Can Skin Aging be Reversible by Anti-Aging Treatments with Genetic Analysis?

Özlem Özge YILMAZ[*], Tolga POLAT[**], Beste TACAL ASLAN[***], Korkut ULUCAN[****]

Abstract

Skin aging is affected by internal and external factors. The stratum corneum consists of keratinocytes, and as these mature in the epidermis, their proliferative potential gradually decreases and the skin undergoes programmed destruction. There are many single nucleotid polymorphism (SNP)s associated with skin aging. The *COL1A1, MMP1,* and *CYP1A2* genes are responsible for collagen degradation and production. Changes in these genes affect collagen degradation and production. The *MCR1* and *STXBP5L* genes are important for ultraviolet (UV) protection and moisturizing the skin. Due to changes in these genes, the skin cannot be well protected from UV rays, and skin aging accelerates. As free radicals in the skin increase, oxidative stress increases. The *SOD2, GPX1,* and *GSTP1* genes play a role in protecting the body against oxidative stress. Also, coenzyme Q10 acts against oxidative stress. The change in the *NQO1* gene cannot convert coenzyme Q10 to its active form, ubiquinol, which causes increased oxidative stress in the skin. Another factor that affects the aging of the skin is the aggressive immune system. The *TNF-α* gene influences the inflammatory responses generated by the immune system. If the *TNF-α* gene is not working properly, it can create an overly aggressive reaction and damage tissue. In addition, vitamin E is a powerful antioxidant, and changes in the *APOA5* gene cause vitamin E deficiency. This affects the protection of the skin from UV rays. Another important vitamin for the skin is vitamin C, and the *SLC23A1* gene is involved in vitamin C transport. Changes in this gene cause vitamin C deficiency and affect oxidative stress and collagen production in the skin. These polymorphisms affect the intrinsic and extrinsic factors that affect the aging of the skin. In order for individuals to prevent skin aging, these polymorphisms should be analyzed, and skin aging can be delayed with skin care products suitable for the person.

Keywords: Skin, aging, internal factors, external factors, polymorphisms

Cilt Yaşlanması, Genetik Analizli Yaşlanma Karşıtı Tedavilerle Geri Döndürülebilir Mi?

Öz

Cilt yaşlanması iç ve dış faktörlerden etkilenir. Stratum corneum keratinositlerden oluşur ve bunlar epidermisi olgunlaştırdıkça proliferatif potansiyelleri yavaş yavaş azalır ve cilt programlanmış yıkıma uğrar.

Derleme Makale (Review Article)
Geliş / Received: 25.08.2021 & **Kabul / Accepted:** 28.11.2023
DOI: https://doi.org/10.38079/igusabder.987140
[*] Masters Student, Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Istanbul, Türkiye. E-mail: ozlem.ozge@marun.edu.tr ORCID https://orcid.org/0000-0002-4085-6159
[**] Masters Student, Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Istanbul, Türkiye. E-mail: tolgapolat.mbg@gmail.com ORCID https://orcid.org/0000-0002-2064-6613
[***] Res. Assist., Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Istanbul, Türkiye. E-mail: btacal@gmail.com ORCID https://orcid.org/0000-0001-5271-7917
[****] Corresponding Author, Prof. Dr., Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Istanbul, Türkiye. E-mail: korkutulucan@hotmail.com ORCID https://orcid.org/0000-0002-1304-9386

