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Polymorphism of NAD (P) H: Quinone Oxidoreductase 1 and Susceptibility to Acute Myeloid Leukemia in Egyptian Patients

GAMAL T. EBID, M.D.*; RANIA M. GAWDAT, M.D** and MANAR M. MOUNIR, M.D.***

The Departments of Clinical & Chemical Pathology, National Cancer Institute, Cairo University, Faculty of Medicine, Beni Suef University** and Biostatistics, National Cancer Institute, Cairo University****

ABSTRACT

Background: Polymorphic variations of several genes associated with dietary effects and exposure to environmental carcinogens may influence susceptibility to leukemia development.

Quinone-Oxidoreductas, NQO1, is one of these genes, it is a two-electron reducing enzyme that is important for the detoxification of quinones compounds, some chemotherapy metabolites and is an activator of bioreductive antitumor agents, such as mitomycin C. It is indicated that NQO1 (C609T) polymorphism has been associated with susceptibility to several malignancies.

Aim of Work: To study the main genetic polymorphism of NQO1 (C609T) and its influence on the risk of acute myeloid leukemia in Egyptian individuals.

Methods: NQO1 (C609T) polymorphism was genotyped in 75 de novo AML patients together with 107 normal age and sex matched healthy controls using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism.

Results: A significant high prevalence of polymorphic variant NQO1 (C609T) was found in AML cases compared to controls (*p* value-0.002). The presence NQO1 polymorphism increases the risk of AML. The odds ratio for heterozygous CT (Pro/Ser) was 2.4, 95% CI 1.0-5.4, for homozygous TT (Ser/Ser) was 5.4, 95% CI 2.1-13.5.

Conclusion: Our results suggest that NQO1 C609T (Pro187Ser) polymorphism seems to be associated with a higher risk of acute myeloid leukemia development in Egyptian people. Further studies are recommended to correlate with different cytogenetic abnormalities.

Key Words: *Quinone oxidoreductase – Acute myeloid Leukemia – PCR-RFLP.*

INTRODUCTION

Clues to the etiology of leukemia may be gained through the study of genetic susceptibility in candidate genes. The carcinogenic effect of xenobiotics is influenced by a series of genes codifying enzymes involved in oxidation/activation [phase l] and conjugation/detoxification [phase ll] of these compounds. Polymorphisms of these genes resulting in functional allelic variants of the corresponding enzymes, have been shown to influence the risk of developing solid tumors, hematologic malignancies and to modify response to cytotoxic treatment **[1]**.

Quinone Oxidoreductase is generally considered as a detoxification enzyme. In 1955, nicotinamide nucleotide-dependent oxidoreductase had been identified in rat liver and named as diphtheria toxin [DT] now known as NAD[P] H; quinone oxidoreductase 1 **[2]**. NQO1 is located on chromosome 16q22, is 20kb in length and has 6 exons and 5 introns. NQO1 is a flavoprotein which functions as a homodimer. The physiological dimer has one catalytic site per monomer. Each monomer consists of 237 amino acids. NQO1 is mainly a cytosolic enzyme although it has also been localized in smaller amounts to mitochondria, endoplasmic reticulum and nucleus **[3]**.

As the name of the enzyme suggests, a common group of substrates are quinones (a large class of aromatic compounds found commonly in plants, benzene metabolites and chemotherapies) which are reduced via a hydride transfer mechanism to generate the corresponding hydroquinone derivative by its unique ability to use either NADH or NADPH as reducing cofactors **[4,5]**. Reduction of these quinone compounds, helps in prevention of the generation of semi-quinone free radicals and reactive oxygen species, thus protecting the cells from oxidative damage. Paradoxically, NQO1 catalyzes the bioactivation of antitumor quinones which

exert their toxicity through direct DNA damage, thereby increasing their antitumor efficacy. Exploitation of this activity is under consideration as therapeutic strategy in treatment cancers. In contrast, the reductive activation of environmental carcinogens such as nitrosamines, heterocyclic amines and dinitropyrines by NQO1 may contribute to carcinogenesis **[6]**.

NQO1 is constitutively expressed in most tissues including human epithelial and endothelial tissues as well as in the bone marrow, where expression is thought to be highly inducible by xenobiotics with quinone moieties and up-regulation occurs during times of oxidative or electrophilic stress **[7]**. NQO1 expression is present at high levels in many human solid tumors as a result of hypoxia compared with normal tissues of the same origin **[3,8]**. Increased expression of NQO1 in tumors suggests that NQO1 may be a marker of neoplasia **[5]**.

