CYP1A2, Caffeine, and Collagen Homeostasis (Literature Review)

Sabrina Frauenschuh[1], Magdalena Behensky[1], René Rohrmanstorfer[1], Thomas Dullnig[1], Daniel Wallerstorfer[1]

[1]Laboratory, Novogenia GmbH, Salzburg, Austria

Corresponding Author: Daniel Wallerstorfer (ceo@novogenia.com)

ABSTRACT

Background:
Collagen is a major structural constituent of the dermal extracellular matrix and a key determinant of skin tensile strength. Age-related reduction in collagen content and integrity contribute substantially to cutaneous fragility and the phenotypic features of skin aging. A mechanistic framework has been proposed in which CYP1A2-dependent caffeine metabolism influences prolidase activity, proline availability, and, consequently, collagen biosynthesis. The *CYP1A2* rs762551 polymorphism is to be interpreted as a modulator of interindividual variation in caffeine metabolism and enzyme inducibility (Varani et al., 2006; Fisher et al., 2009; Cornelis et al., 2006; Djordjevic et al., 2010).

Methods:
A narrative review was undertaken to synthesize current evidence on the relationship between genetic variations in caffeine metabolism and collagen homeostasis. Emphasis was placed on studies examining CYP1A2-dependent caffeine biotransformation, prolidase-mediated regulation of proline recycling and collagen biosynthesis, and the effects of caffeine on dermal fibroblast function and extracellular matrix metabolism. Several studies were evaluated to establish the mechanistic and translational rationale for hydrolyzed collagen, vitamin C, and folic acid as modulators of procollagen synthesis, dermal matrix organization, and connective tissue integrity (Cornelis et al., 2006; Djordjevic et al., 2010; Surazynski et al., 2008; Donejko et al., 2014; Proksch et al., 2014; Nusgens et al., 2001; Knott et al., 2007; Fischer et al., 2011).

Results:
The literature supports three central propositions. First, *CYP1A2* rs762551 meaningfully influences caffeine disposition and caffeine-related physiological responses (Cornelis et al., 2006; Palatini et al., 2009; Guessous et al., 2012; Djordjevic et al., 2010; Yoshihara et al., 2019; Zhou and Hyppönen, 2019). Second, prolidase is a key regulator of collagen turnover and proline recycling, and caffeine suppresses both prolidase activity and collagen biosynthesis in cultured human skin fibroblasts (Palka and Phang, 1997; Surazynski et al., 2008; Donejko et al., 2014). Third, oral collagen peptides, vitamin C, and folate-related interventions each have mechanistic or clinical support for promoting collagen-associated skin endpoints (Proksch et al., 2014; Asserin et al., 2015; de Miranda et al., 2021;

Murad et al., 1981; Tajima and Pinnell, 1996; Nusgens et al., 2001; Knott et al., 2007; Fischer et al., 2011).

Discussion:
The available evidence supports a coherent mechanistic model in which CYP1A2 genotypes associated with slower caffeine metabolism leads to more prolonged caffeine exposure, thereby increasing the likelihood of sustained interference with prolidase-dependent proline recycling and collagen biosynthesis. Pharmacogenetic studies have shown that the rs762551 variant significantly influences caffeine metabolic capacity, whereas experimental studies in human dermal fibroblasts demonstrate that caffeine suppresses prolidase activity and reduces collagen synthesis. Considered collectively, these findings provide a scientifically grounded basis for the view that genotype-dependent differences in caffeine clearance may contribute to interindividual variation in collagen homeostasis, and they support moderation of caffeine intake as a biologically rational strategy for individuals with reduced caffeine-metabolizing capacity (Djordjevic et al., 2010; Donejko et al., 2014).

Subjects Genetics, Collagen **Keywords:** Genetics, Polymorphism, Collagen Production

INTRODUCTION

Skin aging has been associated with alterations in dermal extracellular matrix composition and function, prompting investigation into compounds that may support collagen production and preserve dermal structure. Ascorbic acid is of particular interest, as it has been shown to stimulate collagen synthesis and enhance the gene expression of type I and III collagen in human skin fibroblasts. In addition, topical application has been reported to increase dermal levels of collagens, collagen-processing enzymes, and tissue inhibitor of metalloproteinase-1 (Murad et al., 1981; Tajima and Pinnell, 1996; Nusgens et al., 2001).

