been showed to lead to accelerated aging phenotypes and cellular senescence of skin [8]. The process of skin aging also results in an increase of inflammatory cytokines, which are responsible for many of the degenerative diseases associated with aging [9]. Oxidative stress is related to systemic inflammation, which in turn impair cell aging processes [10].

In recent years, research has focused its attention on the role of genes and their variants, in particular single nucleotide polymorphisms (SNPs), in relation to individual susceptibility to complex diseases. Genetic polymorphisms might provoke a change in the protein or its expression, resulting in alterations in metabolic function. These genetic variants may sometimes be responsible for an unfavorable outcome of a disease, whereas it may also be protective for such pathology. An excellent example of complex disorder that reveals the interactions between genetic (susceptibility gene or variants) and environmental (geographic localization, skin phenotype, exposure, latitude, UV incidence, lifestyle) factors may be the Atopic Eczema (AE, OMIM 603165). AE is the most common chronic inflammatory

skin disease characterized by increased trans-epidermal water loss (TEWL) and skin barrier abnormalities and disruption. On this subject, numerous environmental events (chemical injuries, traumatic wounds, UV exposure) and genomic characteristics can compromise the barrier activity. To date, the mutational spectrum of FLG gene comprises different variations that show an ethno-specific distribution profile, especially among north European and Mediterranean populations. On this subject, the notable variability of FLG variants between European and Mediterranean populations might reflect the influence of the different UV exposure with respect to the geographic localization [11,12].

To combine the relatively small effects of individual SNPs and to better capture the complex relationships between genetics and complex disease, the use of multilocus genetic risk score has been proposed [13]. In fact, several studies demonstrated that the aggregation of the contribution of multiple SNPs, selected from both candidate genes and genes identified through large scale genomic association studies, into a single genetic risk score (GRS) significantly increases the prediction power of the susceptibility to develop complex diseases like cardiovascular disease, type II diabetes, periodontitis or psoriasis [14-17]. Despite the fact that studies have greatly expanded the discovery of genetic markers associated with several complex diseases, there are no studies which evaluate a genetic risk score for skin aging. The aim of this study is to determine the clinical utility of a GRS to estimate the individual susceptibility to skin aging factors. To this end, we concentrated on 8 loci previously reported to have an association with alteration of skin properties and individual response to inflammation and oxidative stress. Identification of the definitive set of SNPs for inclusion in a GRS was not the primary aim of this work, however this pilot study was drawn up with the aim to evaluate whether genetic risk score may increase the prediction of skin aging risk and support the development of personalized aesthetic treatments.

Methods

Study design

The study was conducted in 100 Italian volunteers, with an age between 21 and 66 years old (23 males and 77 females). All selected patients were Caucasian (people with European origin), belonging to Fitzpatrick skin type 2 and 3. Subjects underwent medical history and clinical examination; exclusion criteria included systemic diseases or presence of genetic diseases which were clinically evident. All patients signed written informed consent. The examination of each subject was conducted using a lifestyle questionnaire and, to evaluate the impact of lifetime sun exposure (LSE), using the Sun Exposure and Behavior Inventory (SEBI).

Genetic marker selection

The 8 single nucleotide polymorphisms that make up the genetic risk scores tested were selected on the basis of their involvement in aging factors as previously described in literature. The selected SNPs were COL1A1 rs1800012, involved in the type I collagen turnover, MMP3 rs3025058, that influences the breakdown of extracellular matrix and tissue remodeling; ELN rs2071307, that affects assembly and mechanical properties of the elastic matrix; CAT rs1001179, GPX rs1050450 and MnSOD2 rs1799725, that influence individual antioxidant capacity; IL-1B rs1143634 and TNF-A rs1800629 that modulates anti-inflammatory response [18-22].

Genotype identification

Total DNA was isolated from epithelial oral cells by a masked operator. DNA extraction from buccal swabs was performed using the Sample-to-SNP Kit (Applied Biosystems), following manufacturer's instructions. Genetic determination of was performed by Real Time-PCR method. SNP-specific primers and probes were designed according to the TaqMan genotyping assay by Applied Biosystems, and assays were performed in 25 ml total volume on Stratagene MX3000P following manufacturer's instructions.

