CYP1A2, Caffeine, and Collagen Homeostasis

A Literature Review

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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 represents a functional 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 highlight 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 lead 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 operates 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 impairs 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* represents 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)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Koonrungsesomboon et al., 2018	**Design:** Systematic review and meta-analysis. **Population:** 3,570 human subjects across caffeine-phenotyping studies. **SNP:** 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	**Design:** Population-based case-control study. **Population:** 2,014 first acute nonfatal myocardial infarction cases and 2,014 matched controls from Costa Rica. **SNP:** *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	**Design:** Prospective cohort study. **Population:** 553 young White adults screened for stage 1 hypertension. **SNP:** *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	**Design:** Multicohort observational study with quasi-experimental component. **Population:** Four observational cohorts (n = 16,719) and one quasi-experimental study (n = 106), European adults. **SNP:** 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.

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Yoshihara et al., 2019	**Design:** Prospective double-blind randomized trial. **Population:** 201 healthy volunteers. **SNP:** 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.

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 compromises 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 provide 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 reinforces 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).

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