Collagen-derived interventions represent a complementary approach. Orally administered collagen hydrolysates deliver bioactive peptides to the bloodstream and skin and have been associated with improvements in skin wrinkles, hydration, and dermal matrix synthesis. Furthermore, topical collagen tripeptides may contribute to anti-aging and antiglycation effects (Yazaki et al., 2017; Proksch et al., 2014; Asserin et al., 2015; de Miranda et al., 2021; Lee et al., 2022).

In addition to collagen-targeted strategies, folic acid has been shown to penetrate human skin, improve skin firmness, and support nucleotide excision repair capacity, indicating that maintenance of dermal integrity may depend not only on collagen synthesis but also on efficient cellular repair mechanisms (Knott et al., 2007; Fischer et al., 2011; Burger et al., 2007).

Together, these findings highlight collagen production and matrix homeostasis as important factors in the context of skin aging and suggest potential targets for its modulation.

CYP1A2 as a Nutrigenetic Determinant

Among nutrigenetic determinants, *CYP1A2* is of particular relevance because it mediates a substantial proportion of caffeine biotransformation and thereby influences the magnitude and duration of systemic caffeine exposure. The rs762551 polymorphism functions as a regulatory variant that modifies *CYP1A2* activity and inducibility rather than abolishing enzyme expression. Consequently, genotype-dependent differences in caffeine clearance become especially evident under conditions of regular or high caffeine intake, providing a mechanistic basis for interindividual variability in caffeine-related physiological responses (Koonrungsesomboon et al., 2018; Djordjevic et al., 2010; Cornelis et al., 2006; Palatini et al., 2009). This genotype-dependent variability is of particular importance in nutrigenetic interpretation, as it may influence not only acute responses to caffeine but also the cumulative biological effects associated with repeated exposure. Individuals with reduced *CYP1A2* activity or lower inducibility may experience more sustained systemic caffeine levels, whereas carriers of higher-inducibility genotypes are more likely to metabolize caffeine more efficiently. In this context, rs762551 can be regarded as a functionally relevant determinant of caffeine handling that contributes to biologically meaningful differences in exposure kinetics and downstream physiological effects across individuals (Koonrungsesomboon et al., 2018; Djordjevic et al., 2010; Cornelis et al., 2006; Palatini et al., 2009).

CYP1A2, Caffeine Exposure, and Skin Aging

The relevance of *CYP1A2* to skin aging is most plausibly mediated through collagen-associated metabolic pathways. In dermal fibroblasts, caffeine suppresses collagen biosynthesis and is accompanied by reduced prolidase activity, whereas prolidase is essential for the recycling of proline- and hydroxyproline-containing dipeptides required for collagen resynthesis and extracellular matrix renewal. Accordingly, prolonged caffeine exposure may create a biochemical environment that is less favorable for efficient dermal matrix maintenance and long-term collagen homeostasis (Palka and Phang, 1997; Surazynski et al., 2008; Donejko et al., 2014). This relationship is of particular importance because collagen renewal depends not only on de novo synthesis, but also on effective reutilization of amino acid substrates generated during matrix turnover. Impairment of prolidase-dependent proline salvage may therefore contribute to reduced fibroblast anabolic capacity and diminished extracellular-matrix repair. In this context, interindividual differences in *CYP1A2*-mediated caffeine clearance may influence the extent to which caffeine-related suppression of collagen metabolism is sustained over time. Thus, *CYP1A2* may be regarded as a biologically relevant upstream determinant of collagen-associated processes that contribute to dermal aging and structural decline (Palka and Phang, 1997; Surazynski et al., 2008; Donejko et al., 2014).

Prolidase as a Collagen-Relevant Metabolic Node

Prolidase is a central enzyme in collagen turnover, as it recycles proline- and hydroxyproline-containing dipeptides required for extracellular matrix renewal and collagen resynthesis. In dermal fibroblasts, prolidase activity is functionally linked to matrix-dependent signaling pathways that regulate collagen biosynthesis. Experimental evidence further shows that caffeine reduces collagen production in human skin fibroblasts in a dose-dependent manner, accompanied by diminished prolidase activity and attenuation of β1-integrin- and insulin-like growth factor-related anabolic signaling. Collectively, these findings support a mechanistic model in which reduced caffeine clearance may prolong caffeine exposure and thereby promote suppression of prolidase-dependent collagen synthesis, providing a biologically plausible link between CYP1A2 variation and collagen homeostasis (Djordjevic et al., 2010; Surazynski et al., 2008; Donejko et al., 2014).