The genetic risk score (GRS)

The genetic risk score was calculated using an additive model. In order to combine the effects of all SNPs, risk alleles were counted and used as a sum score [23]. The risk score was calculated for each gene considering the variability of a single or both nucleotides, as follows:

- 1-no risk alleles
- 0,1-risk allele
- 1,2-risk alleles

On this basis, in this study the genetic risk factor may assume a variable value between -8 and 8, where -8 indicates a low genetic predisposition and 8 a high level of susceptibly to aging.

Skin properties measurement

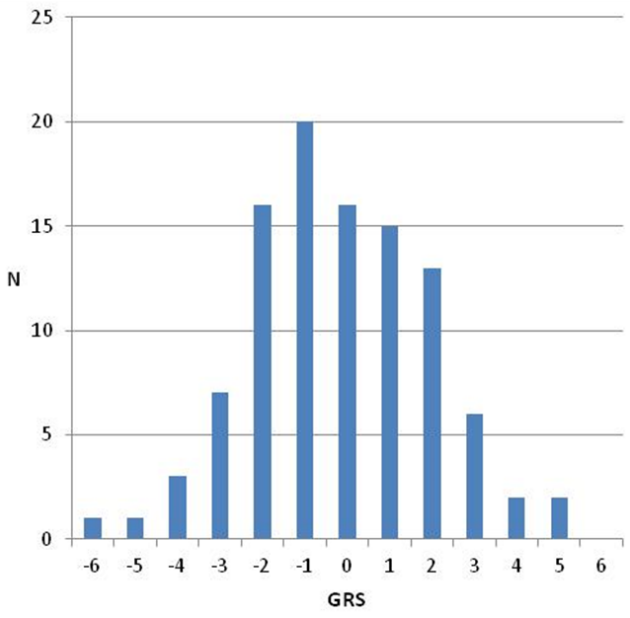

Figure 1: GRS distribution in the analyzed sample.

Skin properties measurement (Figure 1) was taken using a Skin Tester Device (Selenia, Italia). Skin Tester uses ultrasound densitometry for the investigation and the measurement of facial skin properties: elasticity, H2O content and SCT. Skin Tester also uses principles of classical impedenziometry for the determination of the water content. An ultrasound emitted beam is reflected by the dermal tissues, according to its stromal density and vascular tone. Furthermore, impedance variation as related to intracellular and interstitial water content and photoplethysmography, a reflectometric

method to evaluate vascular network dynamics, are encompassed by the diagnostic device. Therefore, total, extracellular and intracellular water can be detected. The device analyses a number of parameters and it has been used to monitor pre- and post-treatment variations [24].

Statistical analysis

Power analysis for multiple regression showed that the number of cases analyzed, with an anticipated effect size (f2) of 6.69, 8.11 and 15.6 (for elasticity, H2O content and SCT respectively), 5 predictors, probability level of 0.01 is sufficient to give a statistical power of more than 90%. The analysis was done using the G*Power software [25,26]. Correlation tests (Pearson Coefficient) and ANCOVA analysis were performed using XLSTAT *vs.* 2015 (Addinsoft) for Windows. Box-Cox transformation implemented in XLSTAT was used to transforms non-normally distributed data to a set of data that has normal distribution.

Results

Genotypic frequencies of the 8 SNPs in the sample population are shown in Table 1. The GRS value may vary from -8 to 8, even if we found no subjects with -8, -7, 6, 7, 8 GRS values. The GRS distribution in our sample is showed in Figure 1. We analyzed the correlation between skin properties measurements (elasticity, SCT, H2O content), and the results show a strong significant positive correlation between H2O content and elasticity, and a strong negative correlation between SCT and elasticity as well between SCT and H2O content (Table 2). The primary aim of this study is the evaluation of the contribution of individual genetic variability to skin aging. The aging process depends on a complex crosstalk between intrinsic and extrinsic factors then, to evaluate the influence of quantitative (GRS, age, LSE) and qualitative variables (gender) on skin properties (SCT, elasticity and H2O content) we use the Analysis of Covariance (ANCOVA).

