Journal of Clinical & Experimental Dermatology Research

Nistico et al., J Clin Exp Dermatol Res 2018, 9:2
DOI: 10.4172/2155-9554.1000443

Research Article Open Access

# Genetic Customization of Anti-aging Treatments

**Steven Paul Nistico**[1], **Ester Dill Duca**[2*] **and Flavio Garoia**[3]

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

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

[3]*Genetic Unit Department, MDM group, Bologna, Italy*

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

**Received date:** September 22, 2017; **Accepted date:** February 09, 2018; **Published date:** February 16, 2018



**Abstract**

Skin aging is a multifactorial process that involves both intrinsic factors of genetic and hormonal origin and extrinsic factors of environmental and nutritional nature.

The purpose of this open study on a case series of volunteers is to evaluate the impact of genetic customization of common anti-aging dermocosmetic treatments. We report how the treatment may be customized by acting selectively on the metabolic impairments identified by the analysis of specific DNA variants. The customized cosmetic method shows a significantly higher efficacy compared to non-specific cosmetic treatments such as radiofrequency, suggesting that the combination genetic signature may provide a useful tool for personalized and more effective anti-aging therapies.

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

## Introduction

Aging is caused by the accumulation of cell damages and nonrepaired cells, which are an uncommon process between all species. Some types of damages are unavoidable such as ultraviolet (UV) radiation, free radicals, and genetic effects, and others involve environmental and behavioural influences.

There are two distinct types of skin aging: chronoaging and photoaging. Chronoaging, the natural aging process, is a continuous process that normally begins in our mid-20s with reducing collagen and production, and that enables skin to conserve its original status: it causes cell hypo activity, i.e., a continuous and progressive slowing of the cell repair and renewal processes, resulting in a decrease in cell efficiency.

Photo aging instead is caused by sun exposure and is characterized by the activation of oxidative stress phenomena and therefore, by cell hyperactivity, whose main outcome is damage to nucleic acids, proteins, and lipids.

Chronoaging and photoaging act synergistically in the generation of the typical signs of skin aging.

The structural alterations responsible for the visible signs of skin aging mainly affect the surface layers of the skin: the increase in keratinocyte terminal differentiation causes a progressive thickening of the stratum corneum due to an accumulation of dead cells at the surface level, forming a compact matrix which alters the hydration functions of the skin and gives it a dry and wrinkled appearance [1]. The lower production of collagen and elastin is responsible for the thinning of the dermis, whose degeneration leads to a reduction in skin elasticity and firmness [2]. Frequent sun exposure can cause photoaging that includes noticeable changes to the skin such as freckles, age spots, telangiectasia, rough and leathery skin, loose skin, actinic keratoses, and eventually skin cancer. Furthermore, repetitive facial exercise and movements actually lead to fine lines and wrinkles; photo-induced genetic damage is, in fact, responsible for the increased expression of inflammatory cytokines, involved in oxidative stress phenomena and in the generation of accelerated aging phenotypes and skin cell senescence phenotypes [1].

In response to genetic and environmental factors, aging skin can be defined as a chronic degenerative disease in which the combination of intrinsic and extrinsic factors play an important role in modifying regenerative, structural, and defensive capability of the epidermis. The importance of genetic variability on the development of complex diseases is well known. In recent years, research focused the role of genes and their variants in the onset of specific diseases.

Modifications to a coding gene may result in the production of proteins with a different functionality, characterized by primary and tertiary structures, different from those expected and potentially responsible for individual predisposition to certain diseases. Single-Nucleotide Polymorphisms (SNPs) are the most common genetic modifications.

In the context of chronoaging, modifications to the genes that encode for type 1 collagen (*COL1A1*) and elastin (*ELN*) are among the most studied individual variability factors. Type 1 collagen is the main structural component of the extracellular matrix of the dermis and its decline in quality and quantity is directly involved in tissue relaxation phenomena typical of senescence. Numerous studies have shown that common polymorphisms of the *COL1A1* gene may change the expression of the above-mentioned protein, consequently altering its production and turnover [3]. Elastin is a structural protein of the connective tissue and is the main component of the elastic fibers that make up the dermis. There are polymorphisms associated to the *ELN* gene that code for proteins with altered mechanical properties, which

are, therefore, responsible for an increased risk of impairment of skin elasticity [4].