Cilt yaşlanması ile ilişkili birçok tek nükleotid polimorfizm (SNP) vardır. *COL1A1*, *MMP1* ve *CYP1A2* genleri, kolajen yıkımı ve üretiminden sorumludur. Bu genlerdeki değişiklikler kolajen yıkımını ve üretimini etkiler. *MCR1* ve *STXBP5L* genleri, ultraviyole (UV) koruması ve cildi nemlendirmek için önemlidir. Bu genlerdeki değişiklikler nedeniyle cilt UV ışınlarından iyi korunamaz ve cilt yaşlanması hızlanır. Derideki serbest radikaller arttıkça oksidatif stres artar. *SOD2*, *GPX1* ve *GSTP1* genleri vücudun oksidatif strese karşı korunmasında rol oynar. Ayrıca koenzim Q10 oksidatif strese karşı da etki eder. *NQO1* genindeki değişiklik, koenzim Q10'u aktif formu olan ubiquinol'e dönüştüremez ve bu da ciltte oksidatif stresin artmasına neden olur. Cildin yaşlanmasını etkileyen bir diğer faktör de agresif bağışıklık sistemidir. *TNF-α* geni, bağışıklık sistemi tarafından üretilen inflamatuar yanıtları etkiler. *TNF-α* geni düzgün çalışmıyorsa, aşırı agresif bir reaksiyon oluşturabilir ve dokuya zarar verebilir. Ayrıca E Vitamini güçlü bir antioksidandır ve *APOA5* genindeki değişiklikler E vitamini eksikliğine neden olur. Bu, cildin UV ışınlarından korunmasını etkiler. Cilt için bir diğer önemli vitamin ise C vitaminidir ve *SLC23A1* geni C vitamini taşınmasında rol oynar. Bu gendeki değişiklikler C vitamini eksikliğine neden olur ve ciltte oksidatif stres ve kolajen üretimini etkiler. Bu polimorfizmler cildin yaşlanmasını etkileyen içsel ve dışsal faktörleri etkiler. Bireylerin cilt yaşlanmasının önüne geçebilmesi için bu polimorfizmlerin analiz edilmesi ve kişiye uygun cilt bakım ürünleri ile cilt yaşlanmasının geciktirilmesi sağlanabilir.

Anahtar Sözcükler: Cilt, yaşlanma, iç faktörler, dış faktörler, polimorfizmler

Introduction

Skin aging is affected by internal and external factors. Internal factors are caused by physical changes and genetic factors that occur in normal aging[1]. Chronoaging occurs in the mid-20s, decreases in dermal mast cells and collagen production[2]. External factors accelerate aging as a result of environmental factors. Photoaging is caused by sunlight consisting of infrared, visible, and ultraviolet (UV) light. Ultraviolet B (UVB) is the main cause of direct DNA damage while Ultraviolet A (UVA) damages connective tissue in the dermis. Therefore, UVA has a larger role in skin photo-aging[3]. All these skin changes also differ by skin type and ethnicity.

The skin epidermis consists of the inanimate layer called the stratum corneum and the keratinocytes that form the viable epidermis[4]. The stratum corneum is the body's main barrier to the environment and is defined by a matrix model of ceramides, cholesterol, and fatty acids. Keratinocytes are proliferative and located in the basal layer of the epidermis. As the keratinocyte cells mature the epidermis, they slowly lose their proliferative potential and undergo programmed destruction[5].

Aging skin causes certain changes in internal and external factors, according to genetic and environmental factors. That's why aging is considered a chronic degenerative disease. Recent research highlights the importance of variants of genes. If the rate of these variants is seen in more than 1% of a population, this change is called polymorphism. If polymorphisms in our genes cause only one nucleotide to change, it's called a single nucleotide polymorphism (SNP)[6].

The Effect of Collagen on the Skin

There are many SNPs associated with skin aging. Type 1 collagen is the main structural component of the extracellular matrix of the dermis and is the form of collagen protein found in tissues. The *COL1A1* gene is located on chromosome 17q21.33 and collagen production and transformation are altered as a result of polymorphisms in the *COL1A1* gene and differences in the expression of the collagen protein[7]. Collagen consists of long, flexible fibers that accumulate in the skin and give it firmness. For long-term youth, old collagen must be destroyed and new collagen must be produced. There are mechanisms that separate and destroy old collagen from the skin. The *MMP1* gene is located on chromosome 11q22.2 and is responsible for the production of the MMP1 enzyme. The MMP1 enzyme (Collagenase) breaks down old collagen. A variation in the *MMP1* gene causes an overproduction of the MMP1 enzyme, and the breakdown of collagen in the skin occurs very quickly. The skin gradually loses its hardness, leading to faster aging. If the MMP1 gene is working properly, a normal amount of MMP1 enzyme is produced. Thus, the old collagen is broken down, and the skin preserves its youth[8,9].

Collagen and Caffeine

Collagen is important for the tensile force in the skin and must be constantly regenerated to maintain the youthfulness of the skin. The prolidase enzyme produces the raw material (proline) for collagen production. If prolidase is not produced for some reason, the skin begins to break down collagen. Caffeine acts as a destructive factor inhibiting Prolidase activity. The *CYP1A2* gene is located on chromosome 15q24.1. If the *CYP1A2* gene is not working properly, caffeine cannot be removed from cells before it affects Collagen production. The normally functioning *CYP1A2* gene enables the breakdown of caffeine in the body without affecting collagen production[10,11].

