The association of a distinctive allele of NAD(P)H:quinone oxidoreductase with pediatric acute lymphoblastic leukemias with *MLL* fusion genes in Japan

Minenori Eguchi-Ishimae*
Mariko Eguchi*
Eiichi Ishii
Deborah Knight
Yujirou Sadakane
Keiichi Isoyama
Hiromasa Yabe
Shuki Mizutani
Mel Greaves

*present address: Department of Hematology, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibumachi, Shimotsugagun Tochigi, 321-0293. Japan.

Background and Objectives. The enzyme NAD(P)H:quinone oxidoreductase (NQO1) detoxifies chemicals with quinone rings including benzene metabolites and flavonoids. Previous studies in Caucasian populations have provided evidence that a loss of function allele at nt 609 (*C609T*, Pro187Ser) is associated with increased risk of infant acute lymphoblastic leukemia (ALL) with *MLL-AF4* fusion genes.

Design and Methods. We genotyped 103 infants (<18 months) with ALL or acute myeloid leukemia (AML) in Japan and 185 controls for the frequency of allelic variation at nt 609 and 465 in *NQO1* using standardized polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology.

Results. The *C609T* polymorphism is very common in Japan but we found no link with altered risk for infant ALL. However, a variant of another allele at nt 465 (*C465T*, Arg139Trp), also associated with diminished enzyme activity, was strongly associated (OR 6.36; CI 1.84-21.90; p=0.002) with infant ALL, especially in t(4;11)(q21;q23), *MLL-AF4*. No association was found between this allele and risk of infant AML with *MLL* gene fusions or infant ALL without *MLL* gene fusions. The same *C465T* allele has been linked recently, in an Oriental population, to sensitivity to benzene hematotoxicity.

Interpretation and Conclusions. These data endorse the notion that infant ALL with *MLL* fusion genes have a unique etiology possibly involving transplacental exposure to chemicals.

Key words: infant acute leukemia, NQO1, polymorphism, chemicals, *in utero*.

Haematologica 2005; 90:1511-1515

©2005 Ferrata Storti Foundation

From the Section of Haemato-Oncology, Institute of Cancer Research, London, UK (ME-I, ME, DK, MG); Department of Pediatrics, Saga University, Saga, Japan (EI, YS); Department of Pediatrics, Showa University Fujigaoka Hospital, Yokohama, Japan (KI); Specialized Clinical Science, Pediatrics, Tokai University School of Medicine, Isehara, Japan (HY); Department of Pediatrics and Developmental Biology, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan (SM)

*Correspondence:
Dr. Mariko Eguchi, Section of Haemato-Oncology, Institute of Cancer Research, Chester Beatty Laboratories, 237 Fulham Road London SW3 6JB, United Kingdom.
E-mail: mariko.eguchi@icr.ac.uk*

Acute leukemia in infants (<1 year) is a distinct biological and clinical entity.[1,2] The prognosis is generally poor and a large proportion of cases have chromosome rearrangements generating chimeric fusions of *MLL* with one of diverse partner genes.[3,4] Studies of identical twin infants with leukemia and retrospective scrutiny of archived neonatal blood spots have revealed that *MLL* gene fusions arise antenatally, during pregnancy.[5,6] These data, together with the very high concordance rate in monozygotic twins and the brief latency of disease, suggest that all essential steps in leukemogenesis may be completed before birth and that any genotoxic exposure is likely to be transplacental.[7,8] *MLL* fusion genes are also common in secondary acute myeloid leukemia (usually French-American-British (FAB) M4/M5) associated with prior therapeutic exposure to topoisomerase-II inhibiting anthracyclines or epidophyllotoxins.[9] These observations have prompted speculation on possible exposure to topoisomerase-II inhibiting substances during pregnancy that might give rise to *MLL* fusions during fetal hematopoiesis.[10,11] This view finds some support in the experimental demonstration that flavonoid chemicals can cleave the *MLL* gene.[12] Preliminary epidemiological data have also implicated excess flavonoid exposure[13] or other maternal chemical exposure[14] during pregnancy. Many topoisomerase-II inhibiting chemicals contain quinone rings,[15-20] the metabolism of which is critically regulated by the enzyme NQO1 or NAD(P)H:quinone oxidoreductase (DT-diaphorase, EC 1.6.99.2) which converts toxic benzoquinones to hydroquinones.[21] Two polymorphic variations in the *NQO1* have been described: a C→T change at nt 609[22] and a C→T substitution at nt 465.[23] The 609 C→T allele (*C609T*) is associated with a loss of enzyme function due to protein instability[24-26] and the 465 C→T allele (*C465T*)

