Genetic Determinants of Telomere Homeostasis in Skin Aging: Functional Contributions of *TERT*, *BICD1*, and *PPARG* (Literature Review)

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ABSTRACT

Background:
Telomere attrition is a central feature of cellular aging and is highly relevant to the skin, where lifelong cell turnover, ultraviolet exposure, and oxidative stress impose sustained demands on tissue renewal. Because epidermal homeostasis depends on the long-term function of proliferative and stem-cell compartments, disruption of telomere maintenance can influence both structural integrity and visible aging. Experimental evidence indicates that telomere shortening and telomerase dysfunction affect epidermal stem-cell behavior, replicative capacity, and cutaneous responses to environmental injury. These mechanisms provide a biologically plausible basis for interindividual differences in the tempo of skin aging. Within this framework, *TERT*, *BICD1*, and *PPARG* are of particular interest because they represent distinct but potentially convergent levels of regulation, spanning direct telomerase control, telomere-associated cellular homeostasis, and metabolically responsive signaling. Genetic variation in telomere-maintenance genes and in metabolically connected pathways may therefore contribute to variation in biological age and cutaneous aging trajectories (Kosmadaki and Gilchrest, 2004; Flores et al., 2005; Buckingham and Klingelhutz, 2011).

Methods:
Current evidence on telomere-associated mechanisms underlying cutaneous biological aging was synthesized with a focus on studies examining common variation in *TERT*, *BICD1*, and *PPARG* in relation to telomere length, telomerase activity, cellular senescence, and metabolically responsive aging pathways. Additional priority was given to experimental and translational reports addressing epidermal stem-cell biology, fibroblast aging, photoaging, and nutritional or phytochemical modulation of telomere homeostasis. Studies were selected according to their direct relevance to the biological themes under consideration and the extent to which they provided mechanistic or translational insight. The evidence was then synthesized within a framework encompassing gene function, variant-associated molecular effects, downstream

physiological consequences, and the biological rationale for pathway-supportive interventions (Matsubara et al., 2006a; Mangino et al., 2008; García-Calzón et al., 2015).

Results:

Collectively, *TERT* is identified as the locus with the most direct mechanistic relevance to telomere maintenance, given that genetic variation at *TERT* can influence telomerase regulation and, in turn, telomere length. By contrast, *BICD1* appears to affect telomere homeostasis more indirectly, most plausibly through regulatory effects on intracellular trafficking-associated processes, whereas *PPARG* is more appropriately viewed as a metabolic and nutrigenomic modulator that shapes the relationship between dietary exposures and telomere dynamics. Although these genes act through distinct proximal mechanisms, their downstream effects converge on central processes of cutaneous biological aging, including replicative senescence, diminished tissue maintenance, and reduced resilience to environmental stress. Importantly, it is indicated that telomere-associated pathways remain biologically responsive to nutritional and metabolic modulation, thereby underscoring the potential relevance of vitamins, fatty acids, and related bioactive compounds as supportive factors in the preservation of telomere homeostasis and cellular function. At the same time, the magnitude and consistency of these effects appear to vary across compounds, biological systems, and study endpoints (Matsubara et al., 2006a; Mangino et al., 2008; García-Calzón et al., 2015).

Discussion:

The available evidence is consistent with a model in which common variation in *TERT*, *BICD1*, and *PPARG* modifies the efficiency of interconnected biological pathways that contribute to aging. Within this framework, nutrients and phytochemicals implicated in telomere biology are more appropriately regarded as downstream modulators of telomerase activity, oxidative stress, inflammatory signaling, and metabolic regulation. This distinction is of particular importance for translational interpretation, as it positions such strategies within a concept of pathway modulation and functional support rather than genotype correction. It is further plausible that genetic background contributes to interindividual differences in response magnitude, especially in pathways that are strongly influenced by diet and metabolic status (Buckingham and Klingelhutz, 2011; Galiè et al., 2020; Tran et al., 2021).