In the context of photoaging, various genetic variability factors can take part in degenerative metabolic processes.

Metalloprotease 3 (also known as MMP3) is a protease involved in the degradation of the constituent components of the extracellular matrix of the dermis and in the tissue remodeling process that is commonly activated during inflammatory phenomena. After sunlight exposure, inflammation, or skin oxidative stress, MMP3 is activated and takes part in the degradation process of collagen fibers and elastic fibers that comprise the dermis; enzymatic activity of MMP3 can be modulated by genetic polymorphisms as shown by the literature [5].

Free radicals (ROS=Reactive Oxygen Species) are highly reactive substances derived from molecular oxygen that can damage the DNA and cell structures, thus altering the metabolic processes. Improper diet, stress, and exposure to cigarette smoke and pollutants are just some of the factors involved in increasing the cellular production of reactive oxygen species; our body is physiologically equipped with protective systems against ROS, in which the enzymes superoxide dismutase 2 (SOD2), glutathione peroxidase 1 (GPX1) and catalase (CAT) play a key role in the transformation of radical species into inert species, which can be easily removed.

It is well known that the variability due to the presence of polymorphisms of the coding genes for these proteins modulates enzymatic activity, thereby causing a different individual susceptibility to oxidative stress [6]. Similarly, allelic variants of the genes that code for the cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) can determine a different susceptibility to inflammatory stimuli [7-9].

The growing understanding of the genetic basis of many common multifactorial diseases has opened the way to personalized medicine, which means the creation of preventive and personalized therapeutic actions based on genetics. Numerous studies have introduced analytical methods able to assess the contribution of multiple variants in the development of complex diseases, significantly increasing the predictive value of the test [10]. Using this approach we have demonstrated how it is possible to correlate a genetic index (GRS-Genetic Risk Score) that takes into account the contribution of individual SNPs involved in the metabolic processes of the skin (collagen turnover, elastin structure, and susceptibility to inflammation and oxidative stress) and that can be used for the formulation of personalized beauty treatments.

The purpose of this work is to evaluate the possibility of genetic customization of an anti-aging radiofrequency treatment, combined with the simultaneous administration of phytotherapeutic active ingredients acting selectively on the metabolic impairments identified by the analysis of specific DNA variants.

## Materials and Methods

### Individual genetic susceptibility to skin aging

The GRS index (Genetic Risk Score) is constructed by means of sampling and genotyping the patient's DNA, i.e., characterization of the genetic constitution of an individual by identifying specific polymorphisms of *COL1A1* genes, *ELN* involved in the chronoaging process, and specific polymorphisms of the genes CAT, GPX, MnSOD2, IL-1β, TNF-α, and MMP3 involved in the photoaging process.

The selected SNPs were *COL1A1* rs1800012, involved in the type I collagen turnover [3], MMP3 rs3025058, that influences the breakdown of extracellular matrix and tissue remodelling [5]; *ELN* rs2071307, that affects assembly and mechanical properties of the elastic matrix4; CAT rs1001179, GPX rs1050450 and MnSOD2 rs1799725, that influence individual antioxidant capacity [6]; IL-1β rs1143634 and TNF-α rs1800629 that modulates anti-inflammatory response [7-9].

Each polymorphism analyzed is assigned an arbitrary numerical value that quantifies the impact of the previously mentioned genetic variation on individual susceptibility to aging, based on the information available in the literature cited above. This arbitrary numerical value is equal to 1 if the detected genotype contains two alleles considered to be unfavorable, and therefore is associated with increased susceptibility to skin aging; it is equal to 0 if only one unfavorable allele was detected; and it is equal to -1 if no unfavorable alleles were detected. The correlation between the assigned numerical value and the genotype and is exemplified in Table 1.

