Pathway SkinFit™

Technical Bulletin
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SKIN PHOTOAGING

WRINKLES AND COLLAGEN DEGRADATION

About: A wrinkle, also known as a rhytide, is a crease or fold in the skin. Wrinkles form as a part of the normal aging process, can range in severity from fine lines to deep furrows and are caused by both intrinsic (e.g. genetics, hormonal state and skin pigment) and extrinsic (e.g. passage of time, chronic exposure to UV radiation, habitual facial expressions, alcohol abuse and smoking) factors. These factors can cause keratinocyte damage and collagen degradation in the dermis of the skin. Collagen is the most abundant protein in the extracellular matrix (ECM) of skin and bone. In chronically UV-irradiated and photodamaged skin, collagen synthesis is reduced. Furthermore, UV-irradiation of the skin alters the balance between ECM synthesis and degradation by triggering an up-regulation of matrix metalloproteinases (MMP) MMP-1 and MMP-3 (enzymes responsible for collagen degradation), while exacerbating the down regulation of tissue specific MMP inhibitors, such as TIMP-1 in aging fibroblasts. A number of hereditary phenotypic features influence the severity of photoaging, most notably skin color, and skin phototype. Wrinkling tends to occur and increases after the age of 30. Lighter skin phototype individuals (I–II) generally show worsening skin wrinkles at early age as well as development of focal depigmentation and dysplastic changes, such as actinic keratosis. Wrinkle appearance occurs at delayed rates in individuals with dark skin phototype (III–IV), but “deep” wrinkling and epidermal thickening is more likely to occur.

Genetics: Genetic variants in the MMP1 gene as well as other genes, such as STXB5P5L, which is expressed in several tissues including skin, have a role in the severity of photoaging skin. Individuals with either the risk allele “TC” (T/TC and TC/TC genotype) at the rs1799750 locus or the risk allele “C” (T/C and C/C genotype) at the rs322458 locus are at an increased risk of developing skin wrinkles. Compound heterozygous also have an increased risk of developing skin wrinkles.

Possible outcomes: Increased Risk or Normal Risk (of developing wrinkles)

Markers Tested:

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Note: All alleles are always displayed in the chromosome forward direction.

TANNING RESPONSE

About: Humans vary more than 100-fold in their sensitivity to the harmful effects of ultraviolet radiation (UVR). The most important factors that determine the skin sun-sensitivity are pigmentation of the epidermis, and differences in skin inflammation and repair response. Tanning is the increased skin pigmentation resulting from the augmented production of melanin induced by UV exposure. In general, those who have difficulty tanning (fair skin) are at higher risks of sunburn, sun spots, wrinkles, folate loss and melanoma. Individuals who tan easily (dark skin) are at risk of vitamin D deficiency as they may derive less vitamin D from sun exposure and their risk of melanoma is lower compare to those with fair skin. However, not all
people with light skin have the same risk for UV skin-damage since their inherent epidermal melanin content (constitutive skin color) and the capacity of the skin to synthesize melanin (tanning capacity or facultative skin color) varies. A careful analysis of each individual’s tendency to develop erythema and capacity to tan, enable the physician to classify fair skin people into skin types (I - IV) using the Fitzpatrick typing system. Therefore, tanning response varies among individuals, and can have both positive and negative effects on skin health.

Genetics: Multiple risk alleles in the genes MC1R, IRF4, HERC2, TYR, EXOC2, SLC45A2, SLC24A5, and NCOA6 are associated with a decreased tanning response (or increased risk of sunburns). Human melanocortin 1 receptor (MC1R), encoded by the MC1R gene, accounts for a large portion of the variations in skin and hair color as well as the incidence of skin cancer. Genetic variants in the MC1R gene have the strongest effect, and individuals carrying these variants tend to exhibit fair, difficult to tan skin, red hair and freckles. Individuals with a risk allele “T” (C/T or T/T genotype) at either rs1805007 or rs1805008 locus have a considerable low tanning ability with an increased photo-sensitivity. A reduction of the tanning ability is also observed in individuals having at least one risk allele “C” at locus rs1015362, a risk allele “T” at either rs4911414 or rs12203592 locus, a risk allele “G” at rs12913832 locus, and a risk allele “A” at either rs1126809 or rs1393350 locus. A normal tanning response is observed in carriers of a single risk allele (homozygous or heterozygous) at any of rs12210050, rs1426654, rs2555364, rs16891982, rs26722, rs1042602 and rs4911442 locus. Compound heterozygous or homozygous individuals in general yield a reduced tanning response.

Possible outcomes: Reduced or Normal (tanning response)

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Note: All alleles are always displayed in the chromosome forward direction.
SUN SPOTS (LENTIGINES)

About: Sun spots, or solar lentigines, are pigmented spots that range from millimeters to centimeters in diameter and can appear light yellow to brown. They appear on areas frequently exposed to the sun, such as face, arms, back of the hands, and trunk.\(^{27,28}\) Solar lentigines are more prevalent than freckles (ephelides) and are found more frequently in males than in females. Lentigines typically appear after the age of 50, and are increased in prevalence and number with age and chronic sun exposure.\(^{27,28}\) They are caused by a local growth of pigment-producing skin cells in response to UV radiation.\(^{28,29}\) Solar lentigines are a sign of skin damage and aging, and are associated sometimes with an increased risk of developing melanoma.\(^{21,28,30}\) Melanin production and the ratio of eumelanin (brown and black pigment) to phaeomelanin (yellow or red pigment) are regulated amongst other aspects by the melanocyte-stimulating hormone (MSH). MSH binds to the melanocortin-1 receptor (MC1R), which upon activation causes the melanocytes to switch from generating the phaeomelanin to producing eumelanin. The \textit{MC1R} gene encodes MC1R protein. There exist a number of \textit{MC1R} major (including R151C, R160W, D294H) and minor (including V60L, V92M, R163Q) diminished-function variants that significantly affects the variations in skin and hair color.