There have been more than 93 single nucleotide polymorphisms [SNPs] identified in the NQO1 gene. The most widely studied SNP is a C to T change at nucleotide position 609, also known as NQO1*2. This results in a proline to serine amino acid change at codon 187 that is associated with a loss of enzyme activity due instability of protein product **[9]**. Thus, the enzyme activity of the homozygous variant genotype [NQO1*2/*2] is almost undetectable and the enzyme activity of the heterozygous genotype [NQO1*1/*2] is intermediate between the homozygous variant genotype and wild type [NQO1*1/*1] **[7]**.

Different studies reported that NQO1 C609T genotype is associated with increased risk of therapy related leukemia **[10,11]**, MDS syndrome **[10]**, myeloid leukemia with abnormalities of chromosome 5 & 7 **[10]** and pediatric leukemia with MLL fusion gene **[12]**.

As ethnic variation in risk susceptibility is well documented **[13]**, it is essential to carry such studies in each population. Results from one ethnic group cannot be extrapolated to other.

Therefore, this cases-controls study was carried out to determine if this NQO1 polymorphism is associated with an altered risk of developing acute myeloid leukemia in our Egyptian population or not.

PATIENTS AND METHODS

The study included 75 newly diagnosed Pediatric AML patients who presented to the Pediatric and Adult Oncology Department, NCI, Cairo University, in the period between January 2008 and January 2009. They included 36 males and 39 females with an age range of 1.2 to 74 years, mean of age was 39.1±18.5 and median of age was 41. Diagnosis was performed according to clinical, morphological, cytochemical and immunophenotyping examination. The criteria for inclusion in this group were:

1- Egyptian origin as judged by their names, language and place of birth;

2- Availability of biological material.

A general population control group composed of 107 individual comprising 89 males and 57 females with an age range of 18 to 53 years, mean of age was 30.8±8.9 and median of age was 29. All of them were randomly selected from blood donors. The criteria for inclusion in the control group were:

1- Anonymous, healthy, and unrelated individuals.

2- Egyptian origin as judged by their names, language and place of birth. The study was approved by the IRB of National Cancer Institute. Informed consent was obtained from all participates involved in the study and/or their parents.

Genotyping:

DNA isolation: DNA was isolated from peripheral blood at diagnosis, as described by Bye et al., 1992 **[14]**.

DNA concentration and quality was determined by measuring absorption at 260 and 280 nm; a ratio of 1.6-1.8 was accepted.

NQO1 C609T Polymorphism:

PCR was performed in 20µL reaction mix containing 20ng of genomic DNA, 0.5µmol/L of each primer (NQO 1 Forward AGT GGC ATT CTG CAT TTC TGT G, and NQO 1 Reverse GAT GGA CTT GCC CAA GTG ATG), 200µmol/L of each dNTPs, 10mmol/L Tris-HCl (pH 8.3), 50mmol/L KCl, 1.5mmol/L MgCl2, and 0.5U of ampliTaq DNA polymerase (Hoff-

man-LaRoche, Branchburg, NJ). After initial denaturation for 10 minutes at 95°C, amplification was performed for 35 cycles of 1 minute at 95°C, 1 minute at 59°C, and 2 minutes at 72°C. The last elongation step was extended to 7 minutes. Overnight incubation of 6U HinF1at 37° with 10ul of PCR product was performed. The resulting restricted fragments were evaluated on a 4% agarose gel at 100 volt for 30min. Larson et al., 1999 **[15]**. The C609T substitution creates another restriction site Hinf1 in 188bp fragment. The homozygous polymorphism gives 151 bp, 85 bp and 37 bp; the wild type gives 188 bp, 85 bp (Fig. 1).

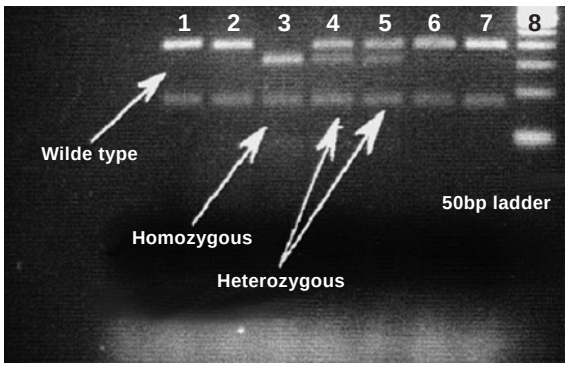

Fig. (1): Pattern of NQO1 C609T Polymorphisms by Hinf1 digest.

Lane 1, 2, 6, 7: Wild (188, 85bp),
Lane 3 : Homo (151, 85, 37bp),
Lane 4 & 5 : Hetero (188, 151, 85, 37 bp),
Lane 8 : 50bp marker.

Statistcal analysis:

Data was coded and entered using statistical package SPSS version 15. Data was summarized using mean ± SD, and median for quantitative data and number and % for qualitative data.