Subjects Genetics, Beauty **Keywords:** Genetics, Polymorphism, Beauty, Telomeres, Biological Age

INTRODUCTION

Telomeres are specialized nucleoprotein structures at chromosome ends that shorten with repeated cell division and under conditions of oxidative or genotoxic stress. In skin, telomere erosion has biological relevance because epidermal renewal, dermal fibroblast longevity, and lifelong ultraviolet exposure together create a strong selective environment for cumulative cellular damage. Accordingly, telomere dynamics have been identified as a central component of cutaneous aging biology, particularly with respect to replicative senescence, tissue repair, and photoaging. Once telomeres become critically shortened, activation of damage-response pathways and senescence-associated programs can compromise regenerative capacity and extracellular matrix homeostasis, thereby contributing to age-related deterioration of skin structure and function (Kosmadaki and Gilchrest, 2004; Boukamp, 2005; Buckingham and Klingelhutz, 2011).

This framework is strengthened by mechanistic studies showing that telomerase dosage and telomere integrity influence epidermal stem-cell behavior and differentiation, while human genetic analyses suggest that longer genetically predicted telomere length is associated with less facial skin aging. In parallel, ultraviolet A exposure can accelerate telomere shortening in dermal fibroblasts, linking environmental injury to the same molecular axis. In a tissue characterized by constant renewal and repeated environmental challenge, telomere-dependent limitations in progenitor-cell function are therefore likely to have consequences not only for cellular lifespan but also for barrier maintenance, repair efficiency, and resilience to photodamage (Flores et al., 2005; Liu et al., 2019; Zhan and Hägg, 2021; Yin and Jiang, 2013).

These observations indicate that cutaneous telomere biology is shaped not only by environmental injury and replicative demand but also by inherited variation in the molecular systems that preserve chromosomal integrity and coordinate cellular adaptation. Genetic influences are likely to be most informative when they capture distinct layers of regulation, including telomerase activity, telomere-associated cellular homeostasis, and metabolically responsive signaling networks. Examining loci across these biological levels provides a useful framework for understanding how genetic background may modulate the pace and phenotypic expression of skin aging (Matsubara et al., 2006a; Mangino et al., 2008; García-Calzón et al., 2015).

Gene-Specific Determinants of Telomere-Associated Cutaneous Aging

Common genetic variation in pathways linked to telomerase regulation, telomere-associated cellular homeostasis, and metabolic signaling may contribute to interindividual differences in cutaneous aging. In this setting, inherited effects are unlikely to act in isolation, as the cutaneous phenotype emerges through interaction with ultraviolet exposure, oxidative stress, inflammation, nutritional factors, and lifelong tissue turnover (Kosmadaki and Gilchrest, 2004; Boukamp, 2005; Buckingham and Klingelhutz, 2011).

Within this framework, *TERT*, *BICD1*, and *PPARG* are of particular interest because they represent distinct but potentially convergent levels of biological regulation. Their relevance lies not in a uniform mechanism, but in the fact that common polymorphisms at these loci can influence pathway efficiency, stress tolerance, and responsiveness to environmental or metabolic inputs, thereby shaping the rate and phenotypic expression of skin aging in a probabilistic rather than deterministic manner (Matsubara et al., 2006a; Mangino et al., 2008; García-Calzón et al., 2015).

TERT and Direct Regulation of Telomerase Function

Among the loci considered, *TERT* has the most direct mechanistic relationship to telomere maintenance because it encodes the catalytic reverse-transcriptase subunit of telomerase. As telomerase counteracts progressive telomere shortening, inherited differences in *TERT* regulation are likely to influence the long-term replicative reserve of highly proliferative tissues, including the epidermis. In this context, reduced telomere maintenance would be expected to promote senescence in keratinocyte and fibroblast lineages, impair tissue renewal, and increase susceptibility to photoaging-associated decline (Matsubara et al., 2006a; Matsubara et al., 2006b; Boukamp, 2005; Buckingham and Klingelhutz, 2011).

The functional heterogeneity of variants within this locus is particularly informative. The most clearly characterized polymorphism at a mechanistic level is rs2735940, as promoter variation at this site has been associated with altered transcriptional activity and differences in leukocyte telomere length, indicating that this variant can modify transcriptional output rather than merely mark a linked region (Matsubara et al., 2006a; Ludlow et al., 2008). By contrast, rs2242652 is more appropriately interpreted as a telomere-relevant locus marker within a broader *TERT* susceptibility region that has been repeatedly associated with telomere-related phenotypes and cancer risk, including skin cancer-related outcomes, although its direct functional consequences remain less clearly resolved than those of rs2735940 (Campa et al., 2015; Nan et al., 2011; Bojesen et al., 2013).

