GPX1 Variation, Selenium Responsiveness, and Molecular Basis of Oxidative Cutaneous Aging

A 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. *GPX1* encodes glutathione peroxidase 1, a selenium-dependent antioxidant enzyme that detoxifies hydrogen peroxide and related hydroperoxides. As a major intracellular selenoenzyme, GPx1 couples selenium availability to the neutralization of peroxide-derived oxidative stress. In the skin, selenium-dependent antioxidant systems are required for keratinocyte growth, viability, and maintenance of epidermal homeostasis. Cutaneous aging, particularly photoaging, is driven in part by chronic ultraviolet-induced reactive oxygen species, which activate stress-responsive signaling cascades and disturb collagen turnover. These processes promote extracellular matrix degradation and progressive structural changes in the dermis. Against this mechanistic background, common functional variation in *GPX1* is biologically relevant because even modest differences in peroxide handling lower the threshold at which oxidative stress is translated into visible tissue aging (Jablonska et al., 2009; Sengupta et al., 2010; Rittie and Fisher, 2002).

Methods. Peer-reviewed evidence on *GPX1*-dependent redox defense, selenium biology, and oxidative mechanisms relevant to skin aging was critically evaluated. Emphasis was placed on experimental and human studies addressing the functional consequences of rs1050450, genotype-related variation in selenium responsiveness, and the relevance of these mechanisms to keratinocyte homeostasis, ultraviolet-induced injury, and matrix-remodeling pathways. Priority was given to studies that linked altered peroxide detoxification to biologically plausible cutaneous outcomes (Jablonska et al., 2009; Sengupta et al., 2010).

Results. Literature supports allelic variation at the GPX1 rs1050450 locus as functionally relevant for the relationship between selenium status, glutathione peroxidase activity, and oxidative stress phenotypes (Jablonska et al., 2009; Almondes et al., 2018). Selenium-dependent pathways contribute to keratinocyte resilience and epidermal maintenance (Sengupta et al., 2010). Because ultraviolet-generated reactive oxygen species are major initiators of cutaneous matrix damage, reduced efficiency of *GPX1*-linked peroxide detoxification provides a plausible mechanistic route to accelerated oxidative skin aging (Rittie and Fisher, 2002). On this basis, selenium sufficiency emerges as the principal mechanism-based intervention for supporting

GPX1-dependent antioxidant defense and limiting oxidative processes relevant to skin aging (Miller et al., 2012; Favrot et al., 2018).

Discussion. Taken together, the available evidence indicates that nutritional support of *GPX1*-dependent antioxidant defense presents the most appropriate approach for modulating the functional consequences of variation in *GPX1*. Within this framework, selenium is of central importance, as its availability directly influences the efficiency of selenoprotein-dependent antioxidant defense and strongly influences genotype-dependent redox responses. The most informative findings arise consistently from selenium-responsive biomarkers, differential redox phenotypes, and experimental measures of cellular protection, indicating that selenium status is a key determinant of how *GPX1* variation is biologically expressed. Intervention data further show that the impact of genotype is best understood in relation to baseline selenium supply and the oxidative endpoint examined, underscoring the importance of adequate selenium availability for maintaining cutaneous redox homeostasis. Collectively, these observations provide a coherent mechanistic basis for the contribution of *GPX1* to oxidative skin aging and support the integration of genotype-stratified nutritional assessment with standardized dermatologic outcome measures in future studies of long-term cutaneous aging trajectories (Miller et al., 2012; Combs et al., 2012; Favrot et al., 2018).

Subjects: Genetics, Beauty. **Keywords:** Genetics, Polymorphism, Beauty, Selenium.

INTRODUCTION

The selenium-dependent antioxidant network centered on *GPX1* represents a mechanistically robust framework for understanding interindividual differences in oxidative stress handling. *GPX1* occupies a central position in peroxide detoxification because the activity of its encoded enzyme is closely linked to selenium availability, thereby connecting micronutrient status with intracellular redox control. Human association studies have shown that common genetic variation in *GPX1* can influence the relationship between selenium status and glutathione peroxidase activity, indicating that the biological effects of selenium are not uniform across individuals. Intervention studies further support this concept by demonstrating that changes in selenium intake translate into different biomarker responses according to genotype. Taken together, these observations support the broader view that antioxidant efficiency and micronutrient responsiveness are shaped by inherited differences in selenoprotein biology (Jablonska et al., 2009; Miller et al., 2012; Donadio et al., 2019).