Comparisons between groups were done using Chi-Square test or Fisher's exact test for qualitative data. While Non-parametrically Mann-Whitney test were used for quantitative variable which are not normally distributed. Risk estimates were done using Odds ratio and 95% CI. Logistic regression analysis to test for significant predictor of leukemia, *p*-value of ≤0.05 was considered statistically significant.

RESULTS

The patients' and control group characteristics are shown in (Table 1).

Statistical comparison between AML patients and control groups subjects as regards NQO1 genotype expression and association with AML risk (Table 2).

Table (1): Characteristics of 75 de novo AML Patients.

Variables	AML group (No; 75)
Age	*39.1±18.5
Gender no. (%)	
Male	36 (48%)
Female	39 (52%)
Laboratory data	
Hg. gm/dl	6.6±2.4 (range 1.7-13.9)
TLC x 10^9/L	83.2±94.3 (range 1.3-740)
Platelets x10^9/L	56±44 (range 3.4-300)
BM Blasts %	52.7±28.4 (1-99)
FAB Subtypes no. (%)	
M0	1 (1.3%)
M1	15 (20%)
M2	32 (42.7%)
M3	9 (12%)
M4	14 (18.7%)
M5a	1 (1.3%)
M5b	2 (2.7%)
M7	1 (1.3%)

*Mean ± SD.

Table (2): Statistical comparison between AML patients and Control subjects as regards NQO1 genotype expression and association with AML risk.

NQO1 (C609T) polymorphism	Wild type (CC) (Reference group)	Heterozygous (CT)	Homozygous (TT)	Hetero+Homo (CT+TT)
AML group (n=75)	54 (72%)	16 (21.3%)	5 (6.7%)	21 (28%)
Control group (n=107)	96 (89.7%)	11 (10.3%)	0	11 (10.3%)
p. value		0.04	0.007	0.002
O.R		2.4	5.4	3.4
95% C.I		1.05-5.4	2.1-13.6	1.5-7.6

NQO1 comparisons revealed highly statistically significant difference between the two groups *p*-value 0.002.

NQO1 mutant types (CT, TT and carrier of the variant allele T of the NQO1 gene) were associated with increased risk (odds ratio 2.4 and 5.4 & 3.4 & 95% CI 1.0-5.4 & 2.1-13.6 & 1.5-7.6), respectively.

Genotype frequencies of NQO1 in AML patients and controls:

The wild type was more frequently encountered in the control group. The heterozygous was more frequently represented in AML group. The homozygous was encountered only in the AML; none in the control is homozygous. Carriers of the heterozygous genotype are at 2.4 folds risk of developing AML while those with the homozygous genotype have a risk of 5.4 folds.

The presence of NQO1 (C609T) polymorphism was analyzed in relation to age, gender, and laboratory data in AML patients:

There was no statistical significant correlation between NQO1 genotypes and age, gender, hemoglobin level, total leucocytic count, platelet count, bone marrow blasts or FAB subtypes *p*-value >0.05.

DISCUSSION

Drug or xenobiotic metabolizing enzymes (DME) include several enzyme families involved in the metabolism, bio-transformation and detoxification of xenobiotics such as chemotherapeutic drug as alkylating agents, intercalating agents and anthracyclins **[16]**.

Detoxification enzymes protect DNA from damage due to both endogenous and exogenous sources. When detoxification is ineffective, DNA damage can cause chromosomal instability leading to severe failure of cell function and either apoptosis or oncogenesis. Genetic differences defined by polymorphisms altering the enzymatic activities in detoxification pathways are prime candidates for studies to explain variation in susceptibility to develop acute myeloid leukemia **[17]**.

Quinone oxidoreductase (NQO1) is considered to be one of the phase II DME which are involved in the detoxification of numerous endogenous, foreign compounds and drugs that contain hydroxyl (OH) functional groups, highly reactive, either present on the parent molecules and/or after biotransformation by the Phase I DME which consists of the cytochrome P450 (CYP) superfamily **[16,18]**.

Lack of NQO1 activity might increase the risk of certain types of toxicity and cancer **[19]**. A number of different clinical studies had been carried on NQO1 genotype, most of which have shown an increased frequency of the NQO1 TT allele in patients with esophageal, gastric, breast cancer **[20,21]**, and both pediatric and adult leukemia **[22,23]**. Frequency of homozygous individuals having T-allele was reported to range from 1.5 to 20.3% among different ethnic groups **[24]**. Several reports suggested that NQO1 Pro 187 Ser polymorphism is associated with cancer risk **[25,26]**.

It was reported that acute and chronic side effects of cancer treatment might be involved in causing genetic variations of NQO1. There are many documented cases of cancer patients receiving chemotherapy with alkylating agents who develop secondary myeloid leukemia **[10, 16,27]**.