UV Rays Protection of Skin

The most important and main factor in skin aging is UV rays. Ultraviolet (UV) rays are the most harmful environmental factor preventing the long-term protection of young skin. UV-induced skin aging or photoaging causes morphological changes in both epidermal and dermal areas. The sun's UV rays can damage the skin if not neutralized properly. UV rays can penetrate deep into tissue and damage skin in the long term if genes do not provide adequate protection against UV rays. If the genes are able to adequately protect the skin against UV rays, the skin will not be damaged[12].

MCR1 and *STXBP5L* genes are gene regions that protect us from UV rays. The *MC1R* gene is located on chromosome 16q24.3 and encodes a protein called melanocortin-1 receptor. This receptor plays an important role in pigmentation. Melanin cells are specialized cells that produce pigment and are the substance that gives color to hair and eyes. Melanocytes form two types of melanin: eumelanin and pheomelanin. Eumelanin protects the skin from damage caused by UV rays. Pheomelanin cannot protect the skin against UV rays, so it causes skin damage when

exposed to excessive sun. The *MCR1* receptor is located on the surface of the melanocytes and controls what type of melanin is produced by the melanocytes. When the MCR1 receptor is activated, it triggers a series of chemical reactions within melanocytes that induce cells to make eumelanin. If the *MCR1* receptor is blocked, melanocytes produce pheomelanin instead of eumelanin. *MCR1* polymorphisms cause melanocytes to produce mostly pheomelanin by reducing the production of eumelanin by the melanocortin-1 receptor[13,14]. The *STXBP5L* gene is located on chromosome 3q13.33 and five contain WD40 repeats, a C-terminal syntax binding (STXB) domain. *STXBP5L* regulates epithelial polarity and its mutation can lead to the development of a tumor-like phenotype. The *STXBP5L* gene has specific gene variations that also affect the skin's UV sensitivity[15].

Hyaluronic Acid

Besides the long strands of collagen, the extracellular matrix of the skin contains Hyaluronic acid, which stores moisture. The hyaluronic acid molecule is found in the collagen matrix in the skin. Hyaluronic acid has many roles in the body: control of tissue hydration and water transport, supramolecular assembly of proteoglycans in the extracellular matrix, and multiple receptor-mediated roles in cell separation[16]. Therefore, hyaluronic acid is found in high concentrations in many soft connective tissues, such as the skin, umbilical cord, and synovial fluid. Hyaluronic acid keeps the skin moist and provides a youthful appearance. Hyaluronic acid is destroyed in the skin if the harmful UV rays (mainly UV-B rays) of the sun are not neutralized by UV protective genes such as *MCR1* and *STXBP5L*[13- 15]. Therefore, the skin loses moisture and ages faster. When the UV protective genes are working properly, harmful UV-B rays cannot penetrate the skin. Hyaluronic acid retains and keeps skin moist and delays aging[17].

Oxidative Stress and Skin

Approximately 5% of the inhaled oxygen is metabolically converted into free radicals, such as superoxide, in the body. In addition, free radicals are formed in the skin from the damage caused by UV rays. These substances are considered to be the main cause of aging skin. If free radicals are not neutralized, they can damage tissues and accelerate aging. If there are too many free radicals in the body, oxidative stress increases. Because free radicals are harmful, there are some genes that protect us against free radicals. The *SOD2* gene is located on chromosome 6q25.3 and encodes the enzyme superoxide dismutase-2. This enzyme is involved in the breakdown of reactive oxygen molecules (ROS). Therefore, these enzymes play a role in protecting the body against oxidative stress. Due to the change in the *SOD2* gene, the activity of this enzyme may decrease, leading to increased oxidative stress in the mitochondria[18].

The GPX1 gene is located on chromosome 3p21.3 and encodes the enzyme glutathione peroxidase, which catalyzes the reduction of peroxide and hydrogen peroxide. This enzyme plays a role in protecting the body from oxidative stress[19]. The GSTP1 gene is located on chromosome 11q13.2

and encodes the GSTP1 enzymes. Glutathione S-transferases are found in the liver and lymphocytes. They play a role in the detoxification of endogenous and exogenous substances. *GSTP1* enzymes are involved in the metabolism of endogenous metabolites and protect cells from oxidative stress similarly to *SOD2* and *GPX*[18,20]. When these genes function normally, they can neutralize free radicals without causing permanent damage. However, if some or all of these genes are dysfunctional, they cannot neutralize free radicals and cause permanent damage.

