Mechanistic Role of *NQO1* in the Antioxidant Conversion of Coenzyme Q10: Genetic Variability and Implications for Ubiquinol Bioavailability (Literature Review)

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ABSTRACT

Background:
Coenzyme Q10 (CoQ10) is a lipid-soluble compound central to mitochondrial energy metabolism and cellular antioxidant defense. In its oxidized form (ubiquinone), CoQ10 participates in electron transfer within the respiratory chain, while its reduced form (ubiquinol) functions as a potent scavenger of reactive oxygen species (ROS) in membranes and lipoproteins. The cellular balance between these two forms is essential for maintaining redox homeostasis, particularly under oxidative stress conditions that arise with aging, metabolic disease, or environmental exposures (Littarru et al., 2010; Fischer et al., 2011).

Methods:
This review aims to examine the molecular role of NAD(P)H:quinone oxidoreductase 1 (*NQO1*) in converting CoQ10 to its antioxidant-active ubiquinol form. Special attention is given to the effects of the 609C>T (P187S) polymorphism in the *NQO1* gene, which has been shown to significantly impair enzymatic activity. To this end, peer-reviewed experimental and clinical literature was evaluated to assess how *NQO1* genotype influences CoQ10 metabolism, antioxidant efficacy, and the outcomes of supplementation. Mechanistic studies, human trials, and pharmacokinetic analyses were synthesized to explore genotype-specific recommendations and implications for bioavailability.

Results:

NQO1 catalyzes the two-electron reduction of quinones, including ubiquinone, thereby supporting the regeneration of ubiquinol and limiting ROS formation. The 609C>T polymorphism in *NQO1* reduces protein stability and FAD binding, resulting in loss of function in homozygous carriers. These individuals exhibit decreased plasma CoQ10 levels and impaired response to ubiquinone supplementation. Supplementing with pre-reduced ubiquinol may bypass this enzymatic bottleneck and restore antioxidant protection in individuals with compromised *NQO1* function (Fischer et al., 2011; Dinkova-Kostova et al., 2010; Ross et al., 2004; Siegel et al., 2000).

Discussion:

NQO1 activity plays a crucial role in sustaining cellular antioxidant capacity through its control of CoQ10 redox cycling (Dinkova-Kostova et al., 2010; Ross et al., 2004; Siegel et al., 2000). Genetic variation in *NQO1* significantly influences this pathway (Fischer et al., 2011; Traver et al., 1997; Kelsey et al., 1997) and should be considered when tailoring antioxidant supplementation strategies. The evidence supports a personalized approach to CoQ10 therapy, particularly in populations with reduced *NQO1* enzymatic efficiency due to common polymorphisms (Niklowitz et al., 2007; Bhagavan et al., 2006).

Subjects Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Coenzyme Q10

INTRODUCTION

Coenzyme Q10 (CoQ10) is a naturally occurring lipophilic quinone that plays a central role in the mitochondrial electron transport chain, where it facilitates the transfer of electrons from complexes I and II to complex III. It is also a critical antioxidant, particularly in its reduced form (ubiquinol), where it helps neutralize lipid peroxyl radicals and regenerates other antioxidants such as vitamin E. The dual functionality of CoQ10, as a bioenergetic intermediate and redox modulator, has garnered significant interest in the context of aging, cardiovascular health, and oxidative stress-related diseases (Littarru et al., 2010).

The physiological efficacy of CoQ10 depends not only on its intake and absorption but also on its intracellular conversion to the reduced form. This redox transformation is essential for CoQ10 to exert its full antioxidant effects. One of the primary enzymes responsible for this conversion is NAD(P)H:quinone oxidoreductase 1 (*NQO1*), which enables the two-electron reduction of ubiquinone to ubiquinol. Variations in the *NQO1* gene, particularly the 609C>T polymorphism (P187S), can result in decreased enzyme activity, impacting an individual's antioxidant capacity and response to CoQ10 supplementation (Fischer et al., 2011; Dinkova-Kostova et al., 2010).

Mechanistic Pathways

NAD(P)H:quinone oxidoreductase 1 is a cytosolic flavoprotein enzyme encoded by the *NQO1* gene located on chromosome 16q22.1. It catalyzes the two-electron reduction of a wide range of quinones to hydroquinones using either NADH or NADPH as electron donors (Dinkova-Kostova et al., 2010what re). This enzymatic activity is not only crucial for antioxidant recycling but also serves broader functions in chemoprotection and redox-sensitive gene regulation, as reviewed extensively by Ross et al. (2000). This mechanism distinguishes *NQO1* from other reductases that perform one-electron reductions and generate semiquinone radicals and reactive oxygen species (ROS), which contribute to oxidative stress (Siegel et al., 2000).