with a diminished activity mainly due to increased alternative splicing events producing a truncated mRNA without exon 4.[23,27] These data led to the prediction that if quinone-containing substances were relevant to the etiology of infant leukemia, i.e. via transplacental exposure, then there might be some significant association between *NQO1* alleles and risk of diseases. This was found to be the case. In a UK-based study of 36 infants with *MLL* fusion gene positive leukemia, there was a highly significant association between the *C609T* allele and risk, selective for *MLL* fusion gene positive leukemia and most pronounced for infant acute lymphoblastic leukemia (ALL) with *MLL-AF4* fusions (OR:8.63).[28] The magnitude of this effect was surprising but was confirmed (for *MLL-AF4* cases) in an independent US-based study of 39 patients (OR:10.82).[29]

We sought to confirm these important genetic data in another ethnic group – the Japanese – and report the finding that there is again a very strong association with an *NQO1* allele, but in this case with *C465T* not *C609T*.

Design and Methods

Patient and control samples

All infants with leukemia diagnosed before the age of 18 months who were registered by the Japan Infant Leukemia Study Group between December 1995 and December 1998 were included in this analysis. Diagnoses were made according to FAB classification. Detailed clinical data, treatment and outcome of some of these patients have been previously described.[30,31] This study group covered approximately 80% of infant leukemias in Japan during the period considered. Informed consent was obtained from parents of each patient as appropriate according to institutional guidelines prior to initiation of therapy.

Mononuclear cells obtained from patients' bone marrow and/or peripheral blood at the time of diagnosis of acute leukemia were screened for the presence of *MLL* gene rearrangement by Southern blotting and fluorescence *in situ* hybridization (FISH).[31] Karyotype analysis was carried out by conventional cytogenetics and translocation partners of *MLL* were confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) in cases with available samples. Controls consisted of umbilical cord blood samples obtained from healthy newborn Japanese infants after obtaining informed consent from their parents.

NQO1 genotyping

Genotyping was performed by polymerase reaction restriction fragment length polymorphism (PCR-RFLP) analysis of DNA extracted from the patients' blood

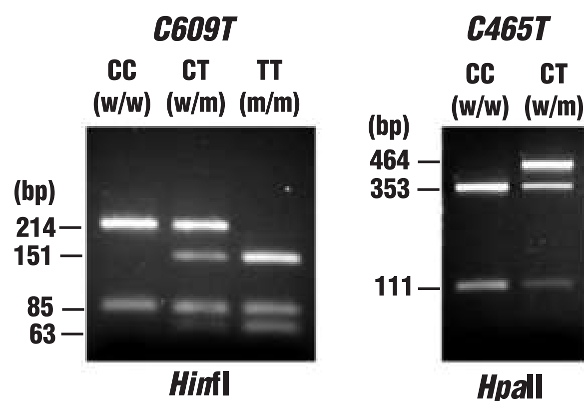

Figure 1. PCR-RFLP analysis of the *NQO1* polymorphisms on a 3% agarose electrophoresis gel. The figure illustrates the results from five representative individuals. w: wild type; m: mutation or polymorphism. m/m of *C465T* did not exist in any of the patients analyzed.

samples and control umbilical cord blood samples. Twenty nmoles of the primers NQO1-609A, 5'-CCTCTCTGTGCTTTCTGTATCC-3' with NQO1-609B, 5'-GATGGACTTGCCCAAGTGATG-3' (for the nt 609 polymorphism) or NQO1 ex4g-1f, 5'-CTAGCTTTACTCGGACCCACTC-3' with NQO1 ex4g-r, 5'-GCAACAAGAGGGAAGCTCCATC-3' (for the nt 465 polymorphism) were mixed with 60 ng of DNA, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 2.5 pmol of each dNTP, and 1.25 units Taq polymerase in a total volume of 25 μL and subjected to PCR with 35 cycles (94°C for 1 min, 60°C for 1 min, and 72°C for 1 min) followed by an extension at 72°C for 10 min.