COL1A1	**rs1800012**	**MMP3**	**rs3025058**	**ELN**	**rs2071307**	**CAT**	**rs1001179**
GG (-1)	59%	TT (-1)	0%	GG (-1)	42%	AA (-1)	6%
GT (0)	33%	T- (0)	82%	AG (0)	44%	AG (0)	36%
TT (1)	8%	-(-1)	18.00%	AA (1)	14%	GG (1)	6%
GPX	**rs1050450**	**MnSOD2**	**rs1799725**	**IL-1B**	**rs1143634**	**TNF-A**	**rs1800629**
CC (-1)	43%	TT (-1)	24%	CC (-1)	63%	AA (-1)	0%
CT (0)	50%	CT (0)	51%	CT (0)	32%	AG (0)	12%
TT (1)	7%	CC (-1)	25%	TT (1)	5%	GG (-1)	88%
Note: GRS score for each genotype is indicated in parenthesis.							

Table 1: SNPs and variant frequencies in the sample population.

	Elasticity	SCT	H2O content
Elasticity	/	-0.957*	0.391*
SCT		/	-0.493*
H2O content			/
*Values are significant at P<0.001.			

Table 2: Correlation values between skin parameters.

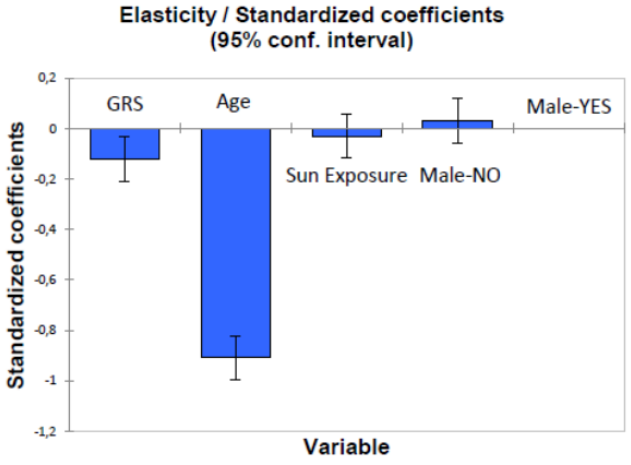

Figure 2: ANCOVA analysis of correlation between skin aging variables and elasticity.

Individual genetic variability, measured as GRS index, significantly affect skin elasticity (Figure 2) and SCT (Figure 3), whereas regarding the H2O content the P value did not quite achieve the threshold for statistical significance (p=0.061, Figure 4). For elasticity and SCT, age is the variable that most heavily influences skin properties (Figures 2 and 3) whereas gender (female) is significantly correlated with SCT and H2O content (Figures 3 and 4). The impact of lifetime sun exposure (LSE), measured using the Sun Exposure and Behavior Inventory (SEBI), was found no significant for all the measured skin properties (Figures 2-4).

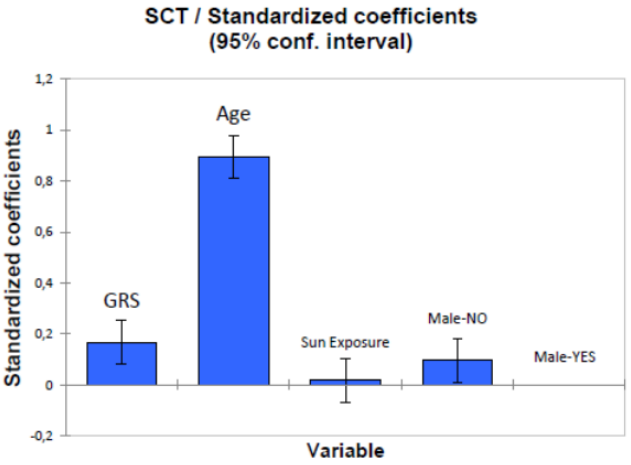

Figure 3: ANCOVA analysis of correlation between skin aging variables and SCT.