Genetics: Genetic variants in the \textit{IRF4} and \textit{MC1R} genes analyzed in this test have been associated with an increased risk of solar lentigines. Individuals with at least one risk allele (heterozygous or homozygous genotype) in the \textit{IRF4} rs12203592 locus or any of the \textit{MC1R} major diminished-function rs1805007 (R151C), rs1805008 (R160W), rs1805009 (D294H) and rs1805006 (D84E) loci are at an increased risk of developing sun spots. Individuals with a risk allele (homozygous, heterozygous or compound heterozygous genotype) in any \textit{MC1R} minor diminished-function rs11547464 (R142H), rs1110400 (I155T), rs1805005 (V60L), rs2228479 (V92M), and rs885479 (R163Q) loci, will result in a “Normal Risk” outcome. Conversely, compound heterozygous individual of any major diminished-function loci will result in an “Increased Risk” outcome.\(^{19,21}\)

Possible outcomes: Increased Risk or Normal Risk (of solar lentigines)

Markers Tested:

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<th>SNP Reference Allele</th>
<th>Alternative Allele</th>
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FRECKLES (EPHELIDES)

About: Freckles, also known as ephelides, are harmless hyperpigmented spots (red to light brown) with distinct borders appearing evenly distributed on the face, neck, chest, arms and trunk. These spots are a result of increased melanin production. Freckles typically appear early in childhood, diminish with age, and can also darken seasonally with sun exposure.\textsuperscript{27,28} Freckles are common in Caucasian and Asian populations, more frequent in fair-skin individuals (skin type I-II) with red or blond hair. Furthermore, there is a higher frequency of freckles in females than males.\textsuperscript{21,31} Freckles are associated with genetic factors present in fair skin populations, such as those responsible for reduced tanning response (or increased likelihood of sunburn), higher likelihood of developing solar lentigines,\textsuperscript{21,28,29} and increased risk of developing malignant melanoma and non-melanoma skin cancers.\textsuperscript{12,17,21}

Genetics: Freckling is most strongly associated with genetic variants in the \textit{IRF4} and \textit{MC1R} genes.\textsuperscript{19,21,28,32} \textit{MC1R} gene is also the largest contributor to a red haired, fair skinned appearance. The degree of freckling often corresponds to the number of \textit{MC1R} variants that an individual carries.\textsuperscript{21} Individuals with at least one risk allele (heterozygous or homozygous genotype) in the \textit{IRF4} locus rs12203592 or any of the \textit{MC1R} major diminished-function loci rs1805007 (also known as R151C), rs1805008 (R160W), and rs1805009 (D294H) are at an increased risk of developing freckles. Individuals with a risk allele (homozygous, heterozygous or compound heterozygous genotype) in \textit{MC1R} minor diminished-function locus rs11547464 (R142H), or intergenic loci rs4911414 and rs1540771, or \textit{NCOA6} locus rs4911442, or \textit{TYR} loci rs1042602 and rs1393350, will result in a “Normal Risk” outcome of developing freckles. Conversely, compound heterozygous individual carrying the risk allele in the \textit{IRF4} locus rs12203592 or any of the \textit{MC1R} major diminished-function loci will result in an “Increased Risk” outcome.\textsuperscript{19,21,28,32}

Possible outcomes: Increased Risk or Normal Risk (of developing freckles)

Markers Tested:

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SKIN TEXTURE AND ELASTICITY

CELLULITE

About: Cellulite (gynoid lipodystrophy) is a non-pathological skin condition commonly known as "orange peel". The bumpy appearance of the skin is due to uneven fibrous tissue and subcutaneous fat. Cellulite mainly appears on the thighs, hips and buttocks, and is present in about 85% of women over the age of 20. Caucasian women are more prone to cellulite than Asian women, partly due to the differences in diet. Genetic predisposition, hormonal changes, gender, ethnicity, age and weight changes contribute to risks of developing cellulite.

Genetics: Studies have shown that genetic variants, such as the ACE gene insertion/deletion (I/D) polymorphism (rs1799752) and the HIF1A gene polymorphism (rs11549465) may act as a major risk factor for cellulite. ACE gene encodes the acetylcholinesterase enzyme, which is involved in catalyzing the conversion of angiotensin I into angiotensin II and degrades bradykinin which contributes to a decreased local blood flow. Women carrying the ACE risk allele "D" at the rs1799752 locus (insertion/deletion (I/D) or the deletion/deletion (D/D) genotype) had a significant risk of developing cellulite, which further increases in women who smoke. HIF1A (hypoxia inducible factor 1-alpha) gene encodes the alpha subunit of HIF1A transcription factor, which is essential for cellular response to systemic oxygen levels in humans. The HIF1A is involved in cellular processes including energy metabolism, angiogenesis, and apoptosis. Individuals carrying the HIF1A risk allele "T" at the rs11549465 locus (1744C>T; P582S) are associated with a reduced risk of developing cellulite. Compound heterozygous individuals having the risk allele "D" at the rs1799752 locus and the risk allele “T” at the rs11549465 locus also have an increased risk of developing cellulite.