Within this framework, common variation in *GPX1* is most appropriately interpreted as a determinant of functional heterogeneity in selenium-dependent antioxidant defense. This perspective allows genotype to be understood more precisely as a modifier of biochemical performance, influencing the efficiency with which selenium-dependent redox mechanisms are engaged under physiological conditions and in response to environmental oxidative stress. Such a perspective also allows nutritional status and genetic background to be considered jointly, rather than as independent determinants of antioxidant capacity. In this context, *GPX1* provides a useful model for examining

how common polymorphisms can shape the efficiency of redox regulation at the interface between micronutrient exposure and cellular defense.

Accordingly, evidence on *GPX1* variation, selenium responsiveness, and related antioxidant mechanisms is examined in relation to tissue resilience and oxidative aging processes (Jablonska et al., 2009; Miller et al., 2012; Donadio et al., 2019).

SELENIUM-DEPENDENT ANTIOXIDANT FUNCTION OF *GPX1* AND ITS ROLE IN EPIDERMAL HOMEOSTASIS AND CUTANEOUS AGING

GPX1 is among the most extensively characterized selenium-dependent antioxidant genes and encodes glutathione peroxidase 1, a major intracellular enzyme responsible for the reduction of hydrogen peroxide and lipid hydroperoxides. Through coupling hydroperoxide detoxification to the oxidation of reduced glutathione, this enzyme limits oxidative injury to proteins, membrane lipids, and nucleic acids, thereby contributing fundamentally to cellular redox homeostasis (Jablonska et al., 2009; Almondes et al., 2018).

The relevance of this pathway to cutaneous biology is considerable. Selenium-dependent proteins are required for normal keratinocyte function, epidermal growth, and skin development, indicating that selenium-mediated redox regulation is an integral component of epidermal homeostasis rather than merely a systemic nutritional correlate. Within the epidermis, oxidative balance influences cell survival, differentiation, barrier integrity, and the capacity of the tissue to withstand environmental stress, thereby positioning selenoprotein activity as a key determinant of skin resilience (Sengupta et al., 2010).

The importance of *GPX1* in skin aging is best understood in the context of established molecular mechanisms of photoaging. Ultraviolet irradiation increases reactive oxygen species generation, activates stress-responsive signaling pathways, induces matrix-degrading enzymes, and disrupts collagen homeostasis, collectively contributing to dermal matrix deterioration and wrinkle formation. Within this mechanistic framework, *GPX1*-dependent peroxide detoxification can be regarded as an endogenous protective system that limits oxidant-driven signaling and may therefore attenuate the progression of cutaneous aging processes (Rittie and Fisher, 2002; Quan et al., 2010).

FUNCTIONAL SIGNIFICANCE OF RS1050450 IN *GPX1* AND ITS PHYSIOLOGICAL RELEVANCE TO OXIDATIVE SKIN AGING

Allelic variation at the GPX1 rs1050450 locus includes a functionally relevant missense change that may modify selenium-dependent GPX1 activity; favorable constellations support normal peroxide detoxification, whereas less favorable constellations may reduce antioxidant protection. Human observational and intervention data support an interaction between *GPX1* genotype, selenium status, and redox phenotype, indicating that the biological effects of allelic variation at this locus are graded and context dependent (Jablonska et al., 2009; Miller et al., 2012; Donadio et al., 2019).

At the systemic level, this functional heterogeneity is reflected in differences in oxidative stress markers, redox balance, and responses to selenium exposure, with genotype-dependent effects becoming most evident under conditions of lower selenium availability or increased oxidative challenge (Karunasinghe et al., 2012; Combs et al., 2012; Almondes et al., 2018). These findings support the view that allelic variation at rs1050450 modulates antioxidant reserve rather than creating a completely inactive enzyme system. Consistent with this interpretation, experimental evidence indicates that genotype can influence the extent of hydrogen peroxide-induced DNA damage, suggesting biologically meaningful variation in peroxide handling capacity (Miranda-Vilela et al., 2010).

In the context of the photoaging mechanisms outlined above, reduced efficiency of *GPX1*-dependent peroxide detoxification would be expected to amplify oxidant-driven signaling and lower the threshold at which cumulative ultraviolet exposure produces biologically significant dermal damage (Rittie and Fisher, 2002; Quan et al., 2010). This interpretation is further supported by experimental studies demonstrating that selenium preserves keratinocyte stemness, supports epidermal adhesion, delays senescence-associated deterioration, and protects primary human keratinocytes against UVA-induced injury (Jobeili et al., 2017; Favrot et al., 2018). Together, these findings support a coherent mechanistic model in which variation in *GPX1* contributes to interindividual differences in susceptibility to oxidative cutaneous damage. In this context, allelic variation at rs1050450 is most appropriately regarded as a modifier of redox resilience that modulates vulnerability to photoaging during sustained ultraviolet exposure (Jablonska et al., 2009; Rittie and Fisher, 2002; Favrot et al., 2018).

