MC1R Variation, Ultraviolet Defense, and Skin Photoaging (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:
Ultraviolet radiation is a major extrinsic determinant of cutaneous aging and carcinogenesis. The melanocortin 1 receptor gene (*MC1R*) is a key regulator of epidermal photoprotection because it controls not only melanogenesis, but also antioxidant and DNA-repair responses in melanocytes. Accordingly, nonsynonymous polymorphisms can influence constitutive pigmentation, tanning capacity, oxidative stress handling, and long-term susceptibility to photoaging and skin cancer (Rouzaud et al., 2005; Abdel-Malek et al., 2008; Swope and Abdel-Malek, 2016). Mechanistically, *MC1R* signaling promotes eumelanin synthesis, which provides more effective photoprotection than pheomelanin by limiting oxidative stress and reducing the biologic impact of ultraviolet exposure. In addition, activation of this pathway contributes to cellular defense by enhancing antioxidant responses and facilitating repair of ultraviolet-induced DNA damage in melanocytes. Variants that attenuate receptor function may therefore compromise both pigment-dependent and pigment-independent protective mechanisms, thereby increasing biological vulnerability to cumulative photodamage. Within this framework, *MC1R* represents a central molecular link between genetic background, ultraviolet response, and the development of visible and subclinical features of skin aging (Rouzaud et al., 2005; Abdel-Malek et al., 2008; Swope and Abdel-Malek, 2016).

Methods:
A focused narrative review was undertaken to synthesize current evidence on *MC1R*-associated cutaneous photoprotection, ultraviolet-response pathways, and skin aging (Rouzaud et al., 2005). Particular emphasis was placed on experimental studies characterizing the functional consequences of *MC1R* variants and their effects on receptor trafficking and signaling, as well as on investigations linking altered receptor activity to melanogenesis, oxidative stress regulation, DNA repair, and photoaging-related tissue remodeling (Beaumont et al., 2005; Beaumont et al., 2007; Song et al., 2009; Kadekaro et al., 2012; Jarrett et al., 2015; Elfakir et al., 2010). Additional consideration was given to clinical and epidemiologic studies evaluating associations with pigmentary phenotype, sun sensitivity, and melanoma susceptibility, together with interventional

studies examining sunscreen and antioxidant-based strategies, particularly vitamin E and the combination of vitamins C and E, as modulators of ultraviolet-induced cutaneous injury and as adjuncts to endogenous photoprotective mechanisms (Raimondi et al., 2008; Wendt et al., 2016; Lin et al., 2003; Hughes et al., 2013).

Results:

Literature supports a mechanistic continuum from *MC1R* genotype to cutaneous phenotype. Reduced-function alleles impair receptor trafficking and/or downstream cAMP signaling, diminish eumelanin induction, weaken antioxidant and DNA-repair responses, and are associated with greater sun sensitivity, more severe photoaging, and increased skin cancer risk. Rs1805006 and rs1805007 represent well-characterized reduced-function variants with substantial effects on receptor activity, rs11547464 is associated with impaired signaling despite relatively preserved receptor expression, and rs885479 exhibits a weaker, population-dependent functional impact. Collectively, these polymorphisms highlight the functional relevance of *MC1R* genetic variability in modulating cutaneous photoprotection and downstream biological responses to ultraviolet exposure. Sunscreen has a very strong clinical outcome evidence and topical vitamin E and especially combined vitamins C and E are best interpreted as adjunctive antioxidant strategies {Beaumont et al., 2005; Beaumont et al., 2007; Elfakir et al., 2010; Hughes et al., 2013; Lin et al., 2003; Krol et al., 2000).

Discussion:

Current evidence indicates that *MC1R* genotype influences relative biological susceptibility to ultraviolet-induced damage, without altering the fundamental requirement for routine photoprotection. Genotypes associated with reduced receptor function provide a mechanistic basis for enhanced reliance on external UV protection and adjunctive antioxidant strategies. In this regard, vitamins E and C are particularly relevant, as they contribute to the mitigation of oxidative stress following ultraviolet exposure, with combined topical application demonstrating synergistic photoprotective effects. Conversely, genotypes consistent with preserved receptor function should be interpreted as conferring comparatively greater endogenous photoprotection, rather than complete resistance to cumulative photoaging, sunburn, or photocarcinogenesis (Beaumont et al., 2005; Elfakir et al., 2010; Raimondi et al., 2008; Wendt et al., 2016).