Possible outcomes: Increased Risk, Normal Risk or Reduced Risk (of developing cellulite)

Markers Tested:

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STRETCH MARKS (STRIAE DISTENSAE)

About: Stretch marks, also known as striae distensae, is a dermal scarring condition characterized by linear bundles of collagen lying parallel to the skin surface with an eventual loss of collagen and elastin fibers. Stretch marks appear initially as red or purple lines on the skin and later as white or silver lines. Mechanical stretching of the skin due to weight loss-regain, obesity, hormonal changes and pregnancy can cause stretch marks. This skin condition frequently affects lower back and knees in adolescent males, while it is more common on thighs and calves in adolescent females. During pregnancy, abdomen and breasts are areas prone to developing stretch marks. The risk of stretch marks varies, ranging from 43 to 88% in pregnant women, 6 to 86% in adolescents, and about 43% in obese individuals. Moreover, about 4 to 7% women who underwent breast augmentation were shown to develop stretch marks and the risk was higher for younger women. African-American women have a significantly higher risk of developing stretch marks than white
women in the same geographic region. Other factors associated with increased risks of stretch marks include Cushing syndrome, Marfan syndrome, diabetes mellitus and long-term systemic or topical steroid use.

**Genetics:** Genetic factors, such as gene polymorphisms ELN (rs7787362), SRPX (rs35318931), HMCN1 (rs10798036) and TMEM18 (rs7594220), are associated with risks of developing stretch marks. ELN gene encodes elastin, a protein associated with connective tissue that helps the skin to regain its shape after stretching and contracting. Individuals with the risk allele “T” (C/T or T/T genotype) at the rs7787362 locus are at a higher risk of developing stretch marks. Individuals with the SRPX risk allele “A” (G/A and A/A genotypes) at the rs35318931 locus are at an increased risk of developing striae gravidarum (a form of stretch marks). HMCN1 (hemicentin-1) gene is associated with age related macular degeneration as well as stretch marks. Individuals with the risk allele “C” (G/C and C/C genotype) at the rs10798036 locus are at an increased risk of developing stretch marks. TMEM18 (transmembrane 18) gene is associated with obesity and obesity related traits. Individuals with the risk allele “G” (A/G and G/G genotype) at the rs7594220 locus are at increased risk of stretch marks, and compound heterozygous of two or more markers also have an increased risk of developing stretch marks.

**Possible outcomes:** Increased Risk, Normal Risk (of developing stretch marks)

**Markers Tested:**

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**VARICOSE VEINS**

**About:** Varicose veins are dilated subcutaneous veins that appear dark purple to blue. These veins are mostly seen on the back of the lower legs and often appear twisted and bulged like cords. Primary varicose veins result from an asymmetric remodeling of extracellular matrix and smooth muscle cells contributing to wall thickening and valve incompetence. Varicose veins affect more than a third of world population. Approximately 23% of US adults have varicose veins. In general, this condition is more common in women and older adults affecting 22 million women and 11 million men between the ages of 40 to 80 years. Varicose veins are often genetically inherited although non-genetic factors may exacerbate the condition including obesity, age, standing and walking upright for long times and hormonal changes. Some individuals are asymptomatic but varicose veins can cause pain, aches, itching and can significantly affect quality of life. Left untreated, venous ulceration and venous thrombosis can result.

**Genetics:** Genetic variants in the MTHFR gene have been associated with an increased risk of developing varicose veins. MTHFR encodes the methylenetetrahydrofolate reductase enzyme, which plays an essential role in maintaining plasma homocysteine levels. Individuals with either risk allele “A” (G/A or A/A genotype) at the rs1801133 locus or the risk allele “G” (T/G of G/G genotypes) for the rs1801131 locus have
an increased risk of developing primary varicose veins. Homozygous individuals with the risk alleles at either locus rs1801133 (A/A) or rs1801131 (G/G) have even higher risk than the heterozygous counterparts. Compound heterozygous individuals are also at an increased risk of developing primary varicose veins.  

**Possible outcomes:** Increased Risk or Normal Risk (of developing varicose veins)

**Markers Tested:**

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**SKIN INFLAMMATION AND ALLERGY RISK**

**ROSACEA**

**About:** Rosacea is a skin disorder characterized by recurrent episodes of inflammation in cheeks, nose, chins, forehead, or eyelids, resulting in flushing, erythema (redness), telangiectasia (permanently distended blood capillary vessels with a spidery appearance), swelling or hyperplasia, or papules / pustules. Rosacea usually appears in the second decade of life and affects 10% of the world population. Generally, women are more often affected than men, and it is more common in fair-skin individuals of northern Europeans and Celtic heritage. However, phymatous subtype of rosacea is more commonly observed in men. Rosacea is relatively harmless, although there are significant morbidities associated with it, including quality of life and psychological well-being. Causal hypotheses of rosacea include vascular abnormalities, dermal matrix degeneration, increased release of cathelicidin antimicrobial peptides, and genetic predispositions. Rosacea can be exacerbated by a variety of triggers including lifestyle changes, environmental (e.g. heat or sunlight), food and chemicals ingested (e.g. alcohol) and skin microorganisms and Demodex parasitic mites.

**Genetics:** Two genetic variants in the intergenic regions analyzed in this test are associated with an increased risk of rosacea occurrence. The polymorphism rs763035 has a significant association with rosacea. This polymorphism is intergenic, and is located upstream of the HLA-DRA (human leukocyte antigen (HLA) class II histocompatibility antigen, DR alpha chain) gene and downstream of the BTNL2 (butyrophilin-like 2, major histocompatibility complex class I associated) gene. A second weakly associated intergenic polymorphism rs111314066 is located downstream of KCTD16 and upstream of PRELID2 gene. Individuals with risk allele “A” (G/A or A/A genotype) at the rs763035 locus are at an increased risk of rosacea, and individuals with risk allele “T” (A/T and T/T genotype) for the rs111314066 locus have slightly increased risk. Compound heterozygous individuals are at an increased risk.

**Possible outcomes:** Increased Risk or Normal Risk (of developing rosacea)
Markers Tested:

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
<th>Risk Allele</th>
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<td>T</td>
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</tr>
</tbody>
</table>

Note: All alleles are always displayed in the chromosome forward direction.