SELENIUM AS A MECHANISM-BASED STRATEGY FOR SUPPORTING *GPX1*-DEPENDENT ANTIOXIDANT DEFENSE

Because genetic variation at rs1050450 cannot be directly corrected, the practical emphasis should be placed on maintaining adequate dietary or supplemental selenium availability to support *GPX1*-dependent antioxidant defense. In this setting, selenium constitutes the principal nutritional support, as GPx1 is a selenium-dependent enzyme whose activity is directly linked to selenium availability. Human supplementation studies using selenomethionine and selenium-rich Brazil nuts show that improved selenium intake favorably influences biomarkers of selenium status and glutathione peroxidase-related functional endpoints, although the magnitude of response is modified by genotype and baseline selenium status (Cominetti et al., 2011; Miller et al., 2012; Donadio et al., 2019).

The biological relevance of selenium in this context extends beyond its general role in antioxidant defense, because it directly supports the enzymatic reduction of hydrogen peroxide and related hydroperoxides. This is particularly important when *GPX1*-related antioxidant reserve is functionally constrained, and intervention data indicate that genotype-dependent responses to selenium are most evident under conditions of lower selenium supply. These observations identify selenium sufficiency as a critical determinant of redox resilience in the context of *GPX1* variation (Miller et al., 2012; Combs et al., 2012; Donadio et al., 2017).

The mechanistic rationale is further strengthened by experimental evidence from skin biology, which indicates that selenium supports epidermal integrity and enhances resistance to UVA-induced oxidative injury. These observations reinforce the view that selenium contributes directly to cutaneous resilience and provide further support for its role as the principal mechanism-based intervention in a *GPX1*-centered redox pathway (Jobeili et al., 2017; Favrot et al., 2018).

TABLE 1. REPRESENTATIVE STUDIES RELEVANT TO *GPX1* RS1050450, SELENIUM RESPONSIVENESS, AND REDOX PHENOTYPE

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Jablonska et al., 2009	**Design:** Human observational genotype–phenotype association study. **Population:** Adult human participants. **SNP:** *GPX1* Pro198Leu (rs1050450).	Demonstrated that the relationship between plasma selenium concentration and GPx1 activity differed by genotype, supporting functional relevance of rs1050450 for selenium-dependent enzyme activity.
Karunasinghe et al., 2012	**Design:** Cross-sectional molecular epidemiologic study. **Population:** 503 healthy Caucasian men from Auckland, New Zealand. **SNP:** *GPX1* Pro198Leu (rs1050450).	Reported associations between selenium status, oxidative-stress markers, and selenoprotein genotype background, supporting a genotype-dependent redox phenotype that included *GPX1*.
Cominetti et al., 2011	**Design:** Nutritional intervention / nutrigenetic study. **Population:** Obese women after Brazil nut consumption. **SNP:** *GPX1* Pro198Leu (rs1050450).	Found associations among *GPX1* genotype, selenium status, and DNA damage levels after Brazil nut intake, linking rs1050450 to differential redox outcomes.
Miller et al., 2012	**Design:** Randomized controlled selenium-supplementation trial. **Population:** Healthy adults. **SNP:** *GPX1* Pro200Leu (rs1050450).	Directly tested rs1050450 in a supplementation setting and showed that any effect of genotype on whole-blood GPx response was modest overall, indicating a context-dependent influence on selenium responsiveness.

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Almondes et al., 2018	**Design:** Human cross-sectional molecular epidemiologic study. **Population:** Healthy Brazilian adults. **SNP:** *GPX1* Pro198Leu (rs1050450).	Showed that redox balance was associated with *GPX1* Pro198Leu, selenium status, and lifestyle-related variables, supporting a role for rs1050450 in antioxidant phenotype.

CONCLUSION

Collectively, the available evidence identifies *GPX1* as a key component of selenium-dependent peroxide detoxification and supports allelic variation at rs1050450 as a functional modifier of antioxidant capacity rather than as an all-or-none loss of *GPX1* function. By influencing how selenium availability is translated into glutathione peroxidase activity, this polymorphism may contribute to interindividual variation in redox balance and susceptibility to oxidative injury. In skin, where chronic ultraviolet exposure promotes reactive oxygen species generation, extracellular matrix remodeling, and progressive dermal alteration, this pathway provides a biologically coherent link between inherited redox heterogeneity and cutaneous aging (Jablonska et al., 2009; Rittie and Fisher, 2002; Quan et al., 2010).