In this molecular epidemiological study, NQO1 C609T polymorphism was investigated in 75 de novo patients with AML and 107 age and sex matched healthy controls using PCR-RFLP. The present work aimed to clarify whether there is an association between mutant NQO1 polymorphism and increased risk of AML development. The results showed that the heterozygous variant CT (Pro/Ser) increased the risk of AML by 2.4-fold, homozygous variant TT alone increase the risk by 5.4-fold while the presence of either TT or CT increased the risk by 3.4.

NQO1 polymorphism had been investigated in several studies, but the results are not consistent. Guha et al. **[13]** explained that heterogeneity between studies may be due to differences in population exposures to NQO1 substrates and small sample sizes, as well as potential population stratification in non-family-based studies.

In a recent study, using RFLP-PCR, Yamaguti et al. **[28]** showed that NQO1 609 CT+TT genotypes were higher in patients than in controls, with carriers of the variant allele T was 1.92-fold increased risk of AML.

Smith et al. **[23]**, reported that AML case subjects exhibited a higher frequency of low or null NQO1 genotypes than controls with relatively increased risk 1.47 folds and this builds upon earlier findings that NQO1 polymorphism is associated with an enhanced risk of myeloid leukemias including de novo AML, myelodysplastic syndromes [MDS] and therapy related AML **[15]**. They stated that NQO1 protein expression in peripheral blood and bone marrow progenitors is normally very low, but is highly inducible **[29]**.

The increased risk of leukemia associated with a deficit in NQO1 levels due to the NQO1 polymorphism may reflect impaired quinone detoxification and an increased susceptibility of endothelial cells in the bone marrow to environmental insults **[30]**.

In agreement with our results, Yang et al. **[31]** reported similar high frequencies of NQO1 (C609T) C/T and T/T genotypes among AML patients significantly higher than that in the normal controls (53.1% and 25% respectively) and the relative risk of t(8;21) was 4.487 for the subjects with NQO1 (C609T) C/T genotype and was 6.293 for the subjects with NQO1 (C609T) T/T genotype while the relative risk of t(15;17) was 2.53 for the subjects with NQO1 (C609T) C/T genotype and was 4.149 for the subjects with NQO1(C609T) T/T genotype. They stated that determination of the NQO1 C609T genotyping may be used as a stratification marker to predict high risk individuals for AML.

It has been also indicated that NQO1*2 polymorphism seems to increase the risk of AML and reduces survival probabilities in children with AML on the basis of drug-associated toxicity **[22,32]**.

In the current study, no association was found in the distribution of NQO1 polymorphism with respect to the clinical characteristics at diagnosis and this is in agreement with other two studies **[23,33]**.

In contrast to our findings, Voso et al. **[17]** reported no difference in the frequency of NQO1, Pro 187 Ser polymorphism between AML and controls although there was a trend for NQO1 Ser/Ser variants to be overexpressed in therapy related AML, when compared with de novo AML in line with other studies **[10]**.

Eyada et al. **[34]** explored the relation of NQO1 polymorphism and acute leukemia, but their studied group (acute leukemia and controls) expressed only Pro/Pro genotype and therefore no linkage to leukemia susceptibility or prognostic output could be made, however, their studied group is very small in number with only 19 cases of AML.

Also, in disagreement with our results, Malik et al. **[35]** demonstrated that there are significant differences in NQO1 genotypes between Arabs and Jewish individuals and this polymorphism did not predispose to AML in either of these ethnic groups. They related this lack of association to a number of factors, including possible lack of NQO1 substrates in their environment and that other genetic factors are more important. The study carried out by Bolufer et al. **[36]**, did not find any statistical difference of NQO1*2 between AML patients and the control group, as well.

The divergent results in the different studies may be attributed to the racial heterogeneity of the populations and to the variation in AML pathogenesis in different countries **[28]**.

We compared the frequencies of NQO1 polymorphism (mutant homozygous T/T) in healthy Egyptian people examined in this study to the frequencies among different healthy ethnic groups from other studies:

Table (3): Frequency of NQO1 TT in different ethnic groups.

Ethnic groups	Egyptians	Arabs	Chinese	Koreans	Japanese	African American	Native American	Mexican Hispanics	Jewish Caucasian & Ethiopian
NQO1 Varient frequencies	None	7.4%	22.4%	18.8%	12.2%	5.2%	17.9%	15.5%	3.2%
References	Current study	35	37	38	13	38	39,13	38	35

Therefore, it was important to study NQO1 Polymorphism as a risk factor in Egyptian AML patients. The present study shows that AML patients expressing NQO1 Pro 187 Ser polymorphism are at high risk of developing AML. Future studies should be conducted in large number of patients. In addition, other SNPs in NQO1-such as the less studied C465T variant (NQO1*3), should be evaluated to comprehensively assess the importance of NQO1 in the development of acute myeloid leukemia in the Egyptian population.

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