CONTACT DERMATITIS

About: Contact dermatitis (CD), also known as occupational dermatitis, is the most common work-related skin disease resulting in disability and decreased quality of life. There are two main types of CD: allergic (ACD) and irritant (ICD). A high prevalence of CD is found in workers of industries including healthcare, skin-care and beauty, food industry, and activities with frequent exposure to metals. Differences in prevalence also depend on age, gender (more common in females), and smoking. Although a major cause for CD is exposure to environmental insults, there is a strong link between CD and genetic variations in the FLG gene. The FLG gene (encodes the epidermis structural protein filaggrin) is involved in the maintenance of the skin-barrier function. A functional skin-barrier influences the amount of irritants that penetrate the skin, consequently affecting the inflammatory response.

Genetics: FLG gene variants that lead to a decrease or loss of the filaggrin protein result in an increase susceptibility to chronic ICD, and contact sensitization to metals, such as nickel. Individuals with either risk allele “A” (G/A or A/A genotype) at the rs61816761 locus (R501X variant), or having the risk allele “C” (CACTG/C or C/C genotype) at the rs558269137 locus (2282del4 variant) are at an increased risk of developing contact dermatitis. Similarly, compound heterozygous individuals are also at an increased risk of developing CD.

Possible outcomes: Increased Risk or Normal Risk (of developing contact dermatitis)

Markers Tested:

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
<th>Risk Allele</th>
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<td>rs558269137</td>
<td>CACTG</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

Note: All alleles are always displayed in the chromosome forward direction.

GENERALIZED PSORIASIS

About: Psoriasis is an immune-mediated, chronic inflammatory condition primarily affecting the skin and joints characterized by raised red skin with white scales. Psoriasis is a worldwide disease (global prevalence of 0–11.8 %), observed in 2% of the population in Europe and North America, and comprising about 4.4% of all dermatological cases in Japan. Healthcare costs associated with psoriasis are comparable to other costly conditions such as pancreatic cancer, melanoma, prostate cancer and asthma. Psoriasis is equally
prevalent in both sexes, although males are more prone than females to develop a severe disease.\textsuperscript{90,95} Psoriasis poses a significant healthcare burden to the patients due to physical and psychological challenges, including visible disfiguration, disability and depression. One of the main components to the etiology and pathogenesis of psoriasis is genetic predisposition.\textsuperscript{96-102} In addition, extrinsic factors may worsen or trigger psoriasis outbreaks including scratching, medications (e.g. beta-blockers and nonsteroidal anti-inflammatory drugs), infections (e.g. HIV and streptococcal pharyngitis), cold temperature and ultraviolet exposure.\textsuperscript{97}

**Genetics:** Variants in the *HLA-C* (also known as *PSORS1*), *IL12B*, *IL23R*, *TNIP1*, *IL13*, *TNFAIP3*, and *MTHFR* genes are strongly associated with psoriasis.\textsuperscript{97,100,103-108} Individuals with a risk allele (homozygous or heterozygous) at either *HLA-C* rs1265181 or rs12191877 locus are at a high risk of developing psoriasis. Furthermore, compound heterozygous having a risk allele in all three loci *IL12B* rs2082412, *IL23R* rs2201841 and *TNIP1* rs17728338 are also at a high risk of developing psoriasis. However, individuals having only one risk allele (homozygous or heterozygous) on any of these *IL12B* rs2082412, *IL23R* rs2201841 and *TNIP1* rs17728338 loci result in an increased risk outcome. Nonetheless, compound heterozygous individuals having a risk allele in all three loci *IL13* rs20541, *TNFAIP3* rs610604 and *MTHFR* rs1801133 are at a normal risk of developing psoriasis.

**Possible outcomes:** High Risk, Increased Risk or Normal Risk (of developing generalized psoriasis)

**Markers Tested:**

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
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<th>Alternative Allele</th>
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</tr>
</tbody>
</table>

**Note:** All alleles are always displayed in the chromosome forward direction.

**ECZEMA (ATOPIC DERMATITIS)**

**About:** Eczema, or atopic dermatitis (AD), is a chronic inflammatory skin disease characterized by acute itching and persistent eczematous lesions predominantly on creases of elbows or knees. Other symptoms include sleep deprivation and psychological issues. AD often starts in infancy, affecting 15-30% of children and 5-10% of adults.\textsuperscript{109,110} In Europeans, 80-90% of AD cases are inherited.\textsuperscript{111,112} Filaggrin, a protein essential for skin barrier formation and hydration, is crucial to maintaining the structure of epidermis. *FLG* gene encodes the filaggrin protein.\textsuperscript{113} AD therapies aim to restore the function of the epidermal barrier and reduce skin inflammation. Treatments often include skin moisturizing, topical anti-inflammatory agents,\textsuperscript{114,115} dietary modifications,\textsuperscript{116,117} and vitamin supplementation.\textsuperscript{118}
**Genetics:** Genetic variants in the *FLG* gene are the strongest risk factors for AD and allergic sensitizations. Certain inherited *FLG* variants lead to a decreased protein expression, diminished function or loss of the filaggrin protein, which results in the AD phenotype. A recent study has identified ten new genetic loci for a total of 31 loci associated with AD. Individuals with a single risk allele (heterozygous or homozygous genotype) in any of the loci rs61816761 locus (R501X), rs558269137 (2282del4) or FLG:1249insG are at a substantially increased risk of developing AD. In addition, individuals with a single risk allele (heterozygous or homozygous) in any of the loci rs150597413, rs138726443, rs200519781, FLG:S2889X and rs121909626 are at an increased risk of developing AD. Furthermore, compound heterozygous will also result in an increased risk outcome.