PCR products were digested with *Hin*fI in the case of nt 609 polymorphism or with *Hpa*II in the case of the nt 465 polymorphism. Digested products were analyzed by electrophoresis in 3% agarose and viewed by ethidium bromide staining. Digestion of the PCR products for nt 609 polymorphism with *Hin*fI yielded two bands for the homozygous wild-type (CC; 85 and 214 bp), four bands for heterozygotes (CT; 63, 85, 151, and 214 bp), and three bands for the homozygous variant (TT; 63, 85, and 151 bp) (Figure 1). Digestion of the PCR products for nt 465 polymorphism with *Hpa*II yielded two bands in the case of homozygous wild-type (CC; 111 and 353 bp), three bands for heterozygotes (CT; 111, 353, and 464 bp), and one band for the homozygous variant (TT; 464 bp).

Statistical analysis

For the statistical analysis of *NQO1* nt 609 variant genotype, individuals with the homozygous and heterozygous variant genotypes were categorized as a group with *low NQO1* activity, as described in a previous report,[28,29] based on observations showing that the individuals with homozygous or heterozygous variant are deficient in *NQO1* protein, primarily

©Ferrata Storti Foundation

Table 1. Subclassification of cases of infant leukemia with *MLL* gene rearrangement.[1]

	Karyotypes (MLL fusion)						
	Total	t(4;11) MLL-AF4	t(9;11) MLL-AF9	t(11;19) MLL-ENL	Others[3]	Normal[4] 46XX/XY	Failure[5]
ALL	49	25[2]	5	6	6	3	4
AML	15	0	2	3	5	3	2

[1]Demonstrated by Southern blotting and/or FISH (see Methods) in all 64 cases.[2]Two patients showed normal karyotype by G-banding but t(4;11) was identified by FISH and MLL-AF4 fusion by RT-PCR. Of these 25 patients, sufficient diagnostic RNA was available to confirm the presence of MLL-AF4 fusion by RT-PCR in 21. [3]Translocation of MLL with other MLL fusion partners (e.g. AF6, AF10). [4]Normal karyotype but cryptic MLL gene rearrangement (detected by Southern blot and FISH). [5]Adequate material for karyotyping was not available in these patients.

because of decreased protein stability.[25,32] For *NQO1* nt 465 variant genotype, individuals with the heterozygous genotype were included in the *low NQO1* group, as no homozygous variant samples were obtained.

The significance of the difference between groups was determined by constructing two-by-two tables; odds ratios (OR) and 95% confidence intervals (CI) were calculated. Two-tailed p values were calculated using the χ^2 test. Fisher's exact methods were used instead of the χ^2 test for calculation of p values when the number of samples was less than five.

Results

The study group consisted of 103 infants with ALL (72 cases) or AML (31 cases). Of these, 49 of the cases of ALL and 15 of the AML cases had *MLL* gene rearrangements involving different gene fusion partners (Table 1). We assayed DNA samples from these cases for the frequency of two allelic polymorphisms at two positions in the *NQO1* gene - *C609T* (Pro187Ser) and *C465T* (Arg139Trp). Control population DNA was from cord blood. The allele frequency of *C609T* in cord blood was 0.34 which is considerably higher than that recorded for Caucasian populations (0.13~0.21)[33-36] but comparable to a previously published frequency for the Japanese population (0.38).[37] In contrast to previous reports,[28,29] we found no association between the *C609T* allele and risk of infant ALL with *MLL-AF4* or any other subgroup of infant leukemia analyzed (Table 2). A possible exception was found with *MLL* fusion gene-positive cases of AML. Only 15 cases were available for analysis but there was a suggestion that the low function *C609T* allele might be connected with increased risk. The relative risk of 3.23 (CI, 0.88-11.80) might become statistically significant in a bigger series.

The frequency of the *C465T* allele in normal individuals was 0.019. In the case of this allele we found a striking and selective association with infant ALL, particularly for infant ALL with *MLL-AF4* (OR 6.36, CI 1.84-21.90; p=0.002) (Table 3). The C465T allele was not associated with altered risk for infant AML with *MLL* gene fusions or for infant ALL or AML without *MLL* gene fusion (Table 3). No case or control had both *C609T* and *C465T* alleles and no haplotype analysis in relation to risk of infant leukemia was performed in this small study group of patients and controls.

Table 2. *NQO1 C609T* (Pro187Ser) polymorphism.

