RESEARCH COMMUNICATION

GSTT1 and *GSTM1* Deletions, *NQO1* C609T Polymorphism and Risk of Chronic Myelogenous Leukemia in Japanese

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Abstract

We conducted a prevalent case-control study with 51 chronic myelogenous leukemia (CML) cases and 476 controls to investigate the associations between glutathione *S*-transferase T1 (*GSTT1*), glutathione *S*-transferase M1 (*GSTM1*) deletions, and the NAD(P)H:quinone oxidoreductase 1 (*NQO1*) C609T polymorphism with risk of chronic myelocytic leukemia in Japanese. For the *GSTT1* deletion, when the *GSTT1* positive genotype was defined as the reference, the OR for the *GSTT1* deletion genotype was 1.32 (95%CI; 0.74-2.36). For the *GSTM1* deletion, when the *GSTM1* positive genotype was defined as the reference, the OR for the *GSTM1* deletion genotype was 0.95 (95%CI; 0.53-1.69). For *NQO1* C609T polymorphism, when the *NQO1* 609CC genotype was defined as the reference, the ORs for the *CT* genotype, *TT* genotype, and *CT* and *TT* genotypes combined together were 2.37 (95%CI, 1.21-4.67, *P*=0.012), 1.44 (0.55-3.74, *P*=0.012) and 2.12 (1.10-4.08, *P*=0.025), respectively. The present study revealed that the risk of CML was modulated little by *GSTT1* and *GSTM1* deletions, but a statistically significant association between *NQO1* C609T polymorphism and CML was observed for Japanese. Incidence case-control studies with a larger statistical power are now required to confirm our findings.

Asian Pacific J Cancer Prev, **6**, 251-255

Introduction

Genetic polymorphisms of various kinds of genes, including those encoding drug metabolizing enzymes, have been recently proved to have important roles in the genesis of human malignancies. Among them, the mechanisms of the genesis of hematological malignancies remain rather unexplored. Aberrations in folate metabolism (Matsuo et al., 2001; Hishida et al., 2003a), or individual differences in drug metabolizing enzyme activities (Kerridge et al., 2002) have been shown to play important roles in their genesis. Other factors have been also examined (Hishida et al., 2003b; Hishida et al., 2004), but most of them are left still unknown.

Genetic polymorphisms associated with cancer susceptibility could be utilized for cancer prevention, by identifying such individuals as are subjective to carcinogenic environmental substances, and by preventing them from high risk behaviors such as smoking or alcohol consumption. Moreover, recent advances in both biological and epidemiological fields proved rather consistent associations between cancer risk and polymorphisms, including *NAD(P)H:quinone oxidoreductase 1* gene (*NQO1*) C609T (Pro187Ser), *glutathione S-transferase M1* (*GSTM1*), and *glutathione S-transferase T1* (*GSTT1*).

In humans, there are two groups of carcinogen metabolizing enzymes, wphase I and phase II. Phase I enzymes are cytochrome P-450 (CYP) enzymes, which converts procarcinogens into genotoxic carcinogenic intermediates which possess reactive electrophiles. Thereafter, phase II enzymes complete the detoxification by neutralizing reactive electrophiles or act as indirect antioxidants. *NQO1* and *GSTs* are both phase II detoxifying enzymes which play important roles in preventing carcinogen-induced disorders. The enzyme encoded by *NQO1* is a flavoprotein involved in the detoxification of

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potentially mutagenic and carcinogenic quinines, which are included in cigarette smoke. This enzyme catalyzes the two-electron reduction of potentially toxic quinoid compounds into their reduced form like hydroquinones (Lafuente et al., 2000). While enzyme encoded by the *CC* genotype has a full activity, that encoded by the *TT* genotype has no activity. The enzyme encoded by the *CT* genotype has intermediate activity between those of the *CC* and *TT* genotypes (Siegel et al., 1999).