For each patient the GRS is calculated by means of an additive model, by adding the scores obtained for each of the single-nucleotide polymorphisms identified in the patient's genome and listed in Table 1, according to the "single SNP based test" model described in the work of Ballard and colleagues [11]. The genetic risk index can ideally assume any value between -8 and 8, in which GRS=-8 indicate the lowest genetic predisposition to skin aging, while GRS=8 indicate the highest susceptibility. Once the patient's GRS has been calculated, individual sensitivity to chronoaging and photoaging is determined by comparing each patient's GRS (Table 2).

Table 2 was created by combining the calculation of GRS with the frequencies of the polymorphisms under examination in the population of European origin, as can be derived from published data collected in the HapMap database [12] and in searchable databases on the website of the National Centre for Biotechnology Information [13].

| Area | Sensitivity | GRS Values | Frequency |
|---|---|---|---|
| Chronoaging | Low | 0 ≤ GRS ≤ -2 | 36.72% |
| | Intermediate | 1 | 40.86% |
| | High | 2 | 22.42% |
| Photoaging | Low | -1 ≤ GRS ≤ -6 | 41.70% |
| | Intermediate | 0 | 26.10% |
| | High | 1 ≤ GRS ≤ 6 | 32.20% |

**Table 2:** Individual sensitivity to chronoaging and photoaging is determined by comparing each patient's GRS.

The distribution of the GRS, in relation to the genotype frequencies of the polymorphisms analyzed, makes it possible to classify the patients' genotypes into three arbitrary categories of sensitivity to chronoaging and photoaging. For each GRS there exists, therefore, a combination of two cosmetic compositions, suitable respectively to chronoaging and photoaging, standardizing the choice of products to the categories of low, intermediate, and high sensitivity.

## Choice of active ingredients for the personalized treatment

The treatment include compositions prepared in the form of inert conductive gels, enriched with specific active ingredients and applied to the patient by means of a radio frequency device, which facilitates the deep absorption of the active ingredients.

The cosmetic compositions are divided into six formulations: three developed for the prevention and personalized treatment of the effects connected with Chronoaging (Table 3) and three containing specific active ingredients for treating the effects of photoaging (Table 4).

| Sensitivity | Composition |
|---|---|
| Low | Aqua [Water], Propylene glycol, Saccharide isomerate, Ammonium acryloyldimethyltaurate/VP copolymer, Sodium gluconate, Benzyl alcohol, Coceth-7, PPG-1-PEG-9 lauryl glycol ether, Dehydroacetic acid, Parfum Fragrance], Hydrolyzed soy protein, PEG-40 hydrogenated castor oil. |
| Intermediate | Aqua [Water], Propylene glycol, Glycerin, Ammonium acryloyldimethyltaurate/VP copolymer, Saccharide isomerate, Sodium gluconate, Benzyl alcohol, Palmitoyl tripeptide-5, Coceth-7, PPG-1-PEG-9 lauryl glycol ether, Dehydroacetic acid, Parfum [Fragrance], PEG-40 hydrogenated castor oil. |
| High | Aqua [Water], Propylene glycol, Glycerin, Ammonium acryloyldimethyltaurate/VP copolymer, Saccharide isomerate, Sodium gluconate, Benzyl alcohol, Fagus sylvatica bud extract, Palmitoyl tripeptide-5, Coceth-7, PPG-1-PEG-9 lauryl glycol ether, Dehydroacetic acid, Parfum [Fragrance], PEG-40 hydrogenated castor oil, Lecithin, Tocopherol, Ascorbyl palmitate, Citric acid. |

**Table 3:** Formulae used according to the genetic predisposition of sensitivity to chronoaging (respectively: low, intermediate, high).

For skin that does not show an impairment in the production of collagen and elastin, the cosmetic composition will be dedicated to increasing the hydration and nourishment of the skin to allow good cell functioning.

In the opposite case, if the genetic test detects a potential impairment in the expression of the proteins that maintain dermal tone, the composition of the gel used for the prevention and treatment of Chronoaging is targeted at stimulating the metabolism of fibroblasts, the cells responsible for collagen and elastin synthesis.

The extract of *Fagus sylvatica* (Beech tree bud) contains a high amount of phytostimulines, which are molecules that are known for their important effect of metabolic activation and have been shown *in vitro* to significantly stimulate the protein synthesis of keratinocyte cultures. *In vivo* studies have shown that *Fagus sylvatica* extract increases the smoothness of the skin by reducing the depth of wrinkles and improving skin hydration [14].

