MC1R Variation, Ultraviolet Defense, and Skin Photoaging

A Literature Review

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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 biological 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 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 highlight 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. Certain non-favorable alleles at the MC1R loci rs1805006 and rs1805007 are well characterized as reduced-function alleles with substantial effects on receptor activity; selected allelic constellations at rs11547464 have been associated with impaired signaling despite relatively preserved receptor expression, while allelic variation at rs885479 appears to show 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 demonstrates strong clinical outcome evidence; 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 biological 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 allelic 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 photobiological 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

Functional interpretation depends on the specific allele or allelic constellation present at each locus. Allelic constellations that preserve MC1R receptor signaling can be considered functionally protective or wild-type-like, whereas non-favorable or reduced-function alleles may decrease receptor signaling and weaken endogenous UV protection. Among the examined *MC1R* loci, certain non-favorable alleles at rs1805006 and rs1805007 are well-established reduced-function alleles associated with impaired receptor activity and increased melanoma susceptibility. The functionally relevant allelic changes at 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 non-favorable allelic forms at rs1805006 and marked functional impairment for risk-associated allelic forms at rs1805007. By contrast, certain allelic constellations at rs11547464 appear to preserve receptor localization more effectively but may still reduce downstream functional responses, suggesting altered G-protein coupling rather than a purely trafficking-related defect. Allelic variation at rs885479 is biologically more subtle: selected allelic forms have been associated with 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 terms. The biological relevance of an SNP lies not simply in the presence of the locus itself, but in the degree to which the specific allelic change 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 viewed as modulators of receptor performance within a broader cutaneous photobiological network (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)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Beaumont et al., 2005	**Design:** Cell-based functional receptor study. **Population:** Recombinant cell systems expressing human *MC1R* variant receptors. **SNP:** 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	**Design:** Functional characterization and phenotype-correlation study. **Population:** Experimental receptor systems with phenotype-linked *MC1R* variant alleles. **SNP:** rs1805006, rs1805007, rs11547464, rs885479.	Demonstrated allele-specific impairment of receptor signaling and dominant-negative activity, with marked deficits for non-favorable allelic forms at rs1805006 and rs1805007, impaired signaling despite preserved expression for selected allelic forms at rs11547464, and a weaker effect for rs885479-associated variation.

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

CONCLUSION

MC1R represents a central regulator of cutaneous photobiology by integrating melanogenesis with antioxidant defense and DNA repair mechanisms. Non-favorable allelic constellations at MC1R loci such as rs1805006, rs1805007 and rs11547464 are associated with reduced receptor activity, while rs885479 appears to show more population-dependent effects; together, these loci illustrate how MC1R variation can influence susceptibility to ultraviolet-induced damage, photoaging, and skin cancer. 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 photo carcinogenesis. 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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