Subjects Genetics, Beauty **Keywords:** Genetics, Polymorphism, Beauty, UV rays

INTRODUCTION

Cutaneous photoaging arises from chronic exposure to solar ultraviolet radiation, which induces DNA damage, reactive oxygen species, inflammatory signaling, and extracellular matrix degradation. Clinically, these processes manifest as wrinkling, laxity, dyspigmentation, textural roughness, and loss of resilience. Within this framework, host genetics help determine how effectively skin absorbs, neutralizes, and repairs UV-mediated injury. Among the best-characterized genes in this context is the *MC1R* gene, whose biologic relevance extends beyond visible pigmentation to genomic stability and stress-response signaling in melanocytes (Fisher et al., 1999; Rouzaud et al., 2005; Abdel-Malek et al., 2008; Swope and Abdel-Malek, 2016).

This review examines the biological function of MC1R, the functional relevance of selected nonsynonymous variants and their combinatorial effects and the consequences of altered receptor activity for cutaneous aging. Furthermore, the evidence supporting photoprotective interventions centered on sunscreen, vitamin E, and combined vitamins C and E is highlighted. Particular emphasis is also placed on the scientific interpretation of genetic variation at key MC1R loci, including rs885479, rs11547464, rs1805006, and rs1805007, and their contribution to interindividual differences in ultraviolet response, melanocytic signaling, and susceptibility to photoaging (Fisher et al., 1999; Rouzaud et al., 2005; Abdel-Malek et al., 2008; Swope and Abdel-Malek, 2016).

MC1R Biology and its Relevance to Skin Aging

MC1R encodes a seven-transmembrane, Gs-coupled receptor expressed primarily on melanocytes. Upon binding of α-melanocyte-stimulating hormone (α-MSH) or adrenocorticotropic hormone, the receptor activates adenylyl cyclase, increases intracellular cAMP, and promotes eumelanin synthesis through downstream signaling cascades that include protein kinase A and melanocytic transcriptional programs. Because eumelanin is substantially more photoprotective than pheomelanin, intact MC1R signaling improves the capacity of skin to dissipate UV energy and reduce oxidative burden (Rouzaud et al., 2005; Abdel-Malek et al., 2008; Swope and Abdel-Malek, 2016).

Importantly, the role of MC1R is not confined to melanin quantity or color. Experimental studies show that α-MSH/MC1R signaling reduces UV-induced oxidative DNA damage, increases antioxidant defenses, promotes p53-dependent stress responses, and enhances nucleotide excision repair through ATR Ser435 phosphorylation and improved XPA recruitment to damaged DNA. These findings indicate that MC1R should be regarded as a broader photobiologic regulator rather than merely a pigmentation gene (Song et al., 2009; Kadekaro et al., 2012; Jarrett et al., 2015).

The connection to skin aging is mechanistically direct. UV radiation stimulates matrix metalloproteinases and collagen breakdown, thereby driving the structural changes that characterize photoaging. Any genetic constellation that weakens baseline UV defense or post-exposure repair can therefore be expected to amplify long-term aging phenotypes, even when the immediate phenotype is described only as increased sun sensitivity or reduced tanning capacity (Fisher et al., 1999).

Functional Significance of Selected *MC1R* Polymorphisms

Among the examined *MC1R* loci, rs1805006 and rs1805007 are well-established reduced-function variants associated with impaired receptor activity and increased melanoma susceptibility. These SNPs act primarily by introducing nonsynonymous sequence changes that alter receptor structure and, consequently, receptor behavior at the cell surface. In functional terms, such variation can impair trafficking of the receptor to the plasma membrane, reduce ligand-dependent signaling efficiency, and weaken downstream cAMP activation. Consistent with this mechanism, functional studies demonstrated reduced cell-surface expression and impaired signaling for rs1805006, and marked functional impairment for rs1805007, which has repeatedly emerged as a clinically relevant risk allele in epidemiologic studies. By contrast, rs11547464 appears to preserve receptor localization more effectively but still reduces downstream functional responses, suggesting altered G-protein coupling rather than a purely trafficking-related defect. rs885479 is biologically more subtle: in vitro studies support diminished signaling, yet its epidemiologic effects appear more population dependent than those of rs1805006 or rs1805007, with associations reported in Mediterranean and Canary Islands melanoma cohorts and in post-burn scarring studies (Valverde et al., 1996; van der Velden et al., 2001; Beaumont et al., 2007; Puig-Butillé et al., 2013).

From this perspective, variation across these loci is best interpreted in functional rather than purely descriptive terms. The biological relevance of an SNP lies not simply in its presence, but in the degree to which it alters receptor conformation, membrane expression, intracellular signaling, and ultimately melanocytic ultraviolet defense. Because *MC1R* is highly polymorphic and UV protection is additionally influenced by other pigmentation and repair genes, these variants are more appropriately viewed as modulators of receptor performance within a broader cutaneous photobiologic network rather than as isolated determinants of phenotype (Rouzaud et al., 2005; Swope and Abdel-Malek, 2016; Beaumont et al., 2007).