**Possible outcomes:** Increased Risk or Normal Risk (of developing eczema)

**Markers Tested:**

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP/Marker</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
<th>Risk Allele</th>
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Note: All alleles are always displayed in the chromosome forward direction.

**SKIN MOISTURE FACTOR**

**DRY SKIN (XEROSIS AND ICHTHYOSIS)**

**About:** Dry skin, also known as xerosis, is a condition of rough, itchy (occasionally painful) skin with fine scaling and small cracks that occurs at all ages. Xerosis may be caused by environmental factors, including dry/cold weather, frequent bathing/removing skin lipids, malnutrition and other medical conditions. Severe forms of dry skin may be inherited and appear during early childhood. The most common of these disorders is ichthyosis vulgaris (IV), or fish scale disease, where dead skin cell accumulation results in thick, dry scales on the skin's surface. Filaggrin, a protein essential for skin barrier formation and hydration, is crucial to maintaining the structure of epidermis. *FLG* gene encodes the filaggrin protein.

**Genetics:** Certain inherited variants in the *FLG* gene lead to decreased protein expression, diminished function or loss of the filaggrin protein, which results in the dry skin phenotype. These *FLG* variants are also found in individuals presenting skin inflammatory disorders, including atopic and contact...
dermatitis. Individuals with either the risk allele “A” (G/A or A/A genotype) at the rs61816761 locus, risk allele “C” (CACTG/C or C/C genotype) at the rs558269137 locus, risk allele “T” (G/T or T/T genotype) at the rs150597413 locus, risk allele “A” (G/A or A/A genotype) at the rs138726443 locus, or the risk allele “C” (CT/C or C/C genotype) at the rs200519781 locus are at an increased risk of developing dry skin. Individuals carrying a single risk allele (homozygous or heterozygous) at the rs397507563 locus are at a normal risk of developing dry skin. Compound heterozygous or homozygous individuals are at an increased risk of developing dry skin.

Possible outcomes: Increased Risk or Normal Risk (of developing dry skin)

Markers Tested:

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<th>Gene/ Locus</th>
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<th>Reference Allele</th>
<th>Alternative Allele</th>
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</table>

Note: All alleles are always displayed in the chromosome forward direction.

SKIN OXIDATION PROTECTION

ANTIOXIDATION RESPONSE

About: Antioxidant response is the body's natural ability to detoxify and counteract harmful agents like ultraviolet (UV) rays, environmental pollutants, and toxins produced by the body. These processes generate reactive oxygen species (ROS), also known as free radicals. ROS can oxidize and damage nucleic acids, proteins and lipids thereby altering their stability and function and result in protein modifications (such as protein carbonylation and nitration) and the formation of lipid peroxidation adducts. Oxidative stress is defined as the imbalance of the production of ROS and their detoxification by the body's antioxidation response. This stress leads to breakdown of skin collagens that provides structural support to the skin, alters cycles of cell regeneration, and causes DNA damage that triggers cytokines release, which modulates skin inflammation. Chronic free radical exposure leads to the appearance of uneven, blotchy pigmentation, and weakens skin structure leading to wrinkles and sagging skin. Moreover, oxidative stress is associated with increased inflammation that could lead to other severe diseases like cancer, atherosclerosis, Alzheimer's disease, schizophrenia and many others. Foods containing antioxidants like tocopherols, polyphenols, aloe vera, red ginseng, coenzyme Q10, lycopene, carotenoids, vitamin E and vitamin C, as well as their topical applications, are beneficial in preventing the UV-induced oxidative damage.

Genetics: Single nucleotide polymorphisms in the genes coding for the antioxidant enzyme including SOD2, GPX1, CAT and NQO1 are associated with the ROS-induced accelerated skin aging. SOD2 gene encodes the antioxidant enzyme superoxide dismutase that acts as a first line of defense against mitochondrial oxidative damage. Individuals with homozygous risk allele “A” (A/A genotype) at the
rs4880 locus have a significantly reduced antioxidant capacity. GPX1 gene encodes the glutathione peroxidase 1 (GPx) enzyme, another antioxidant enzyme. Individuals with homozygous risk allele “A” (A/A genotype) at the rs1050450 locus also have a reduced antioxidant ability. CAT gene encodes catalase, which is a protective enzyme that reduces oxidative stress. Individuals homozygous for risk allele “C” (C/C genotype) at the rs1001179 locus have a considerable reduction of this antioxidant ability. NQO1 gene encodes cytoplasmic 2-electron reductase, an enzyme which prevents the production of free radical species. Individuals homozygous for risk allele “G” (G/G genotype) at either rs1800566 or rs2917666 locus have a reduced antioxidant ability. Individuals, who are compound homozygous for the risk allele at their particular loci, also yield a reduced antioxidation response. Individuals with compound heterozygous variants in any of the genes have a normal antioxidation response.

**Possible outcomes:** Reduced or Normal (antioxidation response)

**Markers Tested:**

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
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</tr>
</tbody>
</table>

**Note:** All alleles are always displayed in the chromosome forward direction.

**SKIN GLYCATION**

**GLYCATION PROTECTION**

**About:** Glycation is a process by which sugar molecules are chemically linked to proteins (e.g. collagen and elastin), lipids, and nucleic acids. These glycation products are referred to as advanced glycation end products (AGEs), and they are implicated in accelerated skin aging and inflammation, which leads to loose, cracked and thinned skin. AGEs accumulation increases with age and becomes more harmful in combination with UV exposure. Glycation stress, and subsequently skin aging, may be reduced by managing levels of blood glucose, low-density lipoprotein cholesterol, and triglycerides through an appropriate diet.