The sugar moisturizing factor is a carbohydrate complex similar to that contained in the skin, which acts by binding to the lysine amino acid residues exposed by the keratins, attracting water [15] and providing deep and lasting hydration, contributing to maintaining the skin barrier's functionality.

Palmitoyl tripeptide-3 is a synthetic peptide, able to penetrate the skin and increase the fibroblasts' production of collagen [16], my mimicking the action of thrombospondin-1, a multifunctional protein that activates the transforming growth factor beta (TGF-β) [17].

It has been shown that the peptides or proteins naturally extracted from soybeans may inhibit the action of the proteinases of the extracellular matrix, helping to maintain the integrity of the skin structure. The use of hydrolyzed soy protein increases the tropism of the fibroblasts [18], thereby promoting the synthesis of collagen and glycosaminoglycans [19]. Moreover, the hydrolyzed soy protein extract contains antioxidant peptides [20] with protective action towards the peroxidation of linoleic acid, neutralizing the effects of the peroxynitrite and oxygen free radicals [21].

The cosmetic method for the prevention and treatment of photoaging employs cosmetic compositions that contain active ingredients capable of combating and preventing the signs of photoinduced skin aging, formulated according to the genetic predisposition of sensitivity to dermatoheliosis (respectively: low, intermediate, high).

These compositions, which are shown in Table 4, act to preventively protect the skin from photoinduced damage, while maintaining over time an effective moisturizing action, preventing damage from free radicals on the cell membranes and DNA, reducing damage from solar radiation, and improving the sensation of well-being of the skin, neutralizing the sensory manifestations of inflammation.

| Sensitivity | Composition |
|---|---|
| Low | Aqua [Water], Propylene glycol, Mentha piperita extract [Mentha piperita (Peppermint) extract], Ammonium acryloyldimethyltaurate/VP copolymer, Saccharide isomerate, Sodium gluconate, Benzyl alcohol, Pyrus malus extract [Pyrus malus (Apple) fruit extract], Coceth-7, PPG-1-PEG-9 lauryl glycol ether, Dehydroacetic acid, Parfum [Fragrance], PEG-40 hydrogenated castor oil, Lecithin, Tocopherol, Ascorbyl palmitate, Citric acid. |
| Intermediate | Aqua [Water], Propylene glycol, Mentha piperita extract [Mentha piperita (Peppermint) extract], Hydrolyzed grape fruit, Ammonium cryloyldimethyltaurate/VP copolymer, Sodium gluconate, Benzyl alcohol, Coceth-7, PPG-1-PEG-9 lauryl glycol ether, Dehydroacetic acid, Parfum [Fragrance], PEG-40 hydrogenated castor oil, Lecithin, Tocopherol, Ascorbyl palmitate, Citric acid. |
| High | Aqua [Water], Propylene glycol, Mentha piperita extract [Mentha piperita (Peppermint) extract], Hydrolyzed grape fruit, Ammonium acryloyldimethyltaurate/VP copolymer, Sodium gluconate, Benzyl alcohol, Coceth-7, PPG-1-PEG-9 lauryl glycol ether, PEG-40 |

| | |
|---|---|
| | hydrogenated castor oil, Dehydroacetic acid, Oleyl alcohol, Parfum [Fragrance], Zanthoxylum bungeanum fruit extract, Lecithin, Tocopherol, Ascorbyl palmitate, Citric acid. |

**Table 4:** Formulae used according to the genetic predisposition of sensitivity to photoaging (respectively: low, intermediate, high).

Peppermint is a perennial herbaceous, stoloniferous, and highly aromatic plant belonging to the Labiatae family (Lamiaceae) and to the genus *Mentha*. *In vitro* studies have demonstrated that peppermint possesses significant antimicrobial, antiviral, and antioxidant action (especially from eriocitrin) as well as anti-allergic action, and that some of the flavonoid glycosides it contains, such as luteolin-7-O-rutinoside, have a powerful effect on the release of histamine triggered by antigen/antibody reactions. Moreover, menthol can significantly suppress the production of inflammatory mediators such as leukotrienes (LT) B4, prostaglandin (PG) E2, and interleukin (IL)-β2.