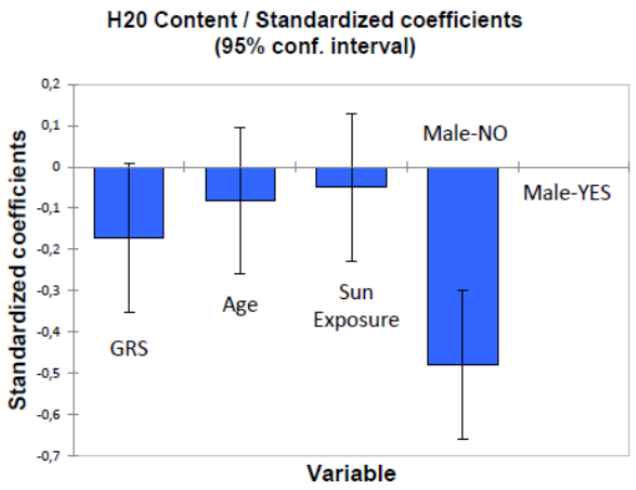

Figure 4: ANCOVA analysis of correlation between skin aging variables and H2O content.

Discussion

The aging process, as we know it today, is influenced by environmental factors as well as genetic factors. A large number of studies have investigated the relationship between genetic polymorphisms and aging factors. Their results showed clearly that most genes involved in aging process are linked to collagen turnover, tissue structure and remodeling, hydration, inflammation and antioxidant capacity [27]. However, it should be emphasized that most of these studies show inconclusive correlations between the presence of aging markers and the tested single nucleotide polymorphisms [28].

For the aging process, like to multi-factorial and polygenic diseases, is known that single genetic polymorphism has only a modest effect since the interaction of each gene and its polymorphism with other ones (gene-gene interaction) and with environmental factors (gene-environment interaction) has a crucial role in the development of the pathology. Moreover, the diversity of ethnic background may be a possible bias in such research. In the light of these considerations we selected Caucasian, Italian subjects only, and we constructed a literature based genetic risk score for skin aging with the aim to evaluate the contribution of individual genetic variability to skin aging.

Our results clearly indicate that the risk score based on the selected genetic markers (GRS) is significantly correlated with the variation of elasticity and stratum corneum thickness (SCT) in our sample, confirming the importance in skin aging of a genetic basis. Regarding the relationship between GRS and H_2O content, our analysis show that the P value did not quite achieve the threshold for statistical significance. Skin water content is dependent from several factors, including dietary water inputs that positively impact normal skin physiology, in addition genetic factors involved in skin hydration such as acquaporin were not evaluated in this study, and this may influence the correlation between GRS and H_2O content. Scientific literature indicated that the genetic risk score was successful in increasing predictive power in complex diseases as cardiovascular diseases, type II diabetes or psoriasis [14-17,29,30]. Identification of the definitive set of SNPs for inclusion in a GRS is not the primary aim of this study, however this pilot study was drown up with the aim to understand if genetic risk prediction could become an important tool for the personalization of anti-aging therapy.

Skin-aging depends on a complex crosstalk between genetic and environmental factors, thus we have also studied the relative influence of these factors in determining skin parameters variability. Looking at skin properties, in our sample the results show a strong, significant correlations between H_2O content, stratum corneum thickness (SCT) and elasticity. Skin water content is known to play an important role in different tissue metabolic functions. It is known that hydration modifies the mechanical properties of the skin, water content and elasticity capacities seem to be closely related to maintaining the skin's in vivo physiological properties. Our results show a significant positive correlation between skin water content and elasticity as suggested by previous studies [31]. Skin hydration has been related to skin mechanics to justify preservation of a healthier skin, then a more hydrated skin may promotes cellular metabolism reducing the aging process.