In the case of CoQ10, *NQO1* is critically involved in maintaining the intracellular redox balance by converting ubiquinone (oxidized form) to ubiquinol (reduced form) (Fischer et al., 2011; Dinkova-Kostova et al., 2010; Ross et al., 2004). This conversion enhances the antioxidant potential of CoQ10, enabling it to prevent lipid peroxidation and protect cellular membranes from oxidative damage, particularly in mitochondria and lipid bilayers (Niklowitz et al., 2007). This distinction is particularly important in mitochondria, where ubiquinol-10 has been shown to provide superior antioxidant protection against lipid peroxidation and ROS accumulation compared to ubiquinone (Sharma et al., 2001).

NQO1 also plays a structural and regulatory role as part of the plasma membrane redox system, which includes cytochrome b5 reductase and other NAD(P)H-dependent enzymes (Traver et al., 1997). These systems collectively contribute to cellular redox

homeostasis and maintain reduced forms of lipophilic antioxidants such as ubiquinol and α-tocopherol (vitamin E) (Ross et al., 2004; Niklowitz et al., 2007).

Additionally, *NQO1* has been shown to stabilize proteins such as p53 by preventing their proteasomal degradation, further underlining its broader function in stress response and cytoprotection (Dinkova-Kostova et al., 2010; Siegel et al., 2000). Its high expression in detoxification organs such as the liver, kidneys, and colon emphasizes its importance in neutralizing endogenous and xenobiotic quinones and maintaining antioxidant defenses throughout the body (Dinkova-Kostova et al., 2010; Niklowitz et al., 2007).

Genetic Polymorphism in *NQO1* and Its Functional Consequences

A prevalent single nucleotide polymorphism (SNP), 609C>T (rs1800566), in the *NQO1* gene results in a substitution of proline with serine at codon 187 (P187S), which severely impairs enzyme stability and activity. The variant form of the enzyme exhibits reduced binding affinity for the FAD cofactor, leading to rapid degradation and loss of function, particularly in homozygous individuals (T/T) (Traver et al., 1997; Kelsey et al., 1997). As a result, *NQO1* activity is nearly absent in these individuals, while heterozygous carriers (C/T) display intermediate activity levels.

Fischer et al. (2011) demonstrated that the P187S polymorphism is associated with significantly lower serum CoQ10 concentrations at baseline and reduced responsiveness to CoQ10 supplementation in healthy males. This suggests that individuals with diminished *NQO1* activity may have impaired ability to convert dietary ubiquinone into active ubiquinol, resulting in lower antioxidant protection. The frequency of the T allele varies among populations, with approximately 9% of individuals being homozygous for the polymorphism (Traver et al., 1997; Niklowitz et al., 2007).

Table 1: **Key Studies on Ubiquinol Conversion**

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) Investigated	Primary Outcome / Key Findings
Fischer et al., 2011	Short intervention + genotype–phenotype association	54 healthy men; ubiquinol 150 mg/day for 14 days	*NQO1* P187S (rs1800566) (plus other CoQ-pathway variants)	rs1800566 associated with baseline CoQ10 status; CoQ10 (reduced-form) supplementation increased serum CoQ10 overall (Fischer, 2011).
Ross et al., 2000	Narrative/mechanistic review	Human/experimental evidence (review)	*NQO1* C609T (rs1800566)	C609T/Pro187Ser produces low/unstable *NQO1* activity, relevant to quinone handling and antioxidant defense (Ross, 2000).

Tijhuis et al., 2008	Human genotype–phenotype study	Human rectal/colonic tissue study (size per paper)	*NQO1* c.609C>T (rs1800566)	Genotype predicts *NQO1* phenotype (lower activity/expression in T-allele carriers), supporting functional consequences of rs1800566 in human tissue (Tijhuis, 2008).
Tijhuis et al., 2008	Diet–gene interaction (adenoma risk)	Adults; colorectal adenoma context (Netherlands cohort setting)	*NQO1* C609T (rs1800566) (with NFE2L2)	Diet/antioxidant exposure may interact with *NQO1* genotype in colorectal neoplasia risk models (Tijhuis, 2008).
Freriksen et al., 2014	Population-based case–control	GI cancer cases/controls (total n≈1457)	*NQO1* Pro187Ser (rs1800566)	CT genotype associated with higher proximal colon cancer risk; no clear association for distal colon/rectal cancer (Freriksen, 2014).
Sepetiene et al., 2023	Applied genetics / personalized profiling study	Adults; "personalized skin aging" investigation	Includes *NQO1* rs1800566 among multiple SNPs	Positions *NQO1* rs1800566 within a broader oxidative-stress/aging genetic panel proposed for personalization in practice (Sepetiene, 2023).

