Acute Myeloid Leukemia • Brief Report

The frequencies of NAD(P)H quinone oxidoreductase (NQO1) variant allele in Israeli ethnic groups and the relationship of NQO1*2 to adult acute myeloid leukemia in Israeli patients

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NAD(P)H:quinone oxidoreductase (NQO1) is a flavoenzyme that has an important role in detoxifying numerous endogenous and environmental quinones and their derivatives. These compounds are widespread in the environment in natural (fruits and vegetables) and man-made (organic solvents such as benzene, cigarette smoke, air pollution) compounds. A polymorphic variant of NQO1 (C609T, codon 609 proline to serine substitution) with greatly reduced activity has been reported to predispose to acute myeloid leukemia (AML). Our aim was to examine the relationship between NQO1*2 and AML in Israeli patients. We analyzed for NQO1*2 in 262 adult Israeli patients with de novo AML and 688 controls of the same ethnic groups (Arabs, and Caucasian and Ethiopian Jews). Our analysis showed significant differences in the frequencies of NQO1*2 by ethnic group (p=0.000068). However, NQO1*2 frequencies did not differ between AML patients and controls. Karyotype was not found to be associated with NQO1*2. In Israeli patients, NQO1*2 does not predispose to de novo AML.

Key words: NAD(P)H:quinone oxidoreductase, myeloid leukemia, predisposing polymorphisms, chromosomal abnormalities.

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compared the allele frequencies with those of nearly 700 controls of similar ethnic backgrounds (Arabs, Caucasian Jews and recently immigrated Ethiopian Jews). In Israel, these ethnic groups are culturally distinct and intermarriage among them is uncommon. The designation Caucasian Jews includes both Ashkenazi and Sepharadic Jews.

Methods

DNA samples were prepared in accordance with the guidelines of the Helsinki Committee of Hadassah Medical Organization. DNA samples were prepared from 262 consecutive AML patients (males: Jews 93, Arabs 66; females: Jews 63, Arabs 40) with sufficient cells for preparation of DNA. These samples were accumulated during the years 1993-2004. The hematologic diagnosis had been made using standard morphologic, immunophenotypic and karyotypic criteria. Karyotyping was performed by standard G-banding techniques and/or fluorescent in situ hybridization (FISH). Anonymous control DNA samples from healthy individuals were either purchased from the National Laboratory for Genetics of the Sackler School of Medicine of Tel Aviv University, which has an ethnic group-specific bank of anonymous DNA samples, or prepared from anonymized samples of individuals referred for various non-malignant hematologic conditions. Analysis of the \textit{NQO1} variant allele was performed as described by Smith \textit{et al.}\(^9\) using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).

Statistical methods

Statistical analyses was performed using Pearson’s $\chi^2$ test (two-sided).

Results and Discussion

Our results are shown in Tables 1 and 2. Table 1 demonstrates that the allele frequency of \textit{NQO1}*2 is significantly different among the three control groups (Arabs compared to Caucasian Jews, $p=0.022$; all three ethnic groups (Arabs, Caucasian Jews and Ethiopian Jews) compared to each other, $p=0.000068$). The distribution of the three genotypes (homozygous normal, heterozygous and homozygous \textit{NQO1}*2) is also different among the various controls (Arabs compared to Caucasian Jews, $p=0.011$; the three ethnic groups compared to each other, $p=0.000068$). Since the genotypes varied significantly among the control ethnic groups, we performed the analysis of allele frequencies of the patients according to their ethnic group. However, since there were very few AML patients of Ethiopian origin, this analysis could not be performed for this group. Table 2 demonstrates the allele frequencies and \textit{NQO1} genotypes for AML patients of Arab and Caucasian Jewish origin. It can be seen that the frequencies are virtually identical to the frequencies in the respective controls (Arab controls versus Arab AML patients, $p=0.767$, Caucasian Jewish controls versus Caucasian Jewish AML patients, $p=0.714$). Karyotypic data were available for 125 of the \textit{de novo} AML patients (Table 3). The \textit{NQO1} genotype was not found to be associated with a particular type of kary-
otypic abnormality. The percentage of patients with a normal karyotype did not differ according to NQO1 genotype; 46% of NQO1*1 homozygotes versus 43% of heterozygotes for NQO1*2 had a normal karyotype (p=0.8). Furthermore, there was no difference in the NQO1 genotypes of patients who had either unbalanced translocations, or gains/losses, as compared to balanced translocations (t(8;21), t(15;17) and inversion 16 (p=0.632).

The age of patients treated at Hadassah Hospital is lower than the mean age of AML patients reported in the literature and the Arab patients are younger than the Jewish patients. The mean age at diagnosis for Arab patients was 41.4±16 years and that for Jewish patients (48.7±18.7).13 This raised the question of whether genetic background contributes to the predisposition to develop AML in young patients of either or both of these ethnic groups.

In our analysis of a large number of Israeli patients with AML, the frequencies of the NQO1 null allele were similar to those found in other populations.13 The frequencies were in accordance with the Hardy-Weinberg equilibrium. However, we did not find any increased risk of de novo adult AML in those carrying NQO1*2. This lack of association may be due to a number of factors. First it is possible that in our environment, NQO1*2 is not a predisposing factor and that other genetic factors are more important. For instance, high CYP2E1 activity may be able to compensate for the NQO1 null allele.4

We did not measure CYP2E1 activity in our patients, and polymorphisms in this gene have not been accurately linked to enzyme activity.4 Furthermore, it is possible that variations in myeloperoxidase, which is in the same metabolic pathway, may contribute to altered predisposition though most studies have not shown this enzyme to be important.15 Alternately, it is possible that the deleterious effect of NQO1*2 may be seen only in Israeli individuals with particular exposure to carcinogens or toxins, but unfortunately our retrospective data did not include detailed information on exposure (occupational or environmental) to enable us to investigate such a hypothesis. In future studies, it will be important to study not just NQO1*2 but also the NQO1 C465T variant which also reduces enzyme activity due to alternative splicing and reduced normal protein product.1 This variant has recently been found to predispose to infant leukemia with MLL translocations.16

The genetic epidemiology of NQO1*2 has been studied, and the allele frequency has been reported to be 0.25 in non-Hispanic Caucasians in the United States which is similar to the frequency that we found in Caucasian Jews (0.206). Ethiopian Jews have a lower frequency (0.148) than that reported for African Americans (0.22).14 We also found small but significant differences in NQO1*2 frequency when comparing Arabs and Caucasian Jews. These groups are genetically similar, but not identical, as was found in studies of Y chromosome polymorphisms.17

In summary, our findings demonstrate that there are significant differences in NQO1 genotypes in different ethnic groups in Israel. However, our data do not support a role for NQO1*2 as a predisposing polymorphism for de novo adult AML. Our results suggest the need for studies in many populations to verify associations of genetic variation data with predisposition to disease. Polymorphisms which may have an impact in one geographic area or ethnic group may not be contributory in others.

All authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria. Specific responsibilities were as follows; EM: performed all the experiments and data analysis, and wrote the first draft of the manuscript; SBC: developed the laboratory methods and supervised EM in all aspects of the laboratory experiments; DS: supervised clinical specimen collection and preparation in Rambam Hospital; EJD: assembled clinical data from Rambam Hospital and recruited patients for study; DR: responsible for the conception of the study, wrote the subsequent drafts of the manuscript, assembled clinical data from Hadassah. The authors declare that they have no potential conflicts of interest.

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NQO1 analysis in de novo adult AML in Israel