Category	n	NQO1 609[1] CC	CT	TT	NQO1 609T allele freq.	Low NQO1 OR[2] (95%CI)	p value
Controls (CB)	197	88	84	25	0.34	1.0	
MLL+ total	64	23	31	10	0.40	1.44 (0.80-2.58)	0.22
ALL	49	20	20	9	0.39	1.17 (0.62-2.21)	0.63
MLL-AF4	25	11	8	6	0.40	1.03 (0.44-2.38)	0.95
AML	15	3	11	1	0.43	3.23 (0.88-11.80)	0.10
MLL– total	39	16	18	5	0.36	1.16 (0.58-2.33)	0.68
ALL	23	9	10	4	0.39	1.26 (0.52-3.04)	0.61
AML	16	7	8	1	0.31	1.04 (0.37-2.90)	0.94

CB: cord blood; [1]CC, homozygous functional allele; CT: heterozygous allele; TT: homozygous non-functional allele. [2]Low NQO1 is defined as homozygous non-functional variant or heterozygous at the nt 609 polymorphism. Odds ratios compare the ratio of low NQO1 patients in each category to controls (reference group).

Table 3. NQO1 C465T (Arg139Trp) polymorphism.

Category	n	NQO1 465[1] CC	CT	NQO1 465T allele freq.	Low NQO1 OR[2] (95% CI)	p value
Controls (CB)	185	178	7	0.019	1.0	
MLL+ total	64	58	6	0.047	2.63 (0.85-8.14)	0.08
ALL	49	43	6	0.061	3.55 (1.13-11.10)	0.02
MLL-AF4	25	20	5	0.1	6.36 (1.84-21.90)	0.001
AML	15	15	0	0	–	0.59
MLL- total	37[3]	36	1	0.014	0.71 (0.08-5.92)	0.75
ALL	21[3]	20	1	0.024	1.27 (0.15-10.87)	0.83
AML	16	16	0	0	–	0.43

CB: cord blood; [1]CC, homozygous functional allele; CT, heterozygous allele. No TT genotype was found in any of the patients and control analyzed. [2]Low NQO1 is defined as homozygous low-functional variant or heterozygous at the nt 456 polymorphism. Note that no cases or controls were homozygous for this allele. Odds ratios compare the ratio of low NQO1 patients in each category to controls (reference group). [3]DNA samples for analysis of C465T polymorphism were not available for two ALL patients out of 39 leukemic patients without MLL gene rearrangement enrolled in this study.

Discussion

In prior analyses of the association between *NQO1* alleles and risk of infant ALL in UK and Caucasian US populations, a striking positive association was found in two independent studies between the *C609T* loss of function allele and risk of infant ALL with *MLL-AF4*

©Ferrata Storti Foundation

fusions (OR ~8 to 10).[28,29] No altered risk for infant ALL was found with the *C465T* allele of *NQO1* in these populations.[28] In a third study involving 50 Italian infants with acute leukemia, an increased risk was also observed among those inheriting the *C609T* of *NQO1* but only for the subgroup (of 18 cases) without a *MLL* gene fusion.[38] A very recent study of infant patients entered into BFM protocols in Germany and Austria also found no positive association between *C609T* and infant ALL with *MLL-AF4* fusions.[39] In the latter two *negative* studies, the *C465T* alleles were not assessed, understandably in terms of the prior lack of associations reported in Caucasian patients.[28] The reason for these discrepant results is unknown. The *C465T* allele is also reported to encode diminished function although it has been less extensively evaluated than the *C609T* allele.[23,27] The frequency of these two alleles varies markedly between different ethnic groups. The *C609T* allele is more common in Orientals than in Caucasians[36] in normal individuals; however, in the current study of Japanese infant patients we found no association of this allele with risk of infant ALL or AML (with or without *MLL* gene fusions). In marked contrast, we found that the *C465T* allele, which is much less common in the Japanese population (~0.012), was strongly associated with an increased risk of infant ALL with *MLL-AF4* (OR: 6.36; 95% CI 1.84-21.90). This implies that the *C465T* allele may be functionally more important in this ethnic population or genetic background than is the *C609T* allele, at least in relation to whatever exposure triggers *MLL-AF4* fusions. We cannot rule out that the *C609T* allele also affects risk in Japanese populations; its high frequency in the normal population may preclude a clear demonstration of such an effect in a rare disease. The biological basis of the predominant impact of *C465T* over *C609T* in our study is unclear but its credibility is significantly endorsed by a recent report of *NQO1* allele associations with benzene hematotoxicity in Chinese workers exposed to low levels of benzene.[40] This study also found a significant positive association for *C465T* but not *C609T* suggesting a potent selective impact of the *C465T* allele on detoxification capacity in the setting of an oriental genetic background.