Glutathione *S*-transferase M1 (*GSTM1*) and glutathione *S*-transferase T1 (*GSTT1*) are cancer susceptibility genes because of their ability to regulate the conjugation of carcinogenic compounds to excretable hydrophilic metabolites. Deletion variants lacking in enzyme activity exist for both genes. Individuals with homozygous deletions in the *GSTM1* or *GSTT1* genes are supposed to have less ability to metabolize carcinogens and may therefore be more susceptible to cancers (Rebbeck, 1997).

To date, several studies have reported that individuals with *NQO1 609TT* genotype are at increased risk of leukemia (Larson et al., 1999; Naoe et al., 2000; Smith et al., 2001), lung cancer (Rosvold et al., 1995), colorectal cancer (Lafuente et al., 2000), urological malignancies (Schulz et al., 1997), and a possible interaction of this genotype with smoking for lung and esophageal cancers are also indicated (Hamajima et al., 2002). To the contrary, there were some studies reporting insignificant, no, or inverse associations for lung cancer (Wiencke et al., 1997; Chen et al., 1999; Lin et al., 1999; Xu et al., 2001; Yin et al., 2001) and renal cell carcinoma (Longuemaux et al., 1999). A meta-analysis of lung cancer showed a significantly increased risk for *GSTM1* null type (Houlston, 1999).

As for hematological malignancies, risk of childhood acute lymphoblastic leukemia (ALL) is associated with *GSTM1* null or *CYP1A1*2A* genotypes, and myelodysplastic syndromes (MDS) is reportedly associated with *GSTT1* null genotype. Also, *GSTT1* null and paraoxonase (*PON1*) BB genotypes are associated with the risk of non-Hodgkin's lymphoma and multiple myeloma in Caucasians (Kerridge et al., 2002, Lincz et al., 2004). The association of *NQO1* C609T polymorphism and risk of child lymphoblastic leukemia (ALL) with or without MLL rearrangement is also now in hot argument (Kracht et al., 2004; Smith et al., 2002; Lanciotti et al., 2004).

For chronic myelogenous leukemia (CML), no significant association with genetic or environmental factors was reported, except for ionizing radiations and benzene. And there is only one study ever that investigated the *GST* polymorphisms in CML patients, which found no association between the *GSTM1* and *GSTT1* genotypes and the risk of CML (Loeffler et al., 2001). However, there is still a possibility that variations in these carcinogen metabolizing enzymes could modulate the risk of CML in another ethnicity, Japanese. Thus, we conducted a prevalent case-control study to clarify the association between *NQO1* C609T and *GST* polymorphisms and risk of CML in Japanese.

Materials and Methods

Study Population and Sample Collection

Case subjects were recruited from the patients at Nagoya University Hospital and related hospitals who were histologically confirmed to have CML between April 1989 and February 2001. Control subjects were health checkup examinees aged 20 years or over who visited Nagoya University Hospital from June 2003 to Feb 2004 (Nishio et al., 2004). Those attending "a basic health checkup" course with blood tests were invited to participate in our polymorphism study, where free genotype announcement was provided to the participants if they wish. All patients and control subjects were Japanese. For control subjects, those who provided written informed consent for participation in this study were asked to complete a self-administered questionnaire and to provide blood from a peripheral vein. For the cases, DNA samples extracted from the bone marrow or peripheral blood samples of those who were diagnosed as CML at Nagoya University Hospital or related hospitals from 1989 to 2001 were shuffled and unidentified according to the genome research guidelines by the Ministry of Education, Science, Sports, Culture and Technology of Japan, and used for the genotype analyses. This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine in 2003 (Approve number 52 and 99).

The characteristics of the study population are as follows: 51 patients (age range, 21-78 years; mean age, 47.4 years; male, 62.7%; age unknown n=23; gender unknown n=1) and 476 control subjects (age range, 17-89 years; mean age, 49.7 years; male, 61.1%) were recruited.