*Pyrus malus* extract is a natural antioxidant, rich in flavonoids and chalcones that preserves the health and vitality of the skin, limiting the oxidation mechanisms of cellular proteins and enzymes, reducing *in vitro* the risk of DNA degradation.

Zanthalene, extracted from *Zanthoxylum bungeanum*, is an active ingredient that is capable of reducing wrinkles. The lipophilic hydroxylamines contained in the Zanthalene extract act transiently and reversibly on the nerve synaptic transmission of $Na^+$-dependent channels, affecting heat and tactile sensitivity, thus reducing skin discomfort such as itching.

*Vitis Vinifera* extract protects the skin from overexposure to UV rays, environmental pollutants, and adverse weather conditions. Its antioxidant efficacy is linked to the abundance of phenols, anthocyanins, and catechins present in the skin of red grapes, demonstrating an antimutagenic, antioxidant, anti-inflammatory and free-radical neutralizing action. *Vitis vinifera* extract possesses an inhibitory action on the metalloproteases responsible for dermal degeneration.

## Experimental Design

The study involved 21 subjects aged between 26 and 49 years. They all signed informed consent to treatment and privacy data. All treatments were applied by means of a radio frequency device, known by its trade name Genotechnology-1®.

Genotechnology-1® device stimulates the regeneration of collagen fibers and the metabolism of fibroblasts at the dermal level through the application of medium frequency radio waves. The device is equipped with a specific bipolar handpiece, capable of delivering exogenous heat that, together with the endogenous heat generated by the passage through the dermis of the radio wave (the principle of radio frequency), makes it possible to increase the penetration of the active ingredients through the skin barrier [22]. The cosmetic compositions were selected on the basis of the degree of personal susceptibility to Chronoaging and Photoaging (Tables 3 and 4).

The first experiment evaluate the variation of skin properties induced by the personalized approach (Genotechnology) towards a standard radiofrequency treatment.

Nine subjects were treated in 10 sessions, one every 14-21 days; on one-half of the face were applied the cosmetic compositions chosen according to the patient's susceptibility, following an application procedure each session with the following order of application: preparatory gel (2 min), chronoaging gel (5 min); photoaging gel (5 min). After each step of treatment, the cosmetic composition was removed and replaced by the following one. The other half of the face was used as a control and was treated by radiofrequency using the same device (which allows the two treatment methods), by applying a standard ultrasound conductive gel (placebo) and using the same specific delivery methods as for the treated part. The choice of protocol based on the treatment of one-half of the face was made in order to eliminate individual variability, caused by exposure to different environmental pressures.

Skin properties measurements were taken using a Skin Tester Device (Selenia, Italia). Skin Tester uses ultrasound densitometry for the investigation and the measurement of facial skin properties:

Total $H_2O$ (T_$H_2O$),

Intracellular $H_2O$ (I_$H_2O$),

Extracellular $H_2O$ (E_$H_2O$),

Skin elasticity (SE),

Thickness of the stratum corneum (SCT).

The device uses an ultrasound-emitted beam that is reflected by the dermal tissues, according to its stromal density and vascular tone, allowing the analysis of skin structure. Furthermore, the diagnostic device encompasses impedance variation as related to intracellular and interstitial water content. Therefore, total, extracellular and intracellular water can be detected [23].

Two measurements per subject were performed in the right cheek and in the left cheek, pre and post treatment. Average of the measurements was calculated. All statistical analyses were performed using the XLSTAT® (Addinsoft) software.

The second experiment evaluate the variation of phenotypic features (wrinkles) induced by the personalized approach (Genotechnology) towards a standard radiofrequency treatment.

In this case 6 subjects were treated in 6 sessions, one every 14-21 days using the cosmetic compositions chosen according to the patient's susceptibility, following an application procedure each session with the following order of application: preparatory gel (2 min), chronoaging gel (5 min); photoaging gel (5 min). After each step of treatment, the cosmetic composition was removed and replaced by the following one. The control group (n=6) was treated by radiofrequency using the same device (which allows the two treatment methods), by applying a standard ultrasound conductive gel (placebo) and using the same specific delivery times and methods as for the Genotechnology group.