From a cutaneous perspective, diminished telomerase support would be expected to accelerate the acquisition of critically short telomeres, thereby promoting replicative senescence, reducing regenerative reserve, and impairing recovery from oxidative and ultraviolet injury. Because epidermal stem-cell behavior is highly sensitive to telomere integrity, the resulting phenotype is most plausibly interpreted as accelerated biological aging of the skin rather than as an isolated cosmetic alteration (Flores et al., 2005; Liu et al., 2019; Zhan and Hägg, 2021).

BICD1 as an Indirect Modulator of Telomere Homeostasis

In contrast to *TERT*, *BICD1* does not encode a core telomerase component but rather a member of the Bicaudal-D family of dynein motor adaptors involved in cargo coupling, microtubule-based transport, and endosomal sorting. Its relevance to aging is therefore likely to be indirect, operating through effects on intracellular trafficking, compartmentalization, receptor turnover, and cellular stress handling, each of which could secondarily influence telomere homeostasis (Terenzio et al., 2014; Hoogenraad and Akhmanova, 2016).

The variant rs2630578 has been described as a regulatory polymorphism associated with interindividual variation in telomere length, this locus is linked not only to telomere shortening but also to reduced *BICD1* mRNA expression. These observations support a regulatory rather than protein-coding mechanism and indicate that the biological consequences of this locus are more likely to arise through altered gene expression than through direct modification of a structural protein domain. Accordingly, rs2630578 is most plausibly interpreted as an indirect modulator of telomere maintenance, acting through altered *BICD1* expression and related cellular pathways rather than through direct effects on telomerase catalysis (Mangino et al., 2008).

In the setting of skin aging, *BICD1* is therefore better regarded as a telomere-length modifier than as a canonical dermatologic aging gene. By predisposing cells to shorter telomeres, such variation could favor earlier accumulation of senescent cells within proliferative and reparative compartments, with downstream effects that overlap with the broader biology of telomere-driven aging, including reduced renewal capacity, impaired tissue homeostasis, and diminished resilience to photodamage (Mangino et al., 2008; Kosmadaki and Gilchrest, 2004; Buckingham and Klingelhutz, 2011).

PPARG **as a Metabolic and Nutrigenomic Determinant**

A distinct level of regulation is represented by *PPARG*, which encodes the ligand-activated nuclear receptor PPARγ, a central regulator of adipogenesis, insulin sensitivity, lipid handling, inflammatory tone, and cellular differentiation. In skin, PPARγ signaling contributes to keratinocyte differentiation, barrier function, sebocyte biology, and inflammatory homeostasis, making *PPARG* relevant to cutaneous aging even though it is not a telomerase gene in the strict sense (Ramot et al., 2015; Mao-Qiang et al., 2004).

Unlike the promoter-associated and regulatory effects described for *TERT* and *BICD1*, the common *PPARG* variant rs1801282 (Pro12Ala) is a missense substitution. Functional studies indicate that this variant alters receptor activity and downstream metabolic signaling, consistent with its established associations with insulin sensitivity and diet response and thereby illustrates a distinct molecular route through which inherited variation can influence aging-related biology (Deeb et al., 1998; Ramot et al., 2015). Its contribution to biological aging is therefore more appropriately interpreted through effects on metabolic control, inflammation, oxidative balance, and nutrient responsiveness than through direct activation of telomerase itself. The strongest telomere-related evidence for rs1801282 derives from gene–diet interaction rather than direct enzymology, as dietary intervention data indicate that the Pro12Ala polymorphism modifies the relationship between Mediterranean dietary exposure and telomere shortening. Subsequent synthesis of literature has reinforced the broader importance of *PPARG2* Pro12Ala as a diet-sensitive locus in chronic disease biology. In the context of skin aging, this suggests that variation in *PPARG* may influence how strongly cutaneous aging pathways respond to dietary quality, particularly through mechanisms involving lipid metabolism, barrier integrity, and low-grade inflammation (García-Calzón et al., 2015; Tran et al., 2021).