Table 1: Genotype-Focused Studies Relevant to *CYP1A2*-Mediated Caffeine Metabolism and Collagen Homeostasis

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) Investigated	Primary Outcome / Key Findings
Koonrung-sesomboon et al., 2018	Systematic review and meta-analysis	3,570 human subjects across caffeine-phenotyping studies	Multiple *CYP1A2* polymorphisms, primarily rs762551 (-163C>A)	Identified rs762551 as the most consistent functional determinant of *CYP1A2* activity and inducibility; carriers of the variant associated with higher inducibility showed greater caffeine metabolic activity, particularly among smokers.

Cornelis et al., 2006	Population-based case-control study	2,014 first acute nonfatal myocardial infarction cases and 2,014 matched controls from Costa Rica	*CYP1A2* rapid/slow metabolizer classification related to *1F / rs762551	Coffee-associated risk was confined to slow metabolizers, supporting the biological importance of *CYP1A2* genotype in determining caffeine-related systemic effects.
Palatini et al., 2009	Prospective cohort study	553 young White adults screened for stage 1 hypertension	*CYP1A2* genotype (*1F-based classification)	The association between coffee intake and incident hypertension varied by *CYP1A2* genotype, reinforcing that genotype materially modifies physiological responses to habitual caffeine exposure.
Guessous et al., 2012	Multicohort observational study with quasi-experimental component	Four observational cohorts (n = 16,719) and one quasi-experimental study (n = 106), European adults	rs762551	The rs762551 C allele was associated with lower *CYP1A2* activity in non-smokers; genotype effects on blood pressure were modified by caffeine intake, confirming functional relevance of *CYP1A2* variation.
Yoshihara et al., 2019	Prospective double-blind randomized trial	201 healthy volunteers	rs762551 (with additional analysis of habitual caffeine intake)	In low habitual caffeine consumers, rs762551 CC carriers exhibited a greater systolic blood pressure response to caffeine than AA/CA carriers, demonstrating genotype-specific sensitivity to acute caffeine exposure.

Supportive Interventions for Collagen-Related Skin Biology

Given that skin aging is accompanied by progressive impairment of collagen synthesis, extracellular-matrix organization, and dermal structural stability, interventions that support collagen homeostasis are of considerable biological relevance. Such approaches may act through complementary mechanisms, including the delivery of bioactive collagen-derived peptides, direct stimulation of collagen biosynthesis, and support of cellular processes required for matrix maintenance and repair. Within this framework, hydrolyzed collagen, vitamin C, and folic acid represent mechanistically distinct but convergent strategies for the preservation of dermal integrity, as each has been associated with pathways relevant to collagen renewal, connective tissue stability, and maintenance of skin structure (Varani et al., 2006; Proksch et al., 2014; Murad et al., 1981; Knott et al., 2007).

Hydrolyzed Collagen

Oral collagen hydrolysates generate bioactive peptides that can enter circulation, and experimental work has demonstrated transport of collagen-derived peptides into skin after ingestion (Yazaki et al., 2017). Clinically, randomized trials report reduced wrinkle volume, increased procollagen I, improved hydration, greater dermal collagen density, and reduced collagen fragmentation following oral collagen peptide supplementation (Proksch et al., 2014; Asserin et al., 2015). A later meta-analysis concluded that hydrolyzed collagen supplementation favorably affects hydration, elasticity, and wrinkles,

supporting the broader concept that oral collagen peptides can improve skin-aging endpoints (de Miranda et al., 2021). This data strongly strengthens the statements that hydrolyzed collagen support dermal matrix biology, especially when administered orally.

A pilot study of topical collagen tripeptide reported improvements in wrinkles, elasticity, and skin density, together with in vitro findings of increased collagen I and reduced matrix metalloproteinase-related damage signals (Lee et al., 2022). This supports the evidence that hydrolyzed evidence is relevant when applied from the outside as well as from within.

Vitamin C

Vitamin C has a very clear mechanistic relationship with collagen synthesis. Ascorbate is essential for the function of collagen-related hydroxylases, and classic fibroblast studies showed strong stimulation of collagen synthesis after ascorbate exposure (Murad et al., 1981). Additional work demonstrated that ascorbic acid increases procollagen mRNA abundance and preferentially enhances transcription of type I and III collagen genes in human skin fibroblasts (Tajima and Pinnell, 1996). Importantly, these effects are not restricted to cell culture: topical vitamin C has been shown to increase the mRNA levels of collagens I and III, procollagen-processing enzymes, lysyl oxidase, and TIMP1 in human dermis (Nusgens et al., 2001). Summarized, it can be stated that vitamin C as a direct stimulator of collagen synthesis is well aligned with published evidence.