Our results show that age is the variable that most heavily influences elasticity and SCT. These data agree with the well know age effect on skin structure. Morphological changes in skin structure during the aging process include irreversible structural and compositional changes in elastic fibers that progress with age, leading to a substitution with amorphous elastin with poor functional activity [30]. The stratum corneum thickness may change during the ageing process because mitotic activity in the epidermis basal layer is reduced. Studies regarding correlation between ageing and SCT showed controversial results; Sandby-Møller and colleagues found no correlation analyzing biopsies taken at defined sites of forearm, shoulder and buttock, on the contrary, Egawa et al. found a significant positive correlation between age and SCT in forearm but not in the cheek. Finally other studies showed an increase in the number of stratum corneum layers with age in the cheek [32]. Our data agree with these observations, showing a significant positive correlation between age and SCT. Finally, skin ageing is characterized by reduction of TEWL and epidermal hydration so the influence of skin ageing on elastic properties has been expected.

Different factors influence the thickness of the stratum corneum, primarily body site and gender [33]. In a recent paper Habi and colleagues showed that female subjects have a higher average value of hydration compared to male subjects. The authors explain the result in terms of differences in individual's daily activity (water intake) and use of skin care products (use of moisturizer) as well as environmental factors. We did not include these variables in the analysis of skin parameters, however our data indicates that gender (female) is significantly correlated to SCT and H2O content. The progressive decline of elastic properties of the skin is accelerated by sun-exposure [34]. Sun-exposure has also been shown to induce a thickening of the stratum corneum [35-38]. Our data showed no significant correlation between LSE and variability of skin parameters. We assess the lifetime sun exposure using the SEBI questionnaire [39]. The SEBI is a brief self-administered questionnaire and may provide useful measures of past and present sun exposure and current sun behavior however, as reported by authors, self-reported questionnaires may be subject to recall error and bias. This may explain the lack of correlation that we observed between sun exposure and skin aging parameters variation.

Prior skin aging studies have analyzed intrinsic and extrinsic skin aging parameters, believed to reflect genetic and environmental factors contributing to skin aging feature [40-42]. Heritability analyses in

twins have shown that genetic component of skin deterioration process accounts for about 60% [3]. In recent years, research on genetic polymorphisms indicate that Genetic Risk Scores (GRSs) allow the composite assessment of genetic risk in complex traits. Although some authors have expressed doubts as to whether a candidate gene approach can ever add significantly to risk prediction, because of the modest impact on risk, and the apparent inconsistency of effect, other authors demonstrate that, depending on the prevalence and heritability of the disease, few genetic variants may have a strong predictive power [14-17,40,43,44].

Our results indicate that the use of the genetic risk score including 8 single nucleotide polymorphisms involved in aging process as previously described in literature, could be promising to predict skin properties evolution and address anti-aging and skin treatment against specific metabolic target. We included in this work few number of genetic variants involved in metabolic processes that influence the aging process. GWAS studies will increase, in the next future, the knowledge of gene variant involved in the aging process, increasing the predictive power of this approach. The combination of genetic signature, environmental and lifestyle information may provide a useful tool for personalized and more effective anti-aging therapies.

Conflict of Interest

All authors declare to have no conflict of interest in this work neither financial nor personal and affirm that the manuscript has not been published previously and is not being considered currently by another publication. We also affirm that all authors and contributors have read and approved the manuscript.