Nutritional and Phytochemical Modulators of Telomere-Associated Aging Pathways

Beyond inherited variation in telomere-associated genes, several nutritional and phytochemical factors - including vitamin D, vitamin E, marine omega-3 fatty acids, Mediterranean dietary patterns, resveratrol, *Ginkgo biloba*, and epigallocatechin-3-gallate (EGCG - have been investigated for their potential to influence telomere homeostasis. These interventions act primarily through modulation of telomerase activity, oxidative stress, inflammatory signaling, and metabolic regulation, thereby affecting biological processes relevant to cellular senescence and cutaneous aging. However, the strength of evidence remains heterogeneous, ranging from human observational and intervention studies to predominantly preclinical mechanistic data (Galiè et al., 2020; Zhu et al., 2012; Jia et al., 2023).

Vitamin D

Vitamin D is one of the nutritional factors for which direct human evidence is available in the context of telomerase-related biology. In a human supplementation study oral vitamin D increased peripheral blood mononuclear-cell telomerase activity, with a mean increase of approximately 19% following intervention. These findings provide human evidence that vitamin D can modulate telomerase-associated pathways. At present, this evidence pertains specifically to systemic supplementation and blood-cell readouts rather than to cutaneous absorption or topical dermatologic efficacy (Zhu et al., 2012).

Omega-3 Fatty Acids and Mediterranean Dietary Patterns

Marine omega-3 fatty acids and Mediterranean dietary patterns represent complementary dimensions of nutritional exposure, encompassing both a specific class of bioactive lipids and a broader dietary architecture, each of which is mechanistically linked to pathways relevant to telomere maintenance. Among nutritional exposures, marine omega-3 fatty acids are supported by a comparatively robust body of human evidence in relation to telomere biology. Observational work linked higher omega-3 status to slower telomeric aging, and a randomized trial associated omega-3 supplementation with lower oxidative stress and more favorable leukocyte telomere dynamics. Mediterranean diet adherence has likewise been associated with longer telomeres, and the *PPARG* Pro12Ala study further suggests that genotype can modulate this response. Taken together, this evidence supports dietary pattern quality as one of the most plausible strategies for attenuating telomere-linked biological aging (Farzaneh-Far et al., 2010; Kiecolt-Glaser et al., 2013; Crous-Bou et al., 2014; García-Calzón et al., 2015).

Resveratrol and Ginkgo Biloba

For resveratrol and *Ginkgo biloba*, the available evidence is predominantly preclinical but mechanistically consistent. In endothelial progenitor-cell models, both compounds have been shown to enhance telomerase activity and delay cellular senescence, indicating effects on pathways relevant to the preservation of replicative capacity and cellular stress resilience. Taken together, these findings provide a coherent experimental basis for considering resveratrol and *Ginkgo biloba* as biologically active modulators of telomere-associated aging processes. Based on available evidence, these compounds may therefore be regarded as pathway-supportive adjuncts with plausible relevance to cutaneous aging biology (Dong et al., 2007; Wang et al., 2011).

Vitamin E

Vitamin E is frequently proposed because of its antioxidant properties. One study reported repression of age-dependent telomere shortening by phosphorylated alpha-tocopherol in human microvascular endothelial cells, but this is not equivalent to robust clinical evidence in skin aging. The current literature therefore supports vitamin E mainly as a plausible modulator of oxidative stress rather than as a proven telomerase-targeted intervention (Tanaka et al., 2007).

Epigallocatechin-3-gallate (EGCG)

EGCG is a tea polyphenol that has been investigated in both cancer-related and skin-relevant experimental systems. Its biological effects have been examined primarily in relation to telomerase regulation, cellular proliferation, oxidative stress, and photoaging-associated responses. EGCG requires particularly careful interpretation because its telomerase effects appear to be context dependent. In cancer-cell models, EGCG inhibited telomerase activity and cell growth. By contrast, in normal human skin fibroblasts exposed to UVA, EGCG showed protective effects against photoaging-associated oxidative stress and inflammation. EGCG should therefore not be classified as having a uniformly telomerase-enhancing or telomerase-suppressive effect; rather, its activity appears to depend on cell type and biological context (Yokoyama et al., 2004; Noguchi et al., 2006; Jia et al., 2023).