Genotype Analyses of the GSTT1 Deletion, GSTM1 Deletion and NQO1 C609T Polymorphisms

DNA was extracted from 200 μl of buffy coat preserved at -40˚C by QIAamp DNA Blood mini kit (Qiagen Inc., Valencia, CA). Triplex PCR was conducted to genotype simultaneously three polymorphisms, *NQO1* C609T, *GSTM1*, and *GSTT1* in one tube (Kawase et al., 2003). Two pairs of four primers were used for *NQO1* C609T genotyping by PCR-CTPP, and one pair of primers was used each for *GSTM1* and *GSTT1* by ordinary PCR.

Genomic DNA was used in a volume of 25 μl with 0.18 mM dNTPs, 12.5 pmol of each primer, 0.5 units of AmpliTaq Gold (Perkin-Elmer Corp., Foster City, CA), and 2.5 μl 10˚C PCR buffer including 15 mM $MgCl_2$. PCR System 9700 (PE Biosystems, Foster City, CA) was used for the DNA amplification. The PCR was performed with initial denaturation at 95˚C for 10 minutes, followed by 35 cycles of denaturation at 95˚C for 1 minute, annealing at 62˚C for 1 minute and extension at 72˚C for 1 minute. The final extension was at 72˚C for 5 minutes. All PCR products were separated by electrophoresis on a 2 % agarose gel containing a 2 μl /100 ml of ethidium bromide.

The representative results of electrophoresis are as shown in the report by Kawase et al (Kawase et al., 2003). The

amplified DNA are 161 base pair (bp) for *NQO1 609C*, 283 bp for *609T*, 219 bp for *GSTM1*, and 507 bp for *GSTT1*, as well as common band with 403 bp for *NQO1*. Bands were clear enough for each sample to be genotyped correctly.

Statistical Analysis

All statistical analyses in this study were performed using STATA (College Station, TX) statistical software. Accordance with the Hardy-Weinberg equilibrium, which indicates an absence of discrepancy between genotype and allele frequency, was checked for control subjects using the χ^2 test. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated by unconditional logistic regression model. Gene-gene interactions were also calculated by an unconditional logistic regression model, as ORs for interaction between the two genotypes with at least one variant allele. Adjustment for multiple comparisons was not performed because the analyses were conducted in an exploratory context, which requires careful interpretation of any *P* values.

Results

Genotyping for the GSTT1 Deletion, GSTM1 Deletion and NQO1 C609T Polymorphisms

Table 1 shows the genotype frequencies, age- and sex-adjusted odds ratios (OR) and 95% confidence intervals (95%CI) for *GSTT1* deletion, *GSTM1* deletion and *NQO1* C609T polymorphisms. Among the cases and controls, the frequencies of the *GSTT1* deletion and *GSTM1* deletion were 56.9% and 51.0% for cases, and 50.0% and 52.3% for controls, respectively. The frequency of the *NQO1* 609TT genotype (which has no enzymatic activity) was 13.7% for cases, and 15.8% for controls, respectively.

Risk Estimation for Genotypes by the Unconditional Logistic Model

For the *GSTT1* and *GSTM1* deletions, when the *GSTT1* positive or *GSTM1* positive genotype was defined as the reference, neither of the *GSTT1* deletion or the *GSTM1* deletion genotype demonstrated statistically significant OR: 1.32 (95%CI; 0.74-2.36) for the *GSTT1* deletion and 0.95 (95%CI; 0.53-1.69) for the *GSTM1* deletion, respectively.

For *NQO1* C609T polymorphism, when the *NQO1* 609CC genotype was defined as the reference, the ORs for the *CT* genotype, *TT* genotype, and *CT* and *TT* genotypes combined together were 2.37 (95%CI, 1.21-4.67), 1.44 (0.55-3.74, *P*=0.012) and 2.12 (1.10-4.08, *P*=0.025), respectively.