References

1. Naylor EC, Watson RE, Sherratt MJ (2011) Molecular aspects of skin ageing. Maturitas 69: 249-256.
2. Velarde MC, Flynn JM, Day NU, Melov S, Campisi J (2012) Mitochondrial oxidative stress caused by Sod2 deficiency promotes cellular senescence and aging phenotypes in the skin. Aging (Albany NY) 4: 3-12.
3. Shekar SN, Luciano M, Duffy DL, Martin NG (2005) Genetic and environmental influences on skin pattern deterioration. J Invest Dermatol 125: 1119-1129.
4. Flament F, Bazin R, Laquieze S, Rubert V, Simonpietri E, et al. (2013) Effect of the sun on visible clinical signs of aging in Caucasian skin. Clin Cosmet Investig Dermatol 6: 221-232.
5. Oblong JE (2012) Comparison of the impact of environmental stress on male and female skin. Br J Dermatol 166 Suppl 2: 41-44.
6. Rawlings AV (2006) Ethnic skin types: are there differences in skin structure and function? Int J Cosmet Sci 28: 79-93.
7. Karran P, Brem R (2016) Protein oxidation, UVA and human DNA repair. DNA Repair (Amst) 44: 178-185.
8. Treiber N, Maity P, Singh K, Ferchiu F, Wlaschek M, et al. (2012) The role of manganese superoxide dismutase in skin aging. Dermatoendocrinol 4: 232-235.
9. Zhai Y, Dang Y, Gao W, Zhang Y, Xu P, et al. (2015) P38 and JNK signal pathways are involved in the regulation of phlorizin against UVB-induced skin damage. Exp Dermatol 24: 275-279.
10. Kim EJ, Kim YK, Kim MK, Kim S, Kim JY, et al. (2016) UV-induced inhibition of adipokine production in subcutaneous fat aggravates dermal matrix degradation in human skin. Sci Rep 10: 25616.
11. Cascella R, Foti Cuzzola V, Lepre T, Galli E, Moschese V, et al. (2011) Full sequencing of the FLG gene in Italian patients with atopic eczema: evidence of new mutations, but lack of an association. J Invest Dermatol 131: 982-984.
12. Cascella R, Strafella C, Germani C, Manzo L, Marsella LT, et al. (2015) FLG (filaggrin) null mutations and sunlight exposure: Evidence of a correlation. J Am Acad Dermatol 73: 528-529.
13. Paynter NP, Chasman DI, Paré G, Buring JE, Cook NR, et al. (2010) Association between a literature-based genetic risk score and cardiovascular events in women. JAMA 303: 631-637.
14. Goldstein BA, Knowles JW, Salfati E, Ioannidis JP, Assimes TL (2012) Simple, standardized incorporation of genetic risk into non-genetic risk prediction tools for complex traits: coronary heart disease as an example. Front Genet 1: 254.
15. Reiling E, van 't Riet E, Groenewoud MJ, Welschen LM, van Hove EC, et al. (2009) Combined effects of single-nucleotide polymorphisms in GCK, GCKR, G6PC2 and MTNR1B on fasting plasma glucose and type 2 diabetes risk. Diabetologia 52: 1866-1870.
16. Drenos F, Whittaker JC, Humphries SE (2007) The use of meta-analysis risk estimates for candidate genes in combination to predict coronary heart disease risk. Ann Hum Genet 71: 611-619.
17. Chen Z, Chen YZ, Wang XF, Wang C, Yan RX, et al. (2011) Prediction of ubiquitination sites by using the composition of k-spaced amino acid pairs. PLoS One 6: e22930.
18. Mann V, Hobson EE, Li B, Stewart TL, Grant SF, et al. (2001) A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. J Clin Invest 107: 899-907.
19. Souslova V, Townsend PA, Mann J, van der Loos CM, Motterle A, et al. (2010) Allele-specific regulation of matrix metalloproteinase-3 gene by transcription factor NFkappaB. PLoS One 5: e9902.
20. Bastaki N, Huek K, Manzanillo P, Chande N, Chen C, et al. (2006) Genotype-activity relationship for Mn-superoxide dismutase, glutathione peroxidase 1 and catalase in humans. Pharmacogenet Genomics 16: 279-286.
21. Buchs N, Di Giovine FS, Silvestri T, Vannier E, Duff GW, et al. (2001) IL-1B and IL-1Ra gene polymorphisms and disease severity in rheumatoid arthritis: interaction with their plasma levels. Genes and Immunity 2; 222-228.
22. Menges T, König IR, Hossain H, Little S, Tchatalbachev S, et al. (2008) Sepsis syndrome and death in trauma patients are associated with variation in the gene encoding tumor necrosis factor. Crit Care Med 36: 1456-1462, e1-6.
23. Ballard DH, Cho J, Zhao H (2010) Comparisons of multi--marker association methods to detect association between a candidate region and disease. Genet Epidemiol 34: 201-212.
24. Di Cerbo A, Laurino C, Palmieri B, Iannitti T (2015) A dietary supplement improves facial photoaging and skin sebum, hydration and tonicity modulating serum fibronectin, neutrophil elastase 2, hyaluronic acid and carbonylated proteins. J Photochem Photobiol B 144: 94-103.
25. Faul F, ErdfelderE, Lang A, Buchner A (2007) G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39; 175-191.
26. Jennings L, Karia PS, Jambusaria-Pahlajani A, Whalen FM, Schmults CD (2013) The Sun Exposure and Behaviour Inventory (SEBI): validation of an instrument to assess sun exposure and sun protective practices. J Eur Acad Dermatol Venereol 27: 706-715.
27. Sandby-Møller J, Poulsen T, Wulf HC (2003) Epidermal thickness at different body sites: relationship to age, gender, pigmentation, blood content, skin type and smoking habits. Acta Derm Venereol 83: 410-413.
28. Egawa M, Hirao T, Takahashi M (2007) In vivo estimation of stratum corneum thickness from water concentration profiles obtained with Raman spectroscopy. Acta Derm Venereol 87: 4-8.
29. Ya-Xian Z, Suetake T, Tagami H (1999) Number of cell layers of the stratum corneum in normal skin-relationship to the anatomical location on the body, age, sex and physical parameters. Arch Dermatol Res 291: 555-559.
30. Zouboulis CC, Boschnakow A (2001) Chronological ageing and photoageing of the human sebaceous gland. Clin Exp Dermatol 26: 600-607.