Clinical Relevance

The health implications of reduced *NQO1* activity extend well beyond CoQ10 metabolism. The loss-of-function P187S polymorphism has been associated with an increased risk of malignancies, particularly in organs exposed to oxidative or xenobiotic stress. Mechanistic studies suggest that impaired detoxification of reactive quinones and a compromised antioxidant response contribute to DNA damage and tumorigenesis in *NQO1*-deficient individuals (Siegel et al., 2000; Begleiter et al., 2006).

Additionally, NQO1 has been shown to play a protective role in cardiovascular and neurodegenerative diseases by preserving redox-sensitive proteins and modulating inflammation (Ross et al., 2004; Traver et al., 1997).

These associations highlight *NQO1's* centrality in maintaining redox integrity and underscore the importance of incorporating genetic screening into disease risk stratification and nutritional planning. This approach aligns with emerging applications of genetic diagnostics in clinical practice, as demonstrated by Sepetiene et al. (2023), who used genotype-based algorithms to personalize skin aging interventions. Such models reinforce the potential of translating redox-related genetic insights — like *NQO1* variation — into targeted health strategies beyond antioxidant support.

Supplementation Implications

Supplemental CoQ10 is commercially available in two principal forms: the oxidized ubiquinone and the reduced ubiquinol. Although both forms are absorbed in the intestines, the reduced form demonstrates significantly greater bioavailability due to improved solubility and better membrane transport (Bhagavan et al., 2006). Ubiquinol supplementation has been shown to produce higher and more sustained plasma CoQ10 levels compared to ubiquinone, particularly in populations with compromised absorption or redox capacity.

For individuals with reduced *NQO1* function — whether due to genetic polymorphisms or age-related decline — supplementing with ubiquinol may offer greater therapeutic efficacy by circumventing the need for enzymatic reduction (Miles, 2007). Additionally, water-soluble or emulsified CoQ10 formulations have been developed to improve absorption, though the intracellular conversion to ubiquinol still requires functional *NQO1* or other cellular reductases (Takahashi et al., 2019).

The effectiveness of CoQ10 supplementation is directly influenced by the body's capacity to convert ubiquinone to ubiquinol, a process that is highly dependent on *NQO1* activity. In individuals carrying the 609C>T polymorphism — particularly in homozygous form — this conversion capacity is severely impaired, rendering traditional ubiquinone supplementation less effective (Fischer et al., 2011; Kelsey et al., 1997). As a result, supplementation with pre-reduced ubiquinol offers a promising alternative, as it bypasses the need for enzymatic activation and provides immediate antioxidant benefits (Kelsey et al., 1997).

Ubiquinol not only has superior bioavailability compared to ubiquinone but also exhibits greater tissue penetration and sustained plasma levels in clinical studies (Bhagavan et al., 2006; Miles, 2007). Its use is especially warranted in aging individuals and those with oxidative stress-related conditions, who may have both genetically and environmentally compromised redox systems. A comprehensive review by Littarru et al. (2010) emphasized ubiquinol's clinical relevance in supporting cardiovascular function, improving mitochondrial efficiency, and mitigating oxidative damage — all of which are heightened concerns in genetically susceptible populations.

CONCLUSION

NQO1 is an essential component of the cellular antioxidant system, playing a key role in the two-electron reduction of CoQ10 to ubiquinol (Dinkova-Kostova et al., 2010; Ross et al., 2004; Siegel et al., 2000). Genetic variation in *NQO1*, particularly the common 609C>T polymorphism, can markedly reduce enzyme activity (Traver et al., 1997; Kelsey et al., 1997), with downstream consequences for antioxidant capacity, redox balance, and responsiveness to CoQ10 supplementation (Fischer et al., 2011; Miles, 2007). These

findings have important implications for personalized nutrition and therapeutic strategies aimed at improving mitochondrial function and reducing oxidative stress-related disease risk (Littarru et al., 2010; Ross et al., 2004). This aligns with broader trends in personalized health, where genetic signatures are increasingly used to tailor clinical interventions, including aging-related outcomes such as skin resilience and oxidative stress (Sepetiene et al., 2023).

Given the variability in *NQO1* activity across individuals, CoQ10 supplementation strategies should consider both the formulation (ubiquinol vs. ubiquinone) and the individual's genetic background (Fischer et al., 2011; Bhagavan et al., 2006). Precision approaches that align CoQ10 form and dosage with *NQO1* status may enhance efficacy, improve bioenergetic resilience, and potentially reduce the burden of diseases linked to impaired redox homeostasis and mitochondrial dysfunction (Littarru et al., 2010; Ross et al., 2004; Begleiter et al., 2006).

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