

# Low NAD(P)H:quinone oxidoreductase activity is associated with increased risk of leukemia with *MLL* translocations in infants and children

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An inactivating polymorphism at position 609 in the NAD(P)H:quinone oxidoreductase 1 gene (*NQO1 C609T*) is associated with an increased risk of adult leukemia. A small British study suggested that *NQO1 C609T* was associated with an increased risk of infant leukemias with *MLL* translocations, especially infant acute lymphoblastic leukemia (ALL) with t(4;11). We explored *NQO1 C609T* as a genetic risk factor in 39 pediatric de novo and 18 pediatric treatment-related leukemias with *MLL* translocations in the United States. Children with de novo B-lineage ALL without *MLL* translocations and a calculation of the expected genotype dis-

tribution in an ethnically matched population of disease-free subjects served as the comparison groups. Patients with de novo leukemias with *MLL* translocations were significantly more likely to be heterozygous at *NQO1 C609T* (odds ratio [OR] = 2.77, 95% confidence intervals [CI] 1.17-6.57;  $P = .02$ ), and significantly more likely to have low/null *NQO1* activity than patients with de novo B-lineage ALL without *MLL* translocations (OR = 2.47, 95% CI 1.08-5.68;  $P = .033$ ). They were also significantly more likely to have low/null *NQO1* activity than expected in an ethnically matched population of disease-free subjects (OR = 2.50,  $P = .02$ ). Infants

younger than 12 months old at diagnosis of leukemia with t(4;11) were most likely to have low/null *NQO1* activity (OR > 10.0). Conversely, the distribution of *NQO1* genotypes among patients with treatment-related leukemias with *MLL* translocations was not statistically different than in the comparison groups. The inactivating *NQO1* polymorphism is associated with an increased risk of de novo leukemia with *MLL* translocations in infants and children. (Blood. 2002;100:4590-4593)

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## Introduction

NAD(P)H:quinone oxidoreductase 1 (*NQO1*) protects cells against oxidative stress and toxic quinones.<sup>1,2</sup> A cytosine to thymine (C→T) polymorphism at position 609 in the *NQO1* gene (*NQO1 C609T*) produces a proline to serine substitution that destabilizes and inactivates the enzyme.<sup>3</sup> Individuals who are homozygous for *NQO1 C609T* are completely lacking in *NQO1* activity, whereas individuals who are heterozygous have low-to-intermediate *NQO1* activity compared with wild-type individuals.<sup>4</sup> The frequency of *NQO1 C609T* is similar in whites and African Americans, but higher in Hispanics and Asians.<sup>5-8</sup> *NQO1 C609T* has been associated with a greater risk of neutropenia in benzene-exposed adult Chinese workers<sup>9</sup> and is significantly overrepresented in therapy-related<sup>10</sup> and de novo leukemias<sup>11</sup> in adults. Recently, Wiemels et al reported that *NQO1 C609T* conferred susceptibility to infant ALL and acute myeloid leukemia (AML) with *MLL* translocations in a British population of 36 cases, with the greatest risk in cases of ALL with t(4;11).<sup>12</sup> Here we expand upon the findings of Wiemels et al<sup>12</sup> by investigating this inactivating *NQO1* polymorphism as a risk factor for pediatric de novo and treatment-related leukemias with *MLL* translocations in a United States population.

## Patients, materials, and methods

### Study subjects and biologic samples

The institutional review boards of our institutions approved this research. Genomic DNAs were prepared from bone marrow or peripheral blood leukemic cells as previously described.<sup>13-15</sup> For cytogenetic studies, the cells were cultured for 24 hours without mitogen and karyotypes were prepared by standard methods.<sup>16</sup>