Folic Acid

Human studies demonstrate that folic acid can penetrate skin and be taken up locally, which supports the feasibility of topical folate delivery (Knott et al., 2007). In addition, a topical formulation containing folic acid and creatine improved skin firmness in vivo and increased collagen gene expression, procollagen levels, and collagen fiber density in dermal equivalents (Fischer et al., 2011). Separate fibroblast work shows that folate depletion impairs nucleotide excision repair capacity, indicating that folate sufficiency contributes to cellular maintenance in the dermal environment (Burger et al., 2007). Taken together, these data support a role for folate in skin biology and collagen-related endpoints.

CONCLUSION

Interindividual variation in *CYP1A2* constitutes a biologically relevant determinant of caffeine metabolism and should be considered an important factor in the regulation of collagen-associated pathways. In particular, the rs762551 polymorphism influences CYP1A2 activity and inducibility, thereby modulating the rate of caffeine clearance and the duration of systemic caffeine exposure. This genotype-dependent difference is mechanistically significant because prolonged caffeine exposure has been associated with reduced prolidase activity in dermal fibroblasts, with subsequent attenuation of collagen biosynthesis. Given the central role of prolidase in the recycling of proline - and

hydroxyproline - containing dipeptides, reduced enzyme activity may compromise the availability of key substrates required for collagen renewal and extracellular-matrix maintenance. Accordingly, genotype should be regarded not merely as a descriptive pharmacogenetic marker, but as a potentially relevant modulator of dermal connective tissue homeostasis, particularly under conditions of habitual caffeine intake (Cornelis et al., 2006; Djordjevic et al., 2010; Denden et al., 2016; Donejko et al., 2014).

Within this framework, hydrolyzed collagen represents a mechanistically meaningful intervention for supporting collagen turnover and matrix integrity. Oral collagen peptides have been associated with enhanced dermal matrix synthesis, improvement of collagen network organization, and favorable effects on skin structure, indicating that they may contribute both substrate support and bioactive signaling relevant to connective tissue maintenance. The importance of such supplementation is particularly evident in contexts in which endogenous collagen synthesis may be suboptimal, as the provision of collagen-derived peptides may help reinforce extracellular-matrix remodeling and structural resilience (Proksch et al., 2014; Asserin et al., 2015).

The biological relevance of vitamin C is direct. Ascorbic acid is essential for efficient collagen formation and has been shown to stimulate procollagen synthesis and enhance collagen gene expression in dermal tissue. Its role therefore extends beyond general antioxidant activity and directly involves the maintenance of collagen architecture and dermal stability. In parallel, folic acid should also be considered an important supportive factor, as it demonstrates cutaneous bioavailability and has been linked to improvements in collagen-related skin properties, particularly in formulations aimed at strengthening dermal structure and cellular function. Taken together, these observations support a model in which genotype-dependent caffeine metabolism influences collagen homeostasis, whereas hydrolyzed collagen, vitamin C, and folic acid provide complementary and biologically plausible means of supporting collagen synthesis, matrix organization, and overall dermal integrity (Murad et al., 1981; Nusgens et al., 2001; Knott et al., 2007; Fischer et al., 2011).