**Genetics:** Genetic variants in AGER and GLO1 genes have been associated with increased AGEs level in both healthy individuals and those with diabetes. AGER gene encodes for Receptor of Advanced Glycation End products (RAGE), which is highly expressed in the skin and is upregulated by AGEs. AGE-RAGE interactions alter several cell functions resulting in the generation of oxidative stress. Alterations in RAGE are linked to chronic conditions including skin aging. Individuals with the risk allele “G” (A/G or G/G genotype) at the rs1800625 locus have a reduced glycation protection. Reduced levels of AGEs in serum have been observed in diabetes patients with allele “T” (homozygous T/T genotype) at the rs1800624 locus, hence homozygous individuals for the “T” allele at this locus are afforded glycation protection and will be reported as “Normal”. A normal glycation protection is observed in carriers of the risk allele (homozygous or
heterozygous) at the rs2070600 locus.\textsuperscript{147-149} \textit{GLO1} gene encodes glyoxalase enzyme that helps to counter the generation of AGEs. Individuals with either the risk allele “A” (G/A or A/A genotype) at the rs1049346 locus or the risk allele “A” (T/A or A/A genotype) at the rs1130534 locus have a reduced glycation protection.\textsuperscript{150}

Possible outcomes: Reduced or Normal (glycation protection)

Markers Tested:

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
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Note: All alleles are always displayed in the chromosome forward direction.

SKIN NUTRITIONAL NEEDS

VITAMIN A DEFICIENCY

About: Vitamin A and its related compounds (beta-carotene, retinol, and retinoic acid) are important for skin growth and damage prevention.\textsuperscript{152-155} Deficiency in vitamin A is associated with various skin conditions, including dry skin, abnormal thickening, atopic dermatitis and delayed wound healing.\textsuperscript{155,156} Both dietary intake and genetic factors influence vitamin A metabolism. The recommended daily vitamin A intake for most adults is 700 to 900 micrograms.\textsuperscript{157} In addition, topical applications of vitamin A derivatives, such as retinol and retinoic acid, have been shown to reduce signs of photoaging including wrinkles, hyperpigmentation and skin roughness.\textsuperscript{158}

Genetics: Vitamin A levels are associated with variants in the \textit{BCMO1} gene, which encodes an enzyme that converts beta-carotene to retinal, the precursor of vitamin A. Both \textit{in vivo} and \textit{in vitro} data show that \textit{BCMO1} common variant rs7501331 (A379V) or a compound rs12934992 (R267S) and rs7501331 variant yield a reduction in beta-carotene metabolism. Individuals with the risk allele “T” (C/T or T/T genotype) at the rs7501331 locus are at an increased risk of vitamin A deficiency. Compound heterozygous individuals with the risk allele “T” (C/T or T/T genotype) at the rs7501331 locus and risk allele “T” (A/T or T/T genotype) at the rs12934922 locus also have an increased risk of vitamin A deficiency.\textsuperscript{159}

Possible outcomes: Increased Risk or Normal Risk (of vitamin A deficiency)
Markers Tested:

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
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</table>

Note: All alleles are always displayed in the chromosome forward direction.

Limitations and warnings: This test reports on genetic predisposition for decreased vitamin A levels. Other tests are available to assess a patient’s vitamin A plasma levels. An “Increased Risk” genetic result does not indicate that the patient’s actual vitamin A plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin A plasma levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual vitamin A plasma levels are optimal.

VITAMIN B2 DEFICIENCY

About: Vitamin B2 (riboflavin) is critical in carbohydrate, fat and protein metabolism. Vitamin B2 deficiency can lead to various skin conditions including angular cheilitis (inflammation of the corners of the mouth) and seborrheic dermatitis. Vitamin B2 acts to improve the secretion of mucus in the skin, which may help to clear up rosacea. It is directly used to prevent and treat dermatitis and eczema. Vitamin B2 is also a cofactor of the enzyme MTHFR, which is involved in folate metabolism. Folate can lower plasma levels of homocysteine. Low vitamin B2 levels have been associated with elevated homocysteine, which subsequently may affect skin aging by degrading skin collagen, fibrillin and elastin, as well as by inducing injury to skin blood vessels. Both dietary intake and genetic factors can influence vitamin B2 levels in the body. The recommended daily vitamin B2 intake for most adults is 1.1-1.3 milligrams. Vegetarians, vegans, pregnant and lactating women are at a higher risk of vitamin B2 deficiency.

Genetics: A genetic variant (rs1801133) in the MTHFR gene has been associated with individuals who tend to have elevated homocysteine levels and are more sensitive to changes in vitamin B2 levels. Individuals homozygous for the risk allele “A” (A/A genotype) at the rs1801133 locus are associated with high homocysteine levels when plasma vitamin B2 levels are low. Vitamin B2 supplementation has been shown to reduce homocysteine levels in these individuals. As high homocysteine levels are known to be a risk factor for cardiovascular disease and stroke, individuals who are homozygous for the risk allele “A” at the rs1801133 locus receive an outcome of “Increased Risk” of Vitamin B2 deficiency.

Possible outcomes: Increased Risk or Normal Risk (of vitamin B2 deficiency)

Markers Tested:

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<th>Gene/ Locus</th>
<th>SNP</th>
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<th>Alternative Allele</th>
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Note: All alleles are always displayed in the chromosome forward direction.
Limitations and warnings: This test reports on genetic predisposition for increased homocysteine levels due to lower levels of vitamin B2. Other tests are available to assess a patient’s levels of homocysteine and riboflavin in blood. An “Increased Risk” genetic result does not indicate that the patient’s actual blood levels of riboflavin are too low, but rather that the patient may be genetically predisposed to have increased homocysteine levels due to lower levels of riboflavin in blood. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual riboflavin levels in blood are optimal.