Premature cell aging is associated with increased free radical concentrations. The body's antioxidant system scavenges or reduces free radicals. Coenzyme Q10 is known to be a powerful antioxidant[21]. Coenzyme Q10 (Ubiquinone) can be produced by the body or absorbed through the skin and through food. Initially, Coenzyme Q10 is not active in the body. The *NQO1* gene is located on chromosome 16q22.1 and Coenzyme Q10 is converted by the *NQO1* gene to its active form, Ubiquinol. It shows its antioxidant effect in the form of ubiquinol. If the *NQO1* gene is functioning normally, the NQO1 protein is sufficiently produced, and the inactive Coenzyme Q10 turns into its active form Ubiquinol. A genetic variation in the *NQO1* gene impairs the function of the protein so that its conversion to active Ubiquinol is inhibited or the conversion occurs slower than normal. This leads to increased oxidative stress and premature aging of the skin[22].

TNF-α Effect of Inflammatory Reactions

Inflammatory responses (inflammation) are responses created by the immune system to protect the body against various diseases or injuries. Inflammatory responses are triggered by the body's immune system, and an extremely aggressive state occurs. This can damage tissue and accelerate aging. The genetically triggered hyper-aggressive immune system damages the skin from within. Inflammatory processes in the skin are mainly caused by the UV rays of the Sun[23]. Some genetic variations make the immune system extremely aggressive, meaning it can cause more damage to tissue. The TNF-alpha gene is located on chromosome 6p21.33. A genetic variation in the promoter of the *TNF-α* gene leads to increased transcription and, thus, increased activation of inflammatory reactions. If the *TNF-α* gene is functioning properly, the immune system will react adequately to the damage caused by the Sun's UV rays. If the *TNF-α* gene is not working properly, it can create an overly aggressive reaction and damage tissue[24].

Vitamin E Deficiency

Vitamin E is a powerful antioxidant agent and contains tocopherol and tocotrienol with antioxidant properties. Alpha-tocopherol is the most important fat-soluble antioxidant. Vitamin E molecules, in combination with high or low lipoproteins, are packaged into chicomicrons and released into the circulation[24]. The *APOA5* gene is located on chromosome 11q23.3 and is an important regulator of circulating triglycerides. Triglycerides turn into lipoproteins and lipoproteins play a role in transporting fatty acids between fat cells and other cells. A variation on *APOA5* gene has been reported to be associated with different α-tocopherol levels due to its effect

on circulating triglycerides and chylomicrons. Low α-tocopherol levels cause vitamin E deficiency and increase collagen loss. High α -tocopherol levels increase vitamin E in the body. Thus, vitamin E in the skin protects the skin from UV rays and strengthens the immune system[25,26].

Vitamin C Deficiency

Humans cannot synthesize vitamin C (L-ascorbic acid). Therefore, humans get vitamin C from dietary sources. Vitamin C is important for collagen production and prevents oxidative stress. After dietary ingestion, vitamin C is transported across the cell membrane by both facilitated and active transport. Active transport of vitamin C in cells is achieved by sodium L-ascorbic acid co-transporters (SVCTs). There are two isoforms of SVCTs: SVCT1 and SVCT2. Mainly SVCT1 plays a role in L-ascorbic acid transport[27]. *SLC23A1* is located on chromosome 5q31.2 and plays a role in the encoding of SVCT1s. If the *SLC23A1* gene is functioning properly, L-ascorbic acid is transported by SVCT1 at a higher rate and capacity. If there is a genetic variation in the *SLC23A1* gene, L-ascorbic acid is transported at a lower level. This causes vitamin C deficiency. Vitamin C deficiency causes abnormal thickening of the outer layer of the skin, delayed healing of wounds, dry and rough skin, hair loss, and tooth loss[28].

Individuals have different skin types due to the genes described above and their effects. Since these changes will vary from person to person, individuals should use personalized skin care products suitable for them. For this reason, we aimed to establish a relationship between polymorphisms in genes and skin, as shown in Table 1. Genotypes with a bad or moderate effect cause premature aging of the skin. Genotypes with good effects aim to prevent skin aging.