31. Weihermann AC, Lorencini M, Brohem CA, de Carvalho CM (2017) Elastin structure and its involvement in skin photoageing. Int J Cosmet Sci 39: 241-247.
32. Anderson RR, Parrish JA (1981) The optics of human skin. J Invest Dermatol 77: 13-19.
33. Huzaira M, Rius F, Rajadhyaksha M, Anderson RR, González S (2001) Topographic variations in normal skin, as viewed by in vivo reflectance confocal microscopy. J Invest Dermatol 116: 846-852.
34. Xin S, Man W, Fluhr JW, Song S, Elias PM, et al. (2010) Cutaneous resonance running time varies with age, body site and gender in a normal Chinese population. Skin Res Technol 16: 413-421.
35. Hadi H, Awadh AI, Hanif NM, Md Sidik NF, Mohd Rani MR, et al. (2016) The investigation of the skin biophysical measurements focusing on daily activities, skin care habits, and gender differences. Skin Res Technol 22: 247-254.
36. Palma L, Marques LT, Bujan J, Rodrigues LM (2015) Dietary water affects human skin hydration and biomechanics. Clin Cosmet Investig Dermatol 8: 413-421.
37. Hara M, Ma T, Verkman AS (2002) Selectively reduced glycerol in skin of aquaporin-3-deficient mice may account for impaired skin hydration, elasticity, and barrier recovery. J Biol Chem 277: 46616-46621.
38. Naval J, Alonso T, Herranz M (2014) Genetic polymorphisms and skin aging: the identification of population genotypic groups holds potential for personalized treatments. Clin Cosmet Investig Dermatol 7: 207-214.
39. Gao W, Tan J, Hüls A, Ding A, Liu Y, et al. (2017) Genetic variants associated with skin aging in the Chinese Han population. J Dermatol Sci 86: 21-29.
40. Ricci M, Garoia F, Tabarroni C, Marchisio O, Barone A, et al. (2011) Association between genetic risk score and periodontitis onset and progression: a pilot study. Arch Oral Biol 56: 1499-1505.
41. Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, et al. (2002) Mechanisms of photoaging and chronological skin aging. Arch Dermatol 138: 1462-1470.
42. Gunn DA, Rexbye H, Griffiths CE, Murray PG, Fereday A, et al. (2009) Why some women look young for their age. PLoS One 4: e8021.
43. Humphries SE, Ridker PM, Talmud PJ (2004) Genetic testing for cardiovascular disease susceptibility: A useful clinical management tool or possible misinformation? Arterioscler Thromb Vasc Bio 24: 628-636.
44. Janssens AC, Aulchenko YS, Elefante S, Borsboom GJ, Steyerberg EW, et al. (2006) Predictive testing for complex diseases using multiple genes: fact or fiction? Genet Med 8: 395-400.