There were 39 patients diagnosed with de novo leukemia characterized by translocation of the *MLL* gene at chromosome band 11q23, and 18 with treatment-related leukemia with *MLL* translocations. We examined 56 patients with de novo B-lineage ALL without *MLL* gene rearrangement as a comparison population with a common pediatric cancer. The demographic features of these patients are shown in Table 1. The 39 *MLL*(+) de novo cases were diagnosed from birth to 18 years, 5 months of age. The karyotypes were previously described.<sup>13,17,18</sup> There were 19 ALL cases, including one case of T-cell ALL; 17 AML cases; and 3 biphenotypic cases. The morphology was French-American-British (FAB) M4 (myelomonocytic) or FAB M5 (monoblastic) in 13 cases of AML and in one of the biphenotypic cases. There were 16 patients with ALL, 12 patients with AML, and all 3 patients with biphenotypic leukemia who were diagnosed before 12 months of age, and 1 patient with AML who was diagnosed at age 15 months; these 32 patients were considered infants. Of the 32 infants,

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**Table 1. Demographic characteristics of pediatric patients with leukemia**

	MLL(+) de novo	MLL(+) therapy-related	MLL(-) de novo B-lineage ALL
<b>Sex</b>			
Male	16	12	37
Female	23	6	18
Unknown	0	0	1
<b>Ethnicity</b>			
White	35	16	36
African American	3	0	8
Hispanic	1	2	3
Asian	0	0	2
Unknown	0	0	7

7 were diagnosed at birth. In all cases there was evidence of *MLL* gene rearrangement by Southern blot analysis.<sup>13</sup> The *MLL* translocations were characterized cytogenetically and/or, in some cases, by panhandle polymerase chain reaction (PCR) approaches.<sup>13,17,19-21</sup>

The 18 *MLL*(+) treatment-related leukemias and prior DNA topoisomerase II inhibitor exposures have also been described.<sup>14,18,22</sup> The ages of the patients ranged from 3 years, 7 months to 17 years, 2 months when the diagnosis of treatment-related leukemia was made. There were 13 treatment-related leukemia patients who presented with AML, 2 with myelodysplastic syndrome (MDS), 2 with ALL, and 1 was biphenotypic. The detection of *MLL* translocations was the same as in the de novo cases.<sup>14,18,22</sup>

The 56 patients with *MLL*(-) de novo B-lineage ALL were included in prior studies.<sup>15,18</sup> The age at diagnosis in 48 of these patients for whom data were available ranged from 1 year, 4 months to 19 years, 11 months.

**NQO1 genotype analysis**

All laboratory personnel were blinded to case-control status. *NQO1* genotypes were analyzed as previously described.<sup>10</sup> Wild-type (CC) individuals were assigned to the high activity category. Individuals who were heterozygous (CT) or homozygous (TT) for the *C609T* polymorphism were assigned to the low/null *NQO1* activity category because the homozygous group was too small to analyze alone.

**Statistical analysis**

*NQO1* genotype frequencies in patients with *MLL*(+) de novo or treatment-related leukemias were compared with *NQO1* genotype frequencies in children with *MLL*(-) de novo B-lineage ALL. The expected *NQO1* allele frequencies in a disease-free population ethnically matched to the *MLL*(+) de novo cases were calculated from previously published data<sup>5,8,9,23</sup> and used as a second comparison group. The significance of the difference between groups was determined by constructing 2-by-2 tables and generating crude odds ratios and 95% confidence intervals using Cornfield approximations, and 2-tailed *P* values were calculated using Fisher exact methods. All results were considered statistically significant if the 2-tailed *P* value was less than .05. The analysis was carried out using the statistical computer program STATA (Stata Corporation, College Station, TX).

**Results**

*NQO1* genotypes in the 3 groups including pediatric patients with *MLL*(+) de novo leukemia (n = 39), pediatric patients with *MLL*(+) treatment-related leukemia (n = 18), and pediatric patients with *MLL*(-) de novo B-lineage ALL (n = 56), are shown in Table 2. In the patients with *MLL*(+) de novo leukemia, there was a strong shift toward heterozygosity at the *NQO1 C609T* allele. These patients were significantly more likely to be heterozygous at *NQO1 C609T* than patients in the comparison group with *MLL*(-) de novo B-lineage ALL (OR = 2.77, 95% CI 1.17-6.57; *P* = .02). Assigning individuals who were heterozygous (CT) or homozygous (TT) for the *C609T* polymorphism to the low/null *NQO1* activity category revealed that patients with *MLL*(+) de novo leukemia were significantly more likely to have low/null *NQO1* activity than patients with *MLL*(-) de novo B-lineage ALL (OR = 2.47, 95% CI 1.08-5.68; *P* = .033) or than would be expected in an ethnically matched population of disease-free subjects (OR = 2.50, *P* = .02) (Table 2). This almost identical finding of an increased OR of approximately 2.5 when the *MLL*(+) group is compared with 2 different groups shows that bias due to ethnic differences or population stratification is unlikely to explain the findings.