Table 1. Correlation between the assigned effect and the genotype

Gene	SNP	Bad Effect	Moderate Effect	Good Effect
COL1A1	rs1800012	TT	GT	GG
MMP1	rs1799750	GG	G/Del	Del/DeL
CYP1A2	rs762551	CC	CA	AA
STXBP5L	rs322458	GG	AG	AA
MCR1	rs1805006	AA	AC	CC
	rs1805007	TT	CT	CC
SOD2	rs4880	TT	CT	CC
GPX1	rs1050450	TT	CT	CC

GSTP1	rs1695	GG	AG	AA
NQO1	rs1800566	TT	CT	CC
TNF-α	rs1800629	AA	GA	GG
APOA5	rs662799	AA	AG	GG
SLC23A1	rs33972313	AA	AG	GG

Conclusion

Aging has a variety of causes. Genetic and environmental effects such as UVR, production or destruction of collagen in the skin, oxidative stress, the coenzyme Q10 effect, inflammatory reactions, and nutritional deficiency play an important role. These effects differ from person to person, and these differences are down to genes. Individuals are equipped with genes that are functioning properly to be protected from the aging process. Polymorphisms in these genes alter the process by affecting the functions of genes that encode aging factors. The skin structure becomes clear by analyzing the polymorphisms in individuals with a genetic test. Thus, the aging of the skin can be slowed down by creating personalized skin care products. In future time, with the discovery of new proteins and polymorhisms related to skin aging mechanism, this new factors should be added to routine genetic analysis. This make the skin care products more effective against skin aging.

REFERENCES

1. Pojšak B, Dahmane RG, Godic A. Intrinsic skin aging: The role of oxidative stress. *Acta Dermatovenerologica*. 2012;21(2):33-36. doi: 10.2478/v10162-012-0009-0.
2. Kosmadaki MG, Gilchrest BA. The role of telomeres in skin aging/photoaging. *Micron*. 2004;35(3):155-159. doi: 10.1016/j.micron.2003.11.002.
3. Yaar M, Gilchrest BA. Photoageing: mechanism, prevention and therapy. *Br J Dermatol*. 2007;157(5):874-887. doi: 10.1111/j.1365-2133.2007.08108.x.
4. Tobin DJ. Introduction to skin aging. *Journal of Tissue Viability*. 2017;26(1):37-46. doi: 10.1016/j.jtv.2016.03.002.
5. Kim JH, Ahn B, Choi SG, et al. Amino acids disrupt calcium-dependent adhesion of stratum corneum. *PloS one*. 2019;14(4):e0215244. doi: 10.1371/journal.pone.0215244.
6. Ulucan K. *Şampiyon Geni*. İstanbul*:* Destek Yayınları; 2019:49-50.

7. Mann V, Hobson EE, Li B, Stewart TL, Grant SF. A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. *J Clin Invest*. 2001;107(7):899-907. doi: 10.1172/JCI10347.

8. Fujimoto T, Parry S, Urbanek M, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 (MMP-1) promoter influences amnion cell MMP-1 expression and risk for preterm premature rupture of the fetal membranes. *J Biol Chem*. 2002;277(8):6296-302. doi: 10.1074/jbc.M107865200.

9. Rutter JL, Mitchell TI, Buttice G, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. *Cancer Res*. 1998;58(23):5321–5325.

10. Thorn CF, Aklillu E, McDonagh EM, Klein TE, Altman RB. PharmGKB summary: caffeine pathway. *Pharmacogenet Genomics*. 2012;22(5):389-395. doi: 10.1097/FPC.0b013e3283505d5e.

11. Womack CJ, Saunders MJ, Bechtel MK, et al. The influence of a CYP1A2 polymorphism on the ergogenic effects of caffeine. *J Int Soc Sports Nutr*. 2012;9(1):7. doi: 10.1186/1550-2783-9-7.

12. Rabe JH, Mamelak AJ, McElgunn PJ, Morison WL, Sauder DN. Photoaging: mechanisms and repair. *J Am Acad Dermatol*. 2006;55(1):1-19. doi: 10.1016/j.jaad.2005.05.010.

13. Mumm CD, Draznin M. Melanocortin-1 receptor: loss of function mutations and skin cancer. *Dermatol Online J*. 2006;12(5):13.