Table 1. Representative Studies Relevant to *TERT*-, *BICD1*-, and *PPARG*-Associated Telomere Homeostasis in Skin Aging

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) Investigated	Primary Outcome / Key Findings
Matsubara et al., 2006a	Functional promoters and human association study	Healthy adult leukocyte cohort	*TERT* rs2735940	Demonstrated that the functional *TERT* promoter polymorphism influences promoter activity and is associated with leukocyte telomere length, supporting a direct role in telomerase regulation.
Matsubara et al., 2006b	Case-control genetic association study	Adults evaluated for coronary artery disease	*TERT* rs2735940	Linked the same functional *TERT* promoter polymorphism to an aging-related cardiovascular phenotype, supporting its broader biological relevance beyond telomere length alone.

Campa et al., 2015	Case-control genetic association study	Multiple myeloma cases and controls	*TERT* rs2242652	Identified rs2242652 as a telomere-relevant *TERT* variant associated with disease susceptibility, reinforcing the functional importance of this locus.
Nan et al., 2011	Case-control genetic association study	Skin cancer cohorts, including melanoma	*TERT* rs2242652	Reported that *TERT* variant, particularly rs2242652 was significantly associated with melanoma susceptibility, supporting relevance of the *TERT* locus to skin-related phenotypes.
Bojesen et al., 2013	Large-scale genetic association with functional follow-up	Breast and ovarian cancer consortia	*TERT* rs2242652	Showed that rs2242652 marks independent *TERT* locus signals; risk alleles were linked to increased silencing or generation of a truncated *TERT* splice variant.
Mangino et al., 2008	Human genetic association and expression study	Human telomere-length cohort with gene-expression analysis	*BICD1* rs2630578	Identified rs2630578 as a regulatory *BICD1* variant associated with shorter telomeres and reduced *BICD1* mRNA expression, consistent with indirect modulation of telomere homeostasis.
Deeb et al., 1998	Functional genetic study	Human metabolic cohort with receptor-function analysis	*PPARG* rs1801282	Demonstrated that the Pro12Ala missense variant alters receptor activity, establishing a mechanistic basis for downstream metabolic and inflammatory effects relevant to aging biology.
García-Calzón et al., 2015	Randomized dietary intervention with genetic stratification	Adults at high cardiovascular risk in the PREDIMED-NAVARRA trial	*PPARG2* rs1801282	Showed that rs1801282 modifies the relationship between Mediterranean dietary exposure and telomere shortening, supporting a nutrigenomic role for *PPARG* in telomere-associated aging pathways.

CONCLUSION

A model in which common variation in *TERT*, *BICD1*, and *PPARG* contributes to cutaneous biological aging through distinct but convergent mechanisms is clearly supported. *TERT* appears to have the most direct mechanistic relevance to telomere maintenance through its role in telomerase regulation, whereas *BICD1* more likely influences telomere homeostasis indirectly through regulatory effects on intracellular trafficking-associated processes, and *PPARG* acts primarily through metabolic and nutrigenomic pathways that shape cellular responses to dietary exposures. Despite these mechanistic differences, the downstream consequences converge on processes central to skin aging, including replicative senescence, impaired tissue maintenance, reduced regenerative reserve, and altered resilience to oxidative and ultraviolet stress.

These observations support the view that common polymorphisms in these loci are best understood as modifiers of pathway efficiency and biological responsiveness (Matsubara et al., 2006a; Mangino et al., 2008; García-Calzón et al., 2015).

It is indicated that telomere-associated pathways remain biologically responsive to nutritional and phytochemical modulation, although the strength of evidence differs across interventions. Human data are most compelling for vitamin D, marine omega-3 fatty acids, and Mediterranean dietary patterns, whereas the evidence for resveratrol, *Ginkgo biloba*, vitamin E, and EGCG, although currently supported more strongly by mechanistic and preclinical studies, is biologically coherent and provides a rationale for further translational investigation. Accordingly, such interventions should be interpreted as supportive modulators of telomerase activity, oxidative stress, inflammatory signaling, and metabolic control rather than as agents capable of reversing the underlying genetic substrate (Zhu et al., 2012; Galiè et al., 2020; Tran et al., 2021).

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