There was no difference in the susceptibility of males and females with *MLL*(+) de novo leukemia (OR = 1.07, 95% CI 0.29-3.86; *P* = .92), indicating that the *NQO1* genotype effect is sex independent. When the *MLL*(+) de novo cases were analyzed by lineage, a statistically significant association of *NQO1 C609T* was only observed with ALL (OR = 3.35) (Table 3). The sample size of patients with *MLL*(+) de novo AML was too small to make strong inferences.

The 39 patients with *MLL*(+) de novo leukemias were further analyzed by age at diagnosis, and by whether t(4;11) was observed in the karyotype (Table 3). Of the 39 *MLL*(+) de novo cases, 32 were classified as infant leukemias as described above. The OR for *NQO1* low/null genotypes among these 32 infant cases compared with the 56 cases of *MLL*(-) de novo B-lineage ALL was 2.25, which is similar to the OR of 2.47 for the entire group of patients with *MLL*(+) de novo leukemia compared with the same comparison group. For the 7 patients who were more than 2 years old at diagnosis of *MLL*(+) de novo leukemia, the OR for *NQO1* low/null genotypes was 3.86 compared with the same comparison group with *MLL*(-) de novo B-lineage ALL, but this was not significantly different than the OR of 2.25 observed for the infants.

The most common *MLL* translocation in infant ALL is t(4;11)(q21;q23),<sup>24,25</sup> which fuses *MLL* with *AF-4*.<sup>26</sup> In the de novo leukemias in the present study, the karyotype revealed t(4;11) in 9 cases of ALL, 2 cases of AML, and one biphenotypic leukemia.

**Table 2. Distribution of *NQO1* genotypes in pediatric patients with *MLL*(+) and *MLL*(-) leukemias**

	High <i>NQO1</i> activity CC genotype (%)	Low <i>NQO1</i> activity CT genotype (%)	Null <i>NQO1</i> activity TT genotype (%)	Low/null <i>NQO1</i> activity CT/TT genotype (%)	OR (95% CI, range)* (vs <i>MLL</i> (-) de novo B-lineage ALL)
<i>MLL</i> (+) de novo	15 (38.5)	22 (56.4)	2 (5.1)	24 (61.5)	2.47 (1.08-5.68) <i>P</i> = .033
<i>MLL</i> (+) therapy-related	13 (72.2)	5 (27.8)	0	5 (27.8)	0.59 (0.19-1.85) <i>P</i> = .378
<i>MLL</i> (-) de novo B-lineage ALL	34 (60.7)	18 (32.2)	4 (7.1)	22 (39.3)	Ref
Expected†	(61)	(34)	(5)	(39)	Ref

Ref indicates reference group.

\*OR generated from 2 × 2 table using chi-square test comparing CC versus CT/TT.

†Expected in the *MLL*(+) de novo group on the basis of ethnicity using the following allele frequencies: white, 0.21; African American, 0.23; Hispanic, 0.39; and Asian, 0.45. Expected allele frequency would therefore be 0.22 based on the ethnic mix shown in Table 1.