REFERENCES

- Varani J, Dame MK, Rittie L, Fligiel SEG, Kang S, Fisher GJ, et al. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Pathol. 2006;168(6):1861-8.
- Fisher GJ, Quan T, Purohit T, Shao Y, Cho MK, He T, et al. Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. Am J Pathol. 2009;174(1):101-14.
- Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA. 2006;295(10):1135-41.
- Palatini P, Ceolotto G, Ragazzo F, Dorigatti F, Saladini F, Papparella I, et al. CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. J Hypertens. 2009;27(8):1594-601.
- Guessous I, Dobrinas M, Kutalik Z, Pruijm M, Ehret G, Maillard M, et al. Caffeine intake and CYP1A2 variants associated with high caffeine intake protect non-smokers from hypertension. Hum Mol Genet. 2012;21(14):3283-92.
- Djordjevic N, Ghotbi R, Jankovic S, Aklillu E. Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2 -163C>A polymorphism. Eur J Clin Pharmacol. 2010;66(7):697-703.
- Denden S, Bouden B, Haj Khelil A, Ben Chibani J, Hamdaoui MH. Gender and ethnicity modify the association between the CYP1A2 rs762551 polymorphism and habitual coffee intake: evidence from a meta-analysis. Genet Mol Res. 2016;15(2).
- Yoshihara T, Zaitsu M, Shiraishi F, Arima H, Takahashi-Yanaga F, Arioka M, et al. Influence of genetic polymorphisms and habitual caffeine intake on the changes in blood pressure, pulse rate, and calculation speed after caffeine intake: a prospective, double blind, randomized trial in healthy volunteers. J Pharmacol Sci. 2019;139(3):209-14.
- Zhou A, Hyppönen E. Long-term coffee consumption, caffeine metabolism genetics, and risk of cardiovascular disease: a prospective analysis of up to 347,077 individuals and 8368 cases. Am J Clin Nutr. 2019;109(3):509-16.
- Palka JA, Phang JM. Prolidase activity in fibroblasts is regulated by interaction of extracellular matrix with cell surface integrin receptors. J Cell Biochem. 1997;67(2):166-75.
- Surazynski A, Miltyk W, Palka J, Phang JM. Prolidase-dependent regulation of collagen biosynthesis. Amino Acids. 2008;35(4):731-8.
- Donejko M, Przylipiak A, Rysiak E, Głuszuk K, Surażyński A. Influence of caffeine and hyaluronic acid on collagen biosynthesis in human skin fibroblasts. Drug Des Devel Ther. 2014;8:1923-8.
- Yazaki M, Ito Y, Yamada M, Goulas S, Teramoto S, Nakaya MA, et al. Oral ingestion of collagen hydrolysate leads to the transportation of highly concentrated Gly-Pro-Hyp and its hydrolyzed form of Pro-Hyp into the bloodstream and skin. J Agric Food Chem. 2017;65(11):2315-22.
- Proksch E, Schunck M, Zague V, Segger D, Degwert J, Oesser S. Oral intake of specific bioactive collagen peptides reduces skin wrinkles and increases dermal matrix synthesis. Skin Pharmacol Physiol. 2014;27(3):113-9.
- Asserin J, Lati E, Shioya T, Prawitt J. The effect of oral collagen peptide supplementation on skin moisture and the dermal collagen network: evidence from an ex vivo model and randomized, placebo-controlled clinical trials. J Cosmet Dermatol. 2015;14(4):291-301.
- de Miranda RB, Weimer P, Rossi RC. Effects of hydrolyzed collagen supplementation on skin aging: a systematic review and meta-analysis. Int J Dermatol. 2021;60(12):1449-61.
- Lee YI, Lee SG, Jung I, Suk J, Lee MH, Kim DU, et al. Effect of a topical collagen tripeptide on antiaging and inhibition of glycation of the skin: a pilot study. Int J Mol Sci. 2022;23(3):1101.
- Murad S, Grove D, Lindberg KA, Reynolds G, Sivarajah A, Pinnell SR. Regulation of collagen synthesis by ascorbic acid. Proc Natl Acad Sci U S A. 1981;78(5):2879-82.
- Tajima S, Pinnell SR. Ascorbic acid preferentially enhances type I and III collagen gene transcription in human skin fibroblasts. J Dermatol Sci. 1996;11(3):250-3.
- Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J. 2018;18(6):760-8.
- Nusgens BV, Humbert P, Rougier A, Colige AC, Haftek M, Lambert CA, et al. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. J Invest Dermatol. 2001;116(6):853-9.

- Knott A, Mielke H, Koop U, Wolber R, Burkhardt T, Vietzke JP, et al. Folic acid: cellular uptake and penetration into human skin. J Invest Dermatol. 2007;127(10):2463-6.
- Fischer F, Achterberg V, März A, Puschmann S, Rahn CD, Lutz V, et al. Folic acid and creatine improve the firmness of human skin in vivo. J Cosmet Dermatol. 2011;10(1):15-23.
- Burger K, Kieser N, Gallinat S, Mielke H, Knott S, Bergemann J. The influence of folic acid depletion on the Nucleotide Excision Repair capacity of human dermal fibroblasts measured by a modified Host Cell Reactivation Assay. Biofactors. 2007;31(3-4):181-90.