Phenotypic features were analyzed using Antera 3D (Miravex, Ireland), an optical skin scanning device able to evaluate the changes over the time of skin profiles. Anthera 3D is based on the acquisition of multiple images obtained with different lighting: diodes at different wavelengths illuminate the skin with the incident light at different illumination direction. The acquired data were used for spatial analysis and multi-spectrum for the reconstruction of the texture of the skin

and the analysis of its chromophores. This device employs a specific algorithm (Spot-On™) that automatically registers two or more images to one another, by correcting displacements due to different positions of the patient when capturing an image. This algorithm allows comparing "before-and-after" images (Figure 1) in an objective manner [24].

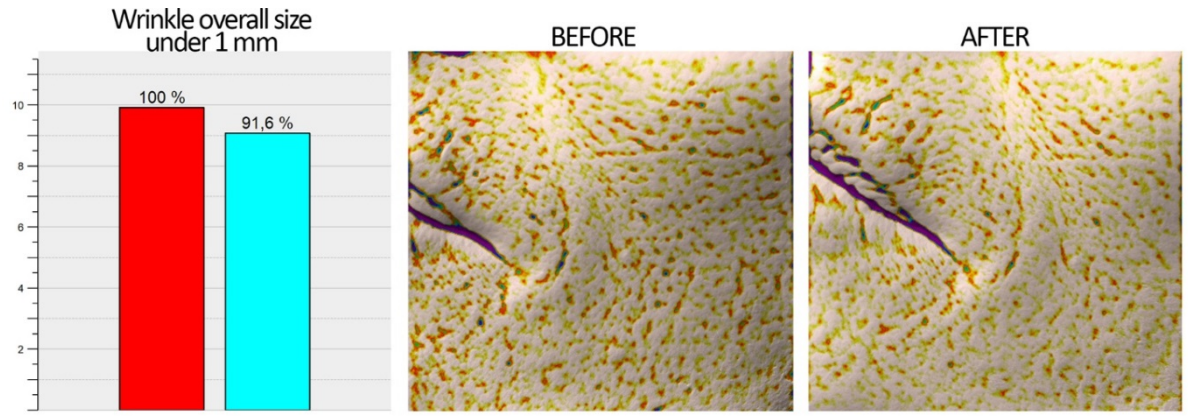



**Figure 1:** Example of Antera 3D® analysis output.

Five measurements were taken for each subject (Figure 2), and the mean variation of wrinkle dimension was calculated. Measurements were taken before the first treatment and after the sixth treatment. All statistical analyses were performed using the XLSTAT® (Addinsoft) software.

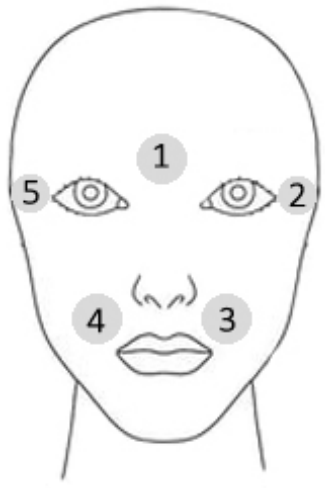



**Figure 2:** Wrinkles measurement areas.

## Results

Regarding the effect of Genotechnology treatment on skin parameters, post treatment results show a statistically significant difference between the groups. A greater efficiency of the Genotechnology-1 treatment *vs.* radiofrequency has been shown in all the parameters examined (Figure 3). The differences between groups were assessed using Student's t-test and were all found to be highly significant (P<0.01%). The relative advantage of Genotechnology treatment range from a reduction of 40.1% more in stratum corneum thickness (from -3.6% to -5.1%) to an increase of 84.6% more in total $H_2O$ content (from +5.1% to +9.4%).