Our data from Japanese patients reinforce the idea that *NQO1* enzyme function is probably involved in the exposure pathway that leads to infant leukemia and highlight the importance of assessing the impact of all functional allelic variations in different positions within a gene. The *C465T* allele effect could easily have been missed. As with prior *NQO1* studies,[28,29] the data also suggest that the *NQO1* functional effect is selective for ALL rather than AML, though the number of patients with AML was small. The basis for this potential selectivity is unclear; to date no epidemiological studies have implicated transplacental exposure during pregnancy that might be specific for ALL.[14] Nevertheless, the leukemic subtype selectivity endorses the credibility of the finding, particularly in the context of an inevitably numerically small cohort of patients.

NQO1 is an inducible enzyme that converts quinone to relatively stable hydroquinones bypassing the production of DNA-damaging semi-quinones and reactive oxygen species. The enzyme thus protects against the toxic and carcinogenic effects of quinones and related chemicals.[41,42] This profile suggests that quinone-containing chemicals could well be relevant to the etiology of infant ALL; this would include benzene and its metabolites as well as flavonoid-containing substances. It should, however, be noted that *NQO1* also exercises other functions, including an endogenous antioxidant activity (via reduction of α-tocopherolquinone)[43,44] and modulation of p53 activity[45-47] so its precise contribution to the etiology of infant ALL remains to be determined.

ME-I, ME: performed the experiments, analyzed and interpreted the data, prepared all the figures and tables, and produced the final version of the paper to be published. EI: provided infant leukemia samples as the representative of the Japan Infant Leukemia Study Group. DK: performed some of the PCR and RFLP analyses. YS: provided RT-PCR data for some infant ALL samples. KI, HY: provided cord blood samples. SM: contributed to the conception and design of the study. MG: responsible for the conception and design of the study, drafting the article, interpretation of the data and production of the final version to be published. All authors reviewed and approved the final version. The authors declare that they have no potential conflicts of interest.

This study was supported by the Leukaemia Research Fund, UK and the Kay Kendall Leukaemia Fund, UK (ME-I, ME, DK and MG), a Grant-in-Aid for Cancer Research from the Ministry of Health and Labor of Japan, Japan Children's Cancer Association and the Japan Leukemia Research Fund (EI, YS, KI, HY and SM).

We thank all the doctors participating in the Japan Infant Leukemia Study Group for providing samples and clinical information.

Manuscript received April 28, 2005. Accepted August 30, 2005.

References

1. Pui CH, Kane JR, Crist WM. Biology and treatment of infant leukemias. Leukemia 1995;9:762-9.
2. Biondi A, Cimino G, Pieters R, Pui CH. Biological and therapeutic aspects of infant leukemia. Blood 2000;96:24-33.
3. Dimartino JF, Cleary ML. MLL rearrangements in haematological malignancies: lessons from clinical and biological studies. Br J Haematol 1999; 106:614-26.
4. Rowley JD. The role of chromosome translocations in leukemogenesis. Semin Hematol 1999;36:59-72.
5. Ford AM, Ridge SA, Cabrera ME, Mahmoud H, Steel CM, Chan LC, et al. In utero rearrangements in the trithorax-related oncogene in infant leukaemias. Nature 1993;363:358-60.
6. Gale KB, Ford AM, Repp R, Borkhardt A, Keller C, Eden OB, et al. Backtracking leukemia to birth: identification of clonotypic gene fusion sequences in neonatal blood spots. Proc Natl Acad Sci USA 1997;94:13950-4.
7. Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: lessons in natural history. Blood 2003;102:2321-33.
8. Eguchi M, Eguchi-Ishimae M, Greaves M. The role of the MLL gene in infant