14. Elfakir A, Ezzedine K, Latreille J, et al. Functional MC1R-gene variants are associated with increased risk for severe photoaging of facial skin. *J Invest Dermatol*. 2010;130(4):1107-1115. doi: 10.1038/jid.2009.366.

15. Le Clerc S, Taing L, Ezzedine K, et al. A genome-wide association study in caucasian women points out a putative role of the STXBP5L gene in facial photoaging. *Journal of Investigative Dermatology*. 2013;133(4):929-935. doi: 10.1038/jid.2012.458.

16. Nobile V, Buonocore D, Michelotti A, Marzatico F. Anti-aging and filling efficacy of six types hyaluronic acid based dermo-cosmetic treatment: double blind, randomized clinical trial of efficacy and safety. *J Cosmet Dermatol*. 2014;13(4):277-287. doi: 10.1111/jocd.12120.

17. Dai G, Freudenberger T, Zipper P, et al. Chronic ultraviolet B irradiation causes loss of hyaluronic acid from mouse dermis because of down-regulation of hyaluronic acid synthases. *The American Journal of Pathology*. 2007;171(5):1451–1461. doi: 10.2353/ajpath.2007.070136.

18. Funke S, Risch A, Nieters A, et al. Genetic polymorphisms in genes related to oxidative Stress (GSTP1, GSTM1, GSTT1, CAT, MnSOD, MPO, eNOS) and Survival of rectal cancer patients after radiotherapy. *Journal of Cancer Epidemiology*. 2009;2009:6. doi: 10.1155/2009/302047.

19. Mohammedi K, Patente TA, Bellili-Muñoz N, et al. Glutathione peroxidase-1 gene (GPX1) variants, oxidative stress and risk of kidney complications in people with type 1 diabetes. *Metabolism*. 2016;65(2):12-19. doi: 10.1016/j.metabol.2015.10.004.

20. Sreeja L, Syamala V, Hariharan S, et al. Glutathione S-transferase M1, T1 and P1 polymorphisms: susceptibility and outcome in lung cancer patients. *J Exp Ther Oncol*. 2008;7(1):73-85.

21. Lohan SB, Bauersachs S, Ahlberg S, et al. Ultra-small lipid nanoparticles promote the penetration of coenzyme 5 Q10 in skin cells and counteract oxidative stress. *Eur J Pharm Biopharm*. 2014;89:201-207. doi: 10.1016/j.ejpb.2014.12.008.

22. Fischer A, Schmelzer C, Rimbach G, Niklowitz P, Menke T, Döring F. Association between genetic variants in the Coenzyme Q10 metabolism and Coenzyme Q10 status in humans. *BMC Res Notes*. 2011;4:245. doi: 10.1186/1756-0500-4-245.

23. Hruza LL, Pentland AP. Mechanisms of UV-induced inflammation. *J Invest Dermatol*. 1993;100(1):35-41. doi: 10.1111/1523-1747.ep12355240.

24. Lakka HM, Lakka TA, Rankinen T, et al. The TNF-α G-308A polymorphism is associated with C-reactive protein levels: The HERITAGE Family Study. *Vascular Pharmacology*. 2006;44(5):377–383. doi: 10.1016/j.vph.2006.02.002.

25. Wu Y, Marvelle AF, Li J, et al. Genetic association with lipids in Filipinos: waist circumference modifies an APOA5 effect on triglyceride levels. *Journal of lipid research*. 2013;*54*(11):3198–3205. doi: 10.1194/jlr.P042077.

26. Jiang CQ, Liu B, Cheung BM, et al. A single nucleotide polymorphism in APOA5 determines triglyceride levels in Hong Kong and Guangzhou Chinese. *Eur J Hum Genet*. 2010;18(11):1255-60. doi: 10.1038/ejhg.2010.93.

27. Wilson JX. Regulation of vitamin C transport. *Annual Review of Nutrition*. 2005;25(1):105-125. doi: 10.1146/annurev.nutr.25.050304.092647.

28. Timpson NJ, Forouhi NG, Brion MJ, et al. Genetic variation at the SLC23A1 locus is associated with circulating concentrations of L-ascorbic acid (vitamin C): evidence from 5 independent studies with>15,000 participants. *The American Journal of Clinical Nutrition*. 2010;92(2):375–382. doi: 10.3945/ajcn.2010.29438.