Table 1. Functional and Association Studies of MC1R Polymorphisms rs1805006, rs1805007, rs11547464, and rs885479

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) Investigated	Primary Outcome / Key Findings
Beaumont et al., 2005	Cell-based functional receptor study	Recombinant cell systems expressing human *MC1R* variant receptors	rs1805006, rs1805007	Demonstrated that reduced-function *MC1R* variants exhibit altered cell-surface expression, supporting receptor trafficking defects as a major mechanism contributing to impaired photoprotective signaling.
Beaumont et al., 2007	Functional characterization and phenotype-correlation study	Experimental receptor systems with phenotype-linked *MC1R* variant alleles	rs1805006, rs1805007, rs11547464, rs885479	Demonstrated variant-specific impairment of receptor signaling and dominant-negative activity, with marked deficits for rs1805006 and rs1805007, impaired signaling despite preserved expression for rs11547464, and a weaker effect for rs885479.

Valverde et al., 1996	Case-control genetic association study	Human melanoma cases and controls	rs1805006	Identified an association between rs1805006 and melanoma susceptibility, providing early evidence that reduced-function *MC1R* alleles have clinically relevant pathogenic consequences.
van der Velden et al., 2001	Familial melanoma association study	Dutch families with melanoma	rs1805007	Reported that rs1805007 modifies melanoma risk in familial melanoma, reinforcing the importance of this reduced-function variant in cutaneous carcinogenic susceptibility.
Puig-Butillé et al., 2013	Melanoma subtype association study	Mediterranean melanoma cohort	rs885479	Demonstrated an association between rs885479 and lentigo maligna melanoma, indicating that this variant may exert clinically relevant but population-dependent effects.
Córdoba-Lanús et al., 2014	Case-control genetic association study	Canary Islands population with sporadic malignant melanoma and controls	rs885479	Supported the contribution of rs885479 to melanoma susceptibility in a population-specific setting, consistent with a context-dependent functional and epidemiologic impact.
Sood et al., 2015	Prospective cohort study	Burn patients evaluated for post-burn hypertrophic scarring	rs885479	Showed that rs885479 is associated with hypertrophic scarring after burn injury, suggesting that the biologic consequences of this variant may extend beyond pigmentary pathways to tissue remodeling and repair responses.

Physiological Consequences of *MC1R* Variation, with Particular Reference to Skin Aging

At the organismal level, reduced *MC1R* signaling shifts skin biology toward weaker constitutive and inducible UV protection. Such skin typically exhibits poorer tanning, greater susceptibility to erythema, more frequent sunburn, and, in some settings, freckling or UV sensitivity that is not fully explained by constitutive skin color alone. (Latreille et al., 2009).

At the cellular level, the consequences are broader still. Experimental work has shown that intact α-*MSH/MC1R* signaling reduces UV-induced 8-oxoguanine formation, increases catalase and ferritin, stabilizes p53-dependent antioxidant responses, and enhances DNA repair through ATR/XPA-linked nucleotide excision repair. Thus, a reduced-function receptor does not merely change pigment output; it can lower the threshold at which UV exposure produces persistent oxidative and genomic damage (Song et al., 2009; Kadekaro et al., 2012; Jarrett et al., 2015).

These mechanisms are compatible with the observed relationship between *MC1R* genotype and photoaging. In a cohort of middle-aged women, cumulative *MC1R* variant burden was associated with severe facial photoaging, with the strongest effect seen when two diminished-function variants were present. Additional evidence suggests that *MC1R* signaling also affects fibroblast behavior and fibrotic responses, implying that polymorphism-dependent effects may extend into the dermal compartment and influence tissue remodeling, wound healing, and scarring biology relevant to visible skin aging (Elfakir et al., 2010; Stanisz et al., 2011; Sood et al., 2015).

Targeted Photoprotective Interventions in *MC1R*-Associated Ultraviolet Susceptibility

Interventions directed at ultraviolet-induced skin damage can be conceptualized within a hierarchical framework that includes both external and internal preventive strategies. Sunscreen acts at the level of primary exposure reduction, whereas antioxidant-based topical strategies target downstream oxidative and molecular consequences that are not fully prevented by UV filtering alone. In the context of *MC1R*-related photobiology, this distinction is particularly relevant, as impaired endogenous defense increases the importance of adjunctive measures that attenuate oxidative stress and support cutaneous resilience (Fisher et al., 1999; Hughes et al., 2013; Krol et al., 2000; Lin et al., 2003).