leukemia. Int J Hematol 2003;78:390-401.
9. Felix CA. Secondary leukemias induced by topoisomerase-targeted drugs. Biochim Biophys Acta 1998; 1400:233-55.
10. Ross JA, Potter JD, Robison LL. Infant leukemia, topoisomerase II inhibitors, and the MLL gene. J Natl Cancer Inst 1994;86:1678-80.
11. Greaves MF. Aetiology of acute leukaemia. Lancet 1997;349:344-9.
12. Strick R, Strissel PL, Borgers S, Smith SL, Rowley JD. Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. Proc Natl Acad Sci USA 2000;97:4790-5.
13. Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer Group. Cancer Causes Control 1996;7:581-90.
14. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 2001;61:2542-6.
15. Powis G. Free radical formation by antitumor quinones. Free Radic Biol Med 1989;6:63-101.
16. Chen H, Eastmond DA. Topoisomerase inhibition by phenolic metabolites: a potential mechanism for benzene's clastogenic effects. Carcinogenesis 1995;16:2301-7.
17. Gantchev TG, Hunting DJ. Inhibition of the topoisomerase II-DNA cleavable complex by the ortho-quinone derivative of the antitumor drug etoposide (VP-16). Biochem Biophys Res Commun 1997;237:24-7.
18. Frydman B, Marton LJ, Sun JS, Neder K, Witiak DT, Liu AA, et al. Induction of DNA topoisomerase II-mediated DNA cleavage by β-lapachone and related naphthoquinones. Cancer Res 1997;57:620-7.
19. Gantchev TG, Hunting DJ. The ortho-quinone metabolite of the anticancer drug etoposide (VP-16) is a potent inhibitor of the topoisomerase II/DNA cleavable complex. Mol Pharmacol 1998;53:422-8.
20. Whysner J, Reddy MV, Ross PM, Mohan M, Lax EA. Genotoxicity of benzene and its metabolites. Mutat Res 2004;566:99-130.
21. Ross D. Metabolic basis of benzene toxicity. Eur J Haematol Suppl 1996; 60:111-8.
22. Traver RD, Horikoshi T, Danenberg KD, Stadlbauer TH, Danenberg PV, Ross D, et al. NAD(P)H:quinone oxidoreductase gene expression in human colon carcinoma cells: characterization of a mutation which modulates DT-diaphorase activity and mitomycin sensitivity. Cancer Res 1992;52:797-802.
23. Pan SS, Forrest GL, Akman SA, Hu LT. NAD(P)H:quinone oxidoreductase expression and mitomycin C resistance developed by human colon cancer HCT 116 cells. Cancer Res 1995; 55:330-5.
24. Ross D, Traver RD, Siegel D, Kuehl BL, Misra V, Rauth AM. A polymorphism in NAD(P)H:quinone oxidoreductase (NQO1): relationship of a homozygous mutation at position 609 of the NQO1 cDNA to NQO1 activity. Br J Cancer 1996;74:995-6.
25. Traver RD, Siegel D, Beall HD, Phillips RM, Gibson NW, Franklin WA, et al. Characterization of a polymorphism in NAD(P)H: quinone oxidoreductase (DT-diaphorase). Br J Cancer 1997; 75: 69-75.
26. Siegel D, Anwar A, Winski SL, Kepa JK, Zolman KL, Ross D. Rapid polyubiquitination and proteasomal degradation of a mutant form of NAD(P)H: quinone oxidoreductase 1. Mol Pharmacol 2001;59:263-8.
27. Pan SS, Han Y, Farabaugh P, Xia H. Implication of alternative splicing for expression of a variant NAD(P)H: quinone oxidoreductase-1 with a single nucleotide polymorphism at 465C→T. Pharmacogenetics 2002;12: 479-88.
28. Wiemels JL, Pagnamenta A, Taylor GM, Eden OB, Alexander FE, Greaves MF. A lack of a functional NAD(P)H: quinone oxidoreductase allele is selectively associated with pediatric leukemias that have MLL fusions. United Kingdom Childhood Cancer Study Investigators. Cancer Res 1999; 59:4095-9.
29. Smith MT, Wang Y, Skibola CF, Slater DJ, Lo Nigro L, Nowell PC, et al. Low NAD(P)H:quinone oxidoreductase activity is associated with increased risk of leukemia with MLL translocations in infants and children. Blood 2002;100:4590-3.