**Table 3. Distribution of *NQO1* genotypes in pediatric patients with leukemias stratified according to sex, leukemia subtype, age, and cytogenetics**

	High <i>NQO1</i> activity CC genotype (%)	Low <i>NQO1</i> activity CT genotype (%)	Null <i>NQO1</i> activity TT genotype (%)	Low/Null <i>NQO1</i> activity CT/TT genotype (%)	OR (95% CI, range)* (vs <i>MLL</i> (-) de novo B-lineage ALL)
<i>MLL</i> (+) de novo	15 (38.5)	22 (56.4)	2 (5.1)	24 (61.5)	2.47 (1.08-5.68) <i>P</i> = .033
Male	6 (37.5)	9 (56.3)	1 (6.2)	10 (62.5)	2.57 (0.84-7.88)
Female	9 (39.1)	13 (56.5)	1 (4.4)	14 (60.9)	2.40 (0.90-6.39)
ALL	6 (31.6)	11 (57.9)	2 (10.5)	13 (68.4)	3.35 (1.13-9.82) <i>P</i> = .028
AML	8 (47.1)	9 (52.9)	0	9 (52.9)	1.74 (0.6-5.06) <i>P</i> = .318
Biphenotypic	1 (33.3)	2 (66.7)	0	2 (66.7)	ND
Infant†	13 (40.6)	18 (56.3)	1 (3.1)	19 (59.4)	2.26 (0.94-5.43) <i>P</i> = .069
Older than 24 mo	2 (28.6)	4 (57.1)	1 (14.3)	5 (71.4)	3.86 (0.78-∞) <i>P</i> = .105
t(4;11)					
Cytogenetic‡	2 (16.7)	9 (75.0)	1 (8.3)	10 (83.3)	7.73 (1.7-∞) <i>P</i> = .006
Cytogenetic‡ (<12 mo)	1 (12.5)	7 (87.5)	0	7 (87.5)	10.82 (1.58-∞) <i>P</i> = .013
Cytogenetic and/or molecular§	2 (14.3)	10 (71.4)	2 (14.3)	12 (85.7)	9.27 (2.08-∞) <i>P</i> = .002
Cytogenetic and/or molecular§ (<12 mo)	1 (10)	8 (80)	1 (10)	9 (90)	13.91 (2.08-∞) <i>P</i> = .003
<i>MLL</i> (-) de novo B lineage ALL	34 (60.7)	18 (32.2)	4 (7.1)	22 (39.3)	Ref

ND indicates not done; Ref, reference group.

\*OR generated from 2 × 2 table using chi-square test comparing CC versus CT/TT.

†Infant defined as ALL/biphenotypic diagnosed before age 12 months and AML diagnosed before age 24 months. There were 16 patients with ALL, 12 patients with AML, all 3 patients with biphenotypic leukemia diagnosed before age 12 months, and 1 patient with AML diagnosed at age 15 months who fit this definition. Ages at diagnosis of *MLL*(+) de novo leukemia of 7 patients not included in the infant group were 18 years, 5 months; 3 years, 8 months; 2 years, 11 months; 16 years, 2 months; 13 years, 7 months; 16 years, 6 months; and 13 years, 2 months.

‡Cytogenetic indicates cases determined to have t(4;11)(q21;q23) by karyotype (includes 8 cases also analyzed by panhandle PCR approaches, which verified fusion of *MLL* to *AF-4*).

§Molecular indicates cases determined to have *MLL-AF-4* fusion by panhandle PCR approaches (includes 2 infant cases in which karyotype of marrow at leukemia diagnosis did not reveal the t(4;11) translocation or was technically unsuccessful).

*NQO1* low/null genotypes were present in 10 (83.3%) of these 12 cases, and the OR compared with the control population of children with *MLL*(-) de novo B-lineage ALL was 7.73 (95% CI 1.7 to infinity) (Table 3). This result is highly statistically significant (*P* = .006). When only those infants diagnosed with leukemia with t(4;11) before 12 months of age (*n* = 8) were analyzed, the OR was even higher at 10.82, and also was highly statistically significant (Table 3). Panhandle PCR and/or cDNA panhandle analysis has been performed in 8 of the 12 cases with cytogenetic evidence of t(4;11) and, in each of the 8 cases, there was evidence of a translocation fusing *MLL* to *AF-4*.<sup>19,21</sup> There were 2 other de novo leukemias with molecular evidence of a translocation fusing *MLL* to *AF-4*. In one case the karyotype was normal<sup>13,19</sup>; in the other case, there were no mitoses in the diagnostic marrow for karyotype analysis but the karyotype at relapse was complex and included evidence of t(4;11).<sup>13,17,21</sup> Both cases were infant ALL and both had low/null *NQO1* activity, such that when these cases were included in the analysis of leukemias with t(4;11), the association of low/null *NQO1* activity with t(4;11) became even stronger in the infants less than 12 months old at diagnosis (OR = 13.91) (Table 3).