VITAMIN B6 DEFICIENCY

About: Vitamin B6 (pyridoxine) is involved in a variety of functions, such as protein and sugar metabolism, neurological development, immune function, and hemoglobin synthesis.\textsuperscript{170,172} Deficiency in vitamin B6 is associated with various skin disorders, such as pellagra-like dermatitis, stomatitis and seborrheic dermatosis.\textsuperscript{171,173,174} Vitamin B6 deficiency can also lead to vitamin B3 deficiency causing a thick, scaly pigmented rash on skin exposed to sunlight.\textsuperscript{161} Both dietary intake and genetic factors can influence vitamin B6 levels in the body. The recommended daily vitamin B6 intake for most adults is 1.3 milligrams.\textsuperscript{172} Individuals with alcohol dependency, pregnant women and pregnant women with preeclampsia or eclampsia may be at risk for vitamin B6 deficiency. However, excessive vitamin B6 intake (over 100 milligrams/day) can lead to skin lesions, dermatitis, and photosensitivity.\textsuperscript{174,175}

Genetics: A genetic variant in the \textit{NBPF3} gene has been associated with reduced levels of vitamin B6. Individuals with the risk allele “C” (T/C and C/C genotype) at the rs4654748 locus are at an increased risk of vitamin B6 deficiency.\textsuperscript{176,177}

Possible outcomes: Increased Risk or Normal Risk (of vitamin B6 deficiency)

Markers Tested:

<table>
<thead>
<tr>
<th>Gene/ Locus</th>
<th>SNP</th>
<th>Reference Allele</th>
<th>Alternative Allele</th>
<th>Risk Allele</th>
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Note: All alleles are always displayed in the chromosome forward direction.

Limitations and warnings: This test reports on genetic predisposition for decreased vitamin B6 levels. Other tests are available to directly assess a patient’s vitamin B6 plasma levels. An “Increased Risk” genetic result does not indicate that the patient’s actual vitamin B6 plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin B6 plasma levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual vitamin B6 plasma levels are optimal.

VITAMIN B12 DEFICIENCY

About: Vitamin B12 (cobalamin) plays an important role in the optimal neurological function. It is essential for hematopoiesis and DNA synthesis.\textsuperscript{176,179} In addition, vitamin B12 and folate aid in the lowering of homocysteine blood levels. Elevated homocysteine blood level is associated with cardiovascular, psychiatric, and skin diseases.\textsuperscript{180-182} Specifically, deficiency in vitamin B12 is associated with oral atrophy and skin hyperpigmentation.\textsuperscript{180,183} Both dietary intake and genetic factors can influence vitamin B12 levels in the body.
The daily recommended vitamin B12 intake for adults is 2.4 micrograms. Older adults and individuals who have limited consumption of animal products (vegans and vegetarians) are at a higher risk of B12 deficiency.178,182

**Genetics:** A genetic variant in the FUT2 gene has been associated with lowered vitamin B12 plasma levels. Individuals with risk allele “G” (A/G and G/G genotype) at the rs602662 locus are at an increased risk of vitamin B12 deficiency.176,177,184,185

**Possible outcomes:** Increased Risk or Normal Risk (of vitamin B12 deficiency)

**Markers Tested:**

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**Note:** All alleles are always displayed in the chromosome forward direction.

**Limitations and warnings:** This test reports on genetic predisposition for decreased vitamin B12 levels. Other tests are available to directly assess a patient’s vitamin B12 plasma levels. An “Increased Risk” genetic result does not indicate that the patient’s actual vitamin B12 plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin B12 plasma levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual vitamin B12 plasma levels are optimal.

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**VITAMIN C DEFICIENCY**

**About:** Vitamin C (L-ascorbic acid) must be acquired from dietary sources, as humans are unable to synthesize the molecule. Deficiency in vitamin C causes scurvy.155 Skin conditions associated with scurvy include abnormal thickening of the outer layer of skin, inflammation, delayed wound healing, and dry, rough skin.186 Both dietary intake and genetic factors can influence vitamin C levels in the body. The recommended daily vitamin C intake for most adults is 75-90 micrograms.187 Vitamin C topical application has also been widely used to improve signs of photoaging, including wrinkles, skin roughness and laxity. Vitamin C also promotes skin hydration and collagen production.155,156

**Genetics:** A genetic variant in the SLC23A1 gene is associated with decreased levels of circulating vitamin C. Individuals with the risk allele “T” (C/T and T/T genotype) at the rs33972313 locus are at an increased risk of vitamin C deficiency.188-190

**Possible outcomes:** Increased Risk or Normal Risk (of vitamin C deficiency)

**Markers Tested:**

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**Note:** All alleles are always displayed in the chromosome forward direction.
Limitations and warnings: This test reports on genetic predisposition for decreased vitamin C levels. Other tests are available to assess a patient’s vitamin C plasma levels. An “Increased Risk” genetic result does not indicate that the patient’s actual vitamin C plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin C plasma levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual vitamin C plasma levels are optimal.

VITAMIN D DEFICIENCY

About: Vitamin D is synthesized in the skin following exposure to ultraviolet (UV) B light, or from certain food consumption. Excessive exposure to UV radiation accelerates skin aging, while deficiency in vitamin D is associated with various skin conditions, such as psoriasis, atopic dermatitis, vitiligo and ichthyosis. Having sufficient vitamin D in the skin helps minimize acne, boost elasticity and skin immunity, stimulate collagen production, enhance radiance, and lessen lines and appearance of dark spots. Both dietary intake and genetic factors can influence vitamin D levels in the body. The recommended vitamin D intake for most adults is 15 micrograms/day (600 IUs/day); however, the American Academy of Dermatology recommends 25 micrograms/day (1000 IUs/day) for individuals who have an increased risk of vitamin D deficiency. Individuals with dark skin, limited sun exposure, older adults and those who choose to photoprotect using excessive sunblock may also be at risk.