30. Kawasaki H, Isoyama K, Eguchi M, Hibi S, Kinukawa N, Kosaka Y, et al. Superior outcome of infant acute myeloid leukemia with intensive chemotherapy: results of the Japan Infant Leukemia Study Group. Blood 2001;98:3589-94.
31. Isoyama K, Eguchi M, Hibi S, Kinukawa N, Ohkawa H, Kawasaki H, et al. Risk-directed treatment of infant acute lymphoblastic leukaemia based on early assessment of MLL gene status: results of the Japan Infant Leukaemia Study (MLL96). Br J Haematol 2002;118:999-1010.
32. Siegel D, McGuinness SM, Winski SL, Ross D. Genotype-phenotype relationships in studies of a polymorphism in NAD(P)H:quinone oxidoreductase 1. Pharmacogenetics 1999; 9:113-21.
33. Rosvold EA, McGlynn KA, Lustbader ED, Buetow KH. Identification of an NAD(P)H:quinone oxidoreductase polymorphism and its association with lung cancer and smoking. Pharmacogenetics 1995;5:199-206.
34. Kelsey KT, Ross D, Traver RD, Christiani DC, Zuo ZF, Spitz MR, et al. Ethnic variation in the prevalence of a common NAD(P)H quinone oxidoreductase polymorphism and its implications for anti-cancer chemotherapy. Br J Cancer 1997;76:852-4.
35. Schulz WA, Krummeck A, Rosinger I, Eickelmann P, Neuhaus C, Ebert T, et al. Increased frequency of a null-allele for NAD(P)H: quinone oxidoreductase in patients with urological malignancies. Pharmacogenetics 1997;7:235-9.
36 Gaedigk A, Tyndale RF, Jurima-Romet M, Sellers EM, Grant DM, Leeder JS. NAD(P)H:quinone oxidoreductase: polymorphisms and allele frequencies in Caucasian, Chinese and Canadian Native Indian and Inuit populations. Pharmacogenetics 1998;8:305-13.
37. Naoe T, Takeyama K, Yokozawa T, Kiyoi H, Seto M, Uike N, et al. Analysis of genetic polymorphism in NQO1, GST-M1, GST-T1, and CYP3A4 in 469 Japanese patients with therapy-related leukemia/ myelodysplastic syndrome and de novo acute myeloid leukemia. Clin Cancer Res 2000;6:4091-5.
38. Lanciotti M, Dufour C, Corral L, Di Michele P, Pigullo S, De Rossi G, et al. Genetic polymorphism of NAD(P)H: quinone oxidoreductase is associated with an increased risk of infant acute lymphoblastic leukemia without MLL gene rearrangements. 2005;19:214-6.
39. Kracht T, Schrappe M, Strehl S, Reiter A, Elsner HA, Trka J, et al. NQO1 C609T polymorphism in distinct entities of pediatric hematologic neoplasms. Haematologica 2004;89:1492-7.
40. Lan Q, Zhang L, Li G, Vermeulen R, Weinberg RS, Dosemeci M, et al. Hematotoxicity in workers exposed to low levels of benzene. Science 2004; 306:1774-6.
41. Ross D, Siegel D. NAD(P)H:quinone oxidoreductase 1 (NQO1, DT-diaphorase), functions and pharmacogenetics. Methods Enzymol 2004; 382: 115-44.
42. Talalay P, Dinkova-Kostova AT. Role of nicotinamide quinone oxidoreductase 1 (NQO1) in protection against toxicity of electrophiles and reactive oxygen intermediates. Methods Enzymol 2004;382:355-64.
43. Siegel D, Bolton EM, Burr JA, Liebler DC, Ross D. The reduction of α-tocopherolquinone by human NAD(P)H: quinone oxidoreductase: the role of α-tocopherolhydroquinone as a cellular antioxidant. Mol Pharmacol 1997;52: 300-5.
44. Siegel D, Gustafson DL, Dehn DL, Han JY, Boonchoong P, Berliner LJ, et al. NAD(P)H:quinone oxidoreductase 1: role as a superoxide scavenger. Mol Pharmacol 2004;65:1238-47.
45. Asher G, Lotem J, Cohen B, Sachs L, Shaul Y. Regulation of p53 stability and p53-dependent apoptosis by NADH quinone oxidoreductase 1. Proc Natl Acad Sci USA 2001;98:1188-93.
46. Asher G, Lotem J, Sachs L, Kahana C, Shaul Y. Mdm-2 and ubiquitin-independent p53 proteasomal degradation regulated by NQO1. Proc Natl Acad Sci USA 2002;99:13125-30.
47. Asher G, Lotem J, Kama R, Sachs L, Shaul Y. NQO1 stabilizes p53 through a distinct pathway. Proc Natl Acad Sci USA 2002;99:3099-104.

©Ferrata Storti Foundation