Gene Section
Mini Review

NQO1 (NAD(P)H dehydrogenase, quinone 1)

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Identity
Other names: DIA4; DT-Diaphorase; NMO1
HGNC (Hugo): DIA4
Location: 16q22.1

DNA/RNA

Description
Spans approximately 20 kb consisting of 6 exons and 5 introns. Highly inducible protein and the 5' flanking region contains an AP2, ARE or EpRE (antioxidant or electrophile responsive element) and an XRE (xenobiotic responsive element).

Transcription
Three mRNA sizes (1.2, 1.7 and 2.7 kb) have been observed due to multiple polyadenylation sites. An alternatively spliced form of NQO1 mRNA lacking exon 4 is also possible although the corresponding truncated protein has not been detected.

Protein

Description
NQO1 is a flavoprotein which functions as a homodimer. The physiological dimer has one catalytic site per monomer. Each monomer consists of 273 amino acids.

Expression
NQO1 is expressed in human epithelial and endothelial tissues and at high levels throughout many human solid tumors.

Localisation
NQO1 is a mainly cytosolic enzyme (approx. 90%) although it has also been localized in smaller amounts to mitochondria, endoplasmic reticulum and nucleus.

Function
NQO1 catalyzes obligate two electron reduction of a wide variety of substrates. The most efficient substrates are quinones but the enzyme will also reduce quinone-imines, nitro and azo compounds. The enzyme functions via a hydride transfer mechanism and requires a pyridine nucleotide cofactor. Reduction proceeds with equal facility with both NADH and NADPH. NQO1 can generate antioxidant forms of both vitamin E and ubiquinone after free radical attack. The capability to protect cells from oxidative challenge and the ability to reduce quinones via an obligate two electron mechanism, which precludes generation of reactive oxygen radicals, demonstrates that NQO1 is a chemoprotective enzyme. Certain compounds such as antitumor quinones, however, can be bioactivated by two electron reduction and in these cases NQO1 serves as an activating enzyme. Because of the high levels of NQO1 in certain tumors, this has led to an interest in designing compounds which can be efficiently bioactivated by NQO1 as antitumor agents.

Homology
Amino acid homology across species is high (mouse/human 86%, mouse/rat -94%, human/rat 86%). NQO2 is a separate gene product demonstrating 49%
and 54% similarity at the amino acid and nucleotide levels respectively.

**Mutations**

**Germinal**

Two polymorphisms have been characterized. The NQO1 *2 allele represents a C609T change in the cDNA coding for a Pro187Ser change in the enzyme. The NQO1 *3 allele is a C465T change in the cDNA coding for a Arg139Trp change. The NQO1 *2 allele is much more frequent than the *3 allele and has profound consequences for phenotype. The NQO1 *2 protein has diminished catalytic activity and the protein is rapidly degraded by the ubiquitin-proteasomal system. As a result, cells and tissues carrying the homozygous NQO1 *2 allele have no detectable NQO1 activity and at best, trace levels of NQO1 protein. The NQO1 *2/*2 genotype is effectively a null activity and at best, trace levels of NQO1 protein. The NQO1 *3 allele is a C465T change in the cDNA coding for a Pro187Ser change in the enzyme. Increased benzene induced myelotoxicity in occupationally exposed individuals has also been linked to the NQO1 *2 polymorphism.

**Implicated in**

**Leukemia**

*Note*

Increased risk of leukemia has been associated with the NQO1 *2 allele and diminished NQO1 activity. Childhood leukemia (particularly with MLL fusions), adult leukemia (ALL, AML particularly with translocations or inversions) and secondary leukemias and myelodysplasias as a result of chemotherapy have been associated with the NQO1 *2 polymorphism. Increased benzene induced myelotoxicity in occupationally exposed individuals has also been linked to the NQO1 *2 polymorphism.

**Solid tumors**

*Note*

Increased risk of renal and urothelial cell carcinomas and cutaneous basal cell carcinomas have also been associated with the NQO1 *2 polymorphism but conflicting results have been obtained in colon cancer and lung cancer.

**References**


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Moran JL, Siegel D, Ross D. A potential mechanism underlying the increased susceptibility of individuals with a polymorphism in NAD(P)H:quinone oxidoreductase 1 (NQO1) to benzene toxicity. Proc Natl Acad Sci U S A. 1999 Jul 6;96(14):8150-5


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