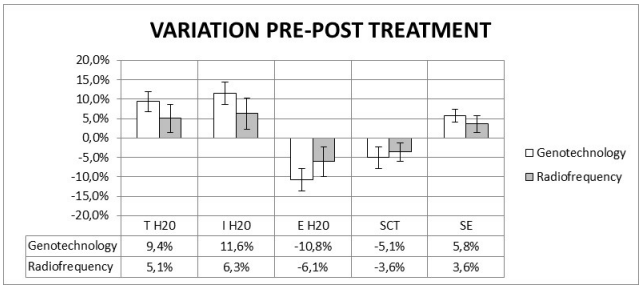
The Antera analysis shows an improvement of skin texture in both groups (Figure 4). The Genotechnology treated group show a greater decrease of wrinkles depth (<1 mm) respect to the Radiofrequency treated group (-20.7% *vs.* -6.1%). The difference was highly significant (P<0.01).

The results suggest a higher efficiency of Genotechnology in the anti-aging treatment.

## Discussion and Conclusions

This is the first study that describes the application of a genetic personalized approach to the treatment of skin aging.

The use of genetic data to personalize medical therapies, based on the assumption that "one size does not fit all" has been demonstrated over the recent years in studies on gene-diet interactions [25], as well in pharmacogenetics [26].




| | T H20 | I H20 | E H20 | SCT | SE |
|---|---|---|---|---|---|
| Genotechnology | 9,4% | 11,6% | -10,8% | -5,1% | 5,8% |
| Radiofrequency | 5,1% | 6,3% | -6,1% | -3,6% | 3,6% |

**Figure 3:** Post treatment results show a statistically significant difference between the groups. The data show increase/decrease in percentage of skin parameters after 10 treatments. Student's t-test highly significant (P<0.01%) for all parameters.

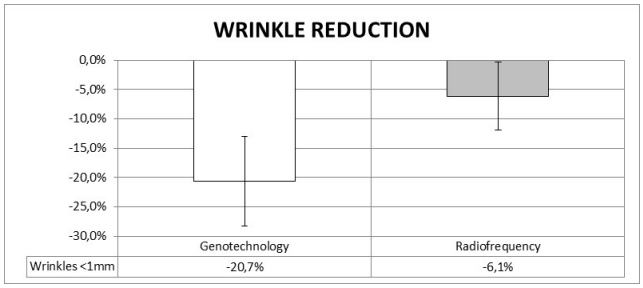



**Figure 4:** Wrinkle reduction results show a statistically significant difference between the groups after 6 treatments. The data show increase/decrease in percentage of wrinkles under 1mm depth. Student's t-test highly significant (P<0.01%).

Naval and colleagues [27] identified genetic clusters defined by genotypic variables linked with polymorphisms in genes associated with inflammation, oxidative stress and skin regeneration that contribute to a person's perceived age, suggesting the possibility to characterize human skin care and anti-aging needs based on individual's genetic signature. Starting from this approach, to better capture the complex relationships between genetics and skin aging, we used a multilocus genetic risk score approach [28].

Our results showed that the clusterization of subjects in different risk levels and the use of cosmetic composition according with individual genetic variability combined to a radiofrequency treatment, lead to a significant improvement of skin parameters as well to a significant decrease of wrinkles depth respect to a standard radiofrequency treatment.

Active ingredients used for the cosmetic composition are well known to act against metabolic impairments involved in accelerated skin aging. Identification of the better cosmetic composition to counteract metabolic mechanisms triggering skin aging was not the primary aim of this work; however, this pilot study was drawn up with the aim to evaluate whether genetic personalization may increase the efficacy of aesthetic treatment.

Limitations of our study include the modest sample size (n=21) and the limited number of SNPs included in the genetic analysis [8]. Only genetic variants with sufficiently described effects on skin properties were included for analysis. Although individually the impact of any one genotype on risk is modest, it has been suggested that when such risk-genotypes are common their combination may have a strong predictive power [29]. 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 [30-33].

Taking account these limitations, aware that further studies will be needed to confirm our data, this pilot study showed that genetic analysis applied to the prevention of chronoaging and photoaging may lead to a customized cosmetic method with significantly higher effectiveness compared to non-specific cosmetic treatments such as radiofrequency.