Sunscreen

From a mechanistic and clinical perspective, sunscreen remains the most direct intervention because it reduces the primary ultraviolet insult before genotype-dependent repair pathways are engaged. Broad-spectrum sunscreen therefore acts upstream of *MC1R*-mediated biological variability. By limiting ultraviolet penetration into the skin, it reduces the initiation of DNA damage, reactive oxygen species formation, and matrix-degrading signaling cascades that contribute to cumulative photoaging. This upstream mode of action is particularly important in biologic settings in which endogenous antioxidant or repair responses may be functionally less efficient. In the strongest clinical trial among the interventions considered here, regular sunscreen use significantly slowed photoaging progression over 4.5 years. This establishes sunscreen as the primary evidence-based strategy for limiting ultraviolet-induced damage, irrespective of whether susceptibility arises from genetic background, phenotypic characteristics, or environmental exposure (Hughes et al., 2013; Fisher et al., 1999).

Vitamin E

Within this framework, antioxidant-based interventions, particularly vitamin E, are of substantial complementary importance, as they target downstream oxidative and molecular consequences of ultraviolet exposure that are not fully mitigated by UV filtering alone. When applied topically, vitamin E functions as a lipid-phase antioxidant that can attenuate ultraviolet-induced oxidative damage, reduce photoproduct formation, and contribute to stabilization of cellular membranes. This property is

especially relevant in ultraviolet-exposed skin, where lipid peroxidation amplifies cellular injury and propagates oxidative stress within cutaneous tissues. By helping to preserve membrane integrity and dampen residual oxidative burden, vitamin E may support the maintenance of cellular resilience after irradiation. Summarized, its role as an adjunctive agent is biologically relevant, particularly in the context of oxidative stress modulation (Krol et al., 2000).

Vitamin C in Combination with Vitamin E

The combination of vitamins C and E is especially noteworthy, as it provides a more comprehensive and synergistic antioxidant defense. Experimental studies have demonstrated that combined application is superior to either vitamin alone in reducing erythema, sunburn cell formation, and thymine dimer accumulation, indicating enhanced protection against ultraviolet-induced cellular damage. In human phototesting, topical vitamins C and E increased the minimal erythemal dose when applied prior to ultraviolet exposure and conferred additional, albeit smaller, protective effects when applied post-exposure. These findings support the interpretation that combined antioxidant strategies directly reinforce endogenous defense mechanisms, particularly those related to oxidative stress and molecular repair pathways (Lin et al., 2003; Aguilera et al., 2012; Eberlein-König and Ring, 2005).

A clinically relevant distinction emerges from these observations: while sunscreen provides primary protection by limiting ultraviolet penetration, vitamins C and E act as mechanistically targeted adjuncts that mitigate residual oxidative damage and support cutaneous resilience. Consequently, the strongest human evidence supports a layered approach to photoprotection, in which sunscreen is complemented by topical antioxidant strategies (Hughes et al., 2013; Krol et al., 2000; Lin et al., 2003; Aguilera et al., 2012; Eberlein-König and Ring, 2005).

CONCLUSION

MC1R represents a central regulator of cutaneous photobiology by integrating melanogenesis with antioxidant defense and DNA repair mechanisms. Reduced-function variants, particularly those corresponding to rs1805006, rs1805007, rs11547464 and rs885479 are associated with diminished receptor activity and increased susceptibility to ultraviolet-induced damage, photoaging, and skin cancer. Collectively, these polymorphisms highlight the functional importance of *MC1R* variability in modulating endogenous photoprotection.

From a mechanistic perspective, impairment of *MC1R* signaling compromises multiple layers of cutaneous defense, including reduced eumelanin production, attenuated antioxidant capacity, and less efficient DNA repair. Consequently, external interventions that either limit ultraviolet exposure or mitigate oxidative damage directly address the biological vulnerabilities associated with reduced receptor function. In this context, sunscreen, topical vitamin E, and particularly the combination of vitamins C and E should be understood as mechanistically targeted strategies that complement endogenous defense systems rather than as nonspecific cosmetic measures (Beaumont

et al., 2007; Song et al., 2009; Kadekaro et al., 2012; Jarrett et al., 2015; Krol et al., 2000; Lin et al., 2003; Aguilera et al., 2012; Hughes et al., 2013).

Conversely, relatively preserved *MC1R* function is consistent with stronger endogenous photoprotection but does not confer immunity against cumulative ultraviolet injury, photoaging, or photocarcinogenesis. Accordingly, routine photoprotective measures remain essential across all genetic backgrounds (Wendt et al., 2016; Hughes et al., 2013; Lin et al., 2003; Aguilera et al., 2012).

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