Genetics: A genetic variant in the GC gene has been associated with decreased blood levels of vitamin D. Individuals with risk allele “G” (T/G or G/G genotype) at the rs2282679 locus are at an increased risk of vitamin D deficiency.

Possible outcomes: Increased Risk or Normal Risk (of vitamin D deficiency)

Markers Tested:

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Note: All alleles are always displayed in the chromosome forward direction.

Limitations and warnings: This test reports on genetic predisposition for decreased vitamin D levels. Other tests are available to assess a patient’s vitamin D plasma levels. An “Increased Risk” genetic result does not indicate that the patient’s actual vitamin D plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin D plasma levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual vitamin D plasma levels are optimal.

VITAMIN E DEFICIENCY

About: Vitamin E refers to a group of eight antioxidant molecules, of which alpha-tocopherol is the most abundant in the body. Vitamin E functions to promote a strong immune system and protects the skin from ultraviolet radiation and inflammation. Deficiency in vitamin E may lead to skin ulcers and increased collagen breakdown. Both dietary intake and genetic factors can influence vitamin E levels in the body. The
recommended daily vitamin E intake for most adults is 15 milligrams. Several studies have demonstrated that vitamin E and vitamin C taken together as oral supplements reduce UV-induced skin inflammation and decrease the skin's susceptibility to sunburn.

**Genetics:** An intergenic variant near the APOA5 gene has been associated with increased plasma levels of alpha-tocopherol or reduced risk of vitamin E deficiency. Individuals with risk allele “A” (C/A or A/A genotype) at the rs12272004 locus are at a reduced risk of vitamin E deficiency.

**Possible outcomes:** Normal Risk or Reduced Risk (of vitamin E deficiency)

**Markers Tested:**

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**Note:** All alleles are always displayed in the chromosome forward direction.

**Limitations and warnings:** This test reports on genetic predisposition for elevated vitamin E levels. Other tests are available to assess a patient’s vitamin E plasma levels. A “Reduced Risk” genetic result does not indicate that the patient’s actual vitamin E plasma levels are optimal, but rather that the patient may be genetically predisposed to have normal vitamin E plasma levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient's actual vitamin E plasma levels are optimal.

**FOLATE-FOLIC ACID DEFICIENCY**

**About:** Folate (folic acid) works synergistically with vitamins B6 and B12 in nucleic acid synthesis and amino acid metabolism. Deficiency in folate can increase the risk of psoriasis, deep venous thrombosis, oral atrophy and skin aging. Individuals with these conditions may benefit from increase uptake of folate rich foods or folic acid supplementation. Increased level of homocysteine, a signature of folate deficiency, is associated with skin aging caused by collagen, fibrillin and elastin degradation in the skin. Folic acid helps improve the firmness of human skin and also helps reduce the signs of skin aging. Both dietary and genetic factors can influence folate levels in the body. Folate is obtained from food or synthetically as folic acid supplement. The recommended daily folate intake for most adults is 400 micrograms (600 micrograms for pregnant women).

**Genetics:** Genetic variants in one or more risk alleles in the MTHFR gene are associated with individuals presenting low plasma folate levels. Individuals with a homozygous risk allele “A” (A/A genotype) at the rs1801133 locus are at a high risk of folate deficiency. Individuals with a heterozygous risk allele “A” (GA genotype) at the rs1801133 locus or individuals with a risk allele “T” (T/G or T/T genotype) at the rs1801131 locus are at an increased risk of folate deficiency. Compound heterozygous individuals with risk alleles in both loci are at high risk of folate deficiency.

**Possible outcomes:** High Risk, Increased Risk or Normal Risk (of folate deficiency)
Markers Tested:

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Note: All alleles are always displayed in the chromosome forward direction.

Limitations and warnings: This test reports on genetic predisposition for decreased folate levels. Other tests are available to assess a patient’s levels of blood folate. A “High Risk” or an “Increased Risk” genetic result does not indicate that the patient’s actual blood folate levels are too low, but rather that the patient may be genetically predisposed to have lower blood folate levels. Similarly, a “Normal Risk” genetic result does not indicate that the patient’s actual blood folate levels are optimal.

OMEGA-3 AND OMEGA-6 DEFICIENCY

About: Omega-3 and omega-6 fatty acids are polyunsaturated fatty acids (PUFAs) important for heart and brain health, anti-inflammatory response and aging. Both omega-3 derivative alpha-linolenic acid (ALA) and omega-6 derivative linoleic acid (LA) are essential fatty acids that must be acquired from dietary sources. In the body, ALA is further converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while LA is converted to arachidonic acid (AA). Deficiencies in these fatty acids can lead to various skin conditions, including dermatitis, acne, scaling, dry skin, and psoriasis. These skin conditions can be alleviated by omega fatty acids supplementation. Omega-3 fatty acids protect against UV-induced skin damage and reduce inflammation. Both dietary intake and genetic factors can influence fatty acid levels in the body. Most western diets contain sufficient omega-6 but insufficient omega-3, thus additional omega-3 intake may be beneficial.

Genetics: A genetic variant in the FADS1 gene has been associated with decreased blood levels of EPA (omega-3 derivative) and AA (omega-6 derivative). Individuals with a risk allele “C” (T/C or C/C genotype) at the rs174547 locus are at an increased risk of omega-3 and omega-6 deficiency.

Possible outcomes: Increased Risk or Normal Risk (of omega-3 and omega-6 deficiency)

Markers Tested:

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Note: All alleles are always displayed in the chromosome forward direction.
REFERENCES