## References

1. 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.
2. Naylor EC, Watson RE, Sherratt MJ (2011) Molecular aspects of skin ageing. Maturitas 69: 249-256.
3. 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.
4. Hanon O, Luong V, Mourad JJ, Bortolotto LA, Jeunemaitre X, et al. (2001) Aging, carotid artery distensibility, and the Ser422Gly elastin gene polymorphism in humans. Hypertension 38: 1185-1189.
5. Vierkötter A, Schikowski T, Sugiri D, Matsui MS, Krämer U, et al. (2015) MMP-1 and -3 promoter variants are indicative of a common susceptibility for skin and lung aging: results from a cohort of elderly women (SALIA). J Invest Dermatol 135: 1268-1274.
6. Bastaki M, Huen 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.
7. 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 Immun 2: 222-228.
8. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW (1997) Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci 94: 3195-3199.
9. Braun N, Michel U, Ernst BP, Metzner R, Bitsch A, et al. (1996) Gene polymorphism at position -308 of the tumor-necrosis-factor-alpha (TNF-alpha) in multiple sclerosis and its influence on the regulation of TNF-alpha production. Neurosci Lett 215: 75-78.
10. 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.
11. 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.
12. Gudmundur AT, Albert VS, Lalitha K, Lincoln DS (2005) The International HapMap Project Web site. Genome Res 15: 1592-1593.
13. Benhäim P (1995) New technology for the stabilization of fresh plants: interest in cosmetics. Söfw seifen öle fette wachse 121: 3-7.
14. Padberg G, Bielicky T (1972) EinflugderBindungyonKohlenhydraten a die Skleroproteine auf dieWasserbindundger Hornschic. J Soc Cosmetics Chemists 23: 271-279.
15. Lupo MP, Cole AL (2007) Cosmeceutical peptides. Dermatol Ther 20: 343-349.
16. Frazier WA (1999) Thrombospondins. Curr Opin Cell Biol 3: 792-799.
17. Südel KM, Venzke K, Mielke H, Breitenbach U, Mundt C, et al. (2005) Novel aspects of intrinsic and extrinsic aging of human skin:beneficial effects of soy extract. Photochem Photobiol 81: 581-587.
18. Andre-Frei V, Perrier E, Augustin C, Damour O, Bordat P, et al. (1999) A comparison of biological activities of a new soya biopeptide studied in an in vitro skin equivalent model and human volunteers. Int J Cosmet Sci 21: 299-311.
19. Chen HM, Muramoto K, Yamauchi F, Fujimoto K, Nokihara K (1998) Antioxidative Properties of Histidine-Containing Peptides Designed from Peptide Fragments Found in the Digests of a Soybean Protein. J Agric Food Chem 46: 49-53
20. Takenaka A, Annaka H, Kimura Y, Aoki H, Igarashi K (2003) Reduction of paraquat-induced oxidative stress in rats by dietary soy peptide. Biosci Biotechnol Biochem 67: 278-283.
21. Clarys P, Alewaeters K, Jadoul A, Barel A, Manadas RO, et al. (1998) In vitro percutaneous penetration through hairless rat skin: influence of

temperature,vehicle and penetration enhancers. Eur J Pharm Biopharm 46: 279-283.

22. Akomeah F, Nazir T, Martin GP, Brown MB (2004) Effect of heat on the percutaneous absorption and skin retention of three model penetrants. Eur J Pharm Sci 21: 337-345.
23. 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.
24. Linming F, Wei H, Anqi L, Yuanyu C, Heng X, et al. (2017) Comparison of two skin imaging analysis instruments: The VISIA® from Canfield vs the ANTERA 3D® CS from Miravex. Skin Res Technol 24 :3-8.
25. Arkadianos I, Valdes AM, Marinos E, Florou A, Gill RD, et al. (2007) Improved weight management using genetic information to personalize a calorie controlled diet. Nutr J 16: 29.
26. Ingelman-Sundberg M (2008) Pharmacogenomic biomarkers for prediction of severe adverse drug reactions. N Engl J Med 358: 637.
27. 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.
28. 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.
29. Yang Q H, Khoury MJ, Friedman JM, Little J, Flanders WD (2005) How many genes underlie the occurrence of common complex diseases in the population? Int J Epidemiol 34: 1129-1137.
30. 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.
31. 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.
32. 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.
33. 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.