Within this framework, selenium emerges as the principal mechanism-based intervention because it supports the enzymatic system most directly affected by *GPX1* variation. Human supplementation studies and experimental skin models indicate that selenium availability influences glutathione peroxidase-related function, keratinocyte integrity, and resistance to oxidative stress, thereby reinforcing its relevance to cutaneous homeostasis and photoaging biology. This interpretation further indicates that the biological consequences of rs1050450 should be considered context dependent, with selenium status acting as a major determinant of how allelic variation at this locus is functionally expressed. Rather than implying a fixed phenotypic outcome, allelic variation at this locus appears to modify the efficiency of endogenous peroxide detoxification and thereby alter tissue vulnerability under conditions of sustained oxidative stress. From a translational perspective, these observations support the incorporation of selenium-responsive biomarkers and genotype-informed nutritional assessment into the study of interindividual differences in skin aging. Such an approach supports the refinement of mechanistic stratification in dermatologic aging research and strengthens the biological basis for preventive strategies targeting oxidative cutaneous damage (Miller et al., 2012; Donadio et al., 2019; Favrot et al., 2018).

REFERENCES

- Jablonska E, Gromadzinska J, Reszka E, Wasowicz W, Sobala W, Szeszenia-Dabrowska N, et al. Association between GPx1 Pro198Leu polymorphism, GPx1 activity and plasma selenium concentration in humans. Eur J Nutr. 2009;48(6):383-386.
- Sengupta A, Lichti UF, Carlson BA, Ryscavage AO, Gladyshev VN, Yuspa SH, et al. Selenoproteins are essential for proper keratinocyte function and skin development. PLoS One. 2010;5(8):e12249.
- Rittie L, Fisher GJ. UV-light-induced signal cascades and skin aging. Ageing Res Rev. 2002;1(4):705-720.
- Almondes KGS, Cardoso BR, Cominetti C, Nogueira NN, Marreiro DN, Oliveira TF, et al. The redox balance of healthy Brazilian adults is associated with *GPX1* Pro198Leu and -602A/G polymorphisms, selenium status, and anthropometric and lifestyle parameters. Food Funct. 2018;9(10):5313-5322.
- Miller JC, Thomson CD, Williams SM, van Havre N, Wilkins GT, Morison IM, et al. Influence of the glutathione peroxidase 1 Pro200Leu polymorphism on the response of glutathione peroxidase activity to selenium supplementation: a randomized controlled trial. Am J Clin Nutr. 2012;96(4):923-931.
- Favrot C, Beal D, Blouin E, Leccia MT, Roussel AM, Rachidi W. Age-Dependent Protective Effect of Selenium against UVA Irradiation in Primary Human Keratinocytes and the Associated DNA Repair Signature. Oxid Med Cell Longev. 2018;2018:5895439.
- Combs GF Jr, Jackson MI, Watts JC, Johnson LK, Zeng H, Idso J, et al. Differential responses to selenomethionine supplementation by sex and genotype in healthy adults. Br J Nutr. 2012;107(10):1514-1525.
- Donadio JLS, Rogero MM, Guerra-Shinohara EM, Barbosa F Jr, Desmarchelier C, Borel P, et al. Genetic variants in selenoprotein genes modulate biomarkers of selenium status in response to Brazil nut supplementation (the SU.BRA.NUT study). Clin Nutr. 2019;38(2):539-548.
- Quan T, Qin Z, Xu Y, He T, Kang S, Voorhees JJ, et al. Ultraviolet irradiation induces CYR61/CCN1, a mediator of collagen homeostasis, through activation of transcription factor AP-1 in human skin fibroblasts. J Invest Dermatol. 2010;130(6):1697-1706.
- Karunasinghe N, Han DY, Zhu S, Yu J, Lange K, Duan H, et al. Serum selenium and single-nucleotide polymorphisms in genes for selenoproteins: relationship to markers of oxidative stress in men from Auckland, New Zealand. Genes Nutr. 2012;7(2):179-190.
- Miranda-Vilela AL, Alves PCZ, Akimoto AK, Lordelo GS, Goncalves CA, Grisolia CK, et al. Gene polymorphisms against DNA damage induced by hydrogen peroxide in leukocytes of healthy humans through comet assay: a quasi-experimental study. Environ Health. 2010;9:21.
- Jobeili L, Rousselle P, Beal D, Blouin E, Roussel AM, Damour O, et al. Selenium preserves keratinocyte stemness and delays senescence by maintaining epidermal adhesion. Aging (Albany NY). 2017;9(11):2302-2315.
- Cominetti C, de Bortoli MC, Purgatto E, Ong TP, Moreno FS, Garrido AB Jr, et al. Associations between glutathione peroxidase-1 Pro198Leu polymorphism, selenium status, and DNA damage levels in obese women after consumption of Brazil nuts. Nutrition. 2011;27(9):891-896.
- Donadio JLS, Rogero MM, Cockell S, Hesketh J, Cozzolino SMF. Influence of genetic variations in selenoprotein genes on the pattern of gene expression after supplementation with Brazil nuts. Nutrients. 2017;9(7):739.