The distribution of *NQO1* genotypes among patients with treatment-related leukemias was not statistically different from that found in patients with *MLL*(-) de novo B-lineage ALL with respect to either low/null *NQO1* activity (OR = 0.59; 95% CI 0.19-1.85; *P* = .38) or the frequency of heterozygosity (OR = 0.73; 95% CI 0.23-2.3; *P* = .6). Moreover, the OR and trend toward heterozygosity appeared to be in the opposite direction compared with that found in pediatric patients with *MLL*(+) de novo leukemias. This may be related to the predominance of other *MLL* translocations, especially t(9;11) and t(11;19), in the treatment-related cases included in this study versus the predominance of t(4;11) in the *MLL*(+) de novo cases or, alternatively, to differing etiologies.

## Discussion

We have shown that the inactivating *NQO1 C609T* polymorphism is associated with an increased risk of leukemia with *MLL* translocations in infants and children in a United States population. These findings are almost identical to those of Wiemels et al<sup>12</sup> in a population of British infants and further support the hypothesis that low/null *NQO1* activity is a risk factor for infant leukemias harboring *MLL* translocations. The odds ratios between 7.7 and 13.9 in the patients with de novo leukemias with t(4;11) compared with a population of children with *MLL*(-) de novo B-lineage ALL are consistent with the findings of Wiemels et al, who observed an 8-fold increased risk for infant leukemias with t(4;11) when using normal cord blood samples as controls.<sup>12</sup> Moreover, in the present study, the odds ratios became even higher (10.82 to 13.91) when considering only infant leukemias with t(4;11). While the total number of subjects studied is still small and the confidence intervals quite wide, this analysis by karyotype may imply that there may be different risk factors for de novo leukemias harboring different *MLL* translocations.

The reason why low/null *NQO1* activity appears to be so strongly associated with the t(4;11) translocation in particular is unknown. However, the finding of the same *NQO1* genotype-leukemia association in 2, albeit small, independent studies supports a role for *NQO1* substrate(s) such as benzoquinone and related compounds and/or oxidative stress as causative factors in leukemias with *MLL* translocations, especially infant leukemias with t(4;11). Because similar *MLL* translocations are found in leukemias related to chemotherapy with DNA topoisomerase II inhibitors, DNA topoisomerase II has been implicated in the generation of *MLL* gene rearrangements (reviewed in Felix<sup>27</sup>). *MLL* translocations in infant leukemias arise in utero,<sup>28,29</sup> and maternal

prenatal consumption of food items containing DNA topoisomerase II inhibitors may increase the risk of infant AML.<sup>30,31</sup> Flavonoids such as genistein, quercetin, and daidzein are examples of dietary DNA topoisomerase II inhibitors,<sup>32</sup> and it has been shown that quercetin induces *NQO1* gene expression.<sup>33</sup> In addition, there are numerous potential dietary and environmental sources of the *NQO1* substrate 1,4-benzoquinone,<sup>34</sup> which potentially may interfere with the catalytic activity of DNA topoisomerase II<sup>35</sup> or interact with DNA directly. Therefore, it is biologically plausible that the *NQO1* genotype is a host factor that modulates the risk of leukemia in infants. Exactly how low/null *NQO1* activity may contribute to the increased risk remains unknown, but these findings suggest that the pursuit of *NQO1* substrate(s) as potential causative factors in infant leukemia is warranted.

The present study also provides new information on the group of pediatric patients with treatment-related leukemias with *MLL* translocations. Although the sample size for this group was small, the results suggest that *NQO1* does not have a protective role against *MLL*(+) leukemias arising after chemotherapeutic DNA topoisomerase II inhibitors, where the *CYP3A4* wild-type genotype has been shown to confer susceptibility.<sup>18</sup>

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