We also calculated The ORs for the combinations of *GSTT1* deletion and *GSTM1* deletion polymorphisms. None of the combined genotypes revealed statistically significant ORs (data not shown).

The *P* value for the deference between genotype frequency of *NQO1* C609T polymorphism among the control subjects and the Hardy-Weinberg's equilibrium was 0.0486.

Discussion

In the present study, we examined the association between the polymorphisms in the three carcinogen metabolizing genes (*GSTT1, GSTM1, NQO1*) and the risk of chronic myelocytic leukemia. To our knowledge, this is the second report that investigated the influence of the *GSTT1* and *GSTM1* polymorphisms on the genesis of CML, and as for *NQO1* C609T polymorphism, this is the first report ever. The first study that investigated the *GST* polymorphisms in CML patients found no association between the *GSTM1* and *GSTT1* genotypes and the risk of CML (Loeffler et al., 2001). As for other hematological malignancies, associations between the *GST* polymorphisms and the risk of therapy-related leukemia/MDS, *de novo* acute myeloid leukemia, non-Hodgkin's lymphoma and multiple myeloma have been reported. As for *NQO1* polymorphism, there are several reports about TRL/MDS and *de novo* AML risk, however, ours is the first report about CML.

Our study results revealed that the influence of *GST* polymorphisms on the risk of CML is limited for Japanese, which confirmed the previous report in Caucasians. For *NQO1* polymorphism, possible association between poor metabolizing genotypes and increased risk of CML was found. However, these associations could be different in other ethnicities, influenced by different kinds of lifestyles or circumstances (e.g., smoking habits, environmental pollutants like benzene, and so on), or difference of the gene-gene interactions between the ethnicities. Accordingly, better-designed studies with much larger populations or in

Table 1. Comparison of GST T1, GST M1, NQO1 Polymorphism Frequencies in Cases and Controls (univariate analysis).

Polymorphism		CML patients n (%)	Controls n (%)	OR	95%CI	P value
GST T1	pos	22 (43.1)	238 (50.0)	referent		
	null	29 (56.9)	238 (50.0)	1.32	0.74-2.36	0.353
GST M1	pos	25 (49.0)	227 (47.7)	referent		
	null	26 (51.0)	249 (52.3)	0.95	0.53-1.69	0.857
NQO1 C609T	CC	13 (25.5)	200 (42.0)	referent		
	TC	31 (60.8)	201 (42.2)	2.37	1.21-4.67	0.012
	TT	7 (13.7)	75 (15.8)	1.44	0.55-3.74	0.458
	TC+TT	38 (74.5)	276 (58.0)	2.12	1.10-4.08	0.025

other ethnicities are required to verify our findings. Moreover, further studies to clarify the gene-environment interactions between gene polymorphisms encoding these carcinogen detoxifying enzymes (GSTs and NQO1) and environmental exposure to carcinogenic substances like cigarette smoking, pollutants might possibly provide potent clues to prevent the genesis of CML.

Interestingly, it was reported that NQO1 makes cells subjective to apoptosis by tumor necrosis factor-alpha and subsequently, wild-type NQO1 was shown to stabilize wild-type p53 whereas inactive NQO1 wasn't (Siemankowski et al., 2000; Asher et al., 2002). It is suggested that in individuals with lower NQO1 activity, exposure to carcinogenic substrates of NQO1 could lead to increased genotoxic damage at lower p53 levels compared to wild-type NQO1 individuals (Asher et al., 2002). As p53 is important for growth arrest and induces apoptosis of cells including cancer or leukemic cells, lower NQO1 activity on carcinogenic exposure may lead to a higher susceptibility for accumulation of genetic mutations or chromosomal translocations like t(9;22)(q34;q11)) in hematopoietic precursor cells and finally lead to CML.

NQO1 genotype frequencies are significantly different between the ethnicities, where the frequencies of *NQO1* 609T allele are reported approximately one half among the Caucasians and similar in Hispanic populations (allele frequencies 0.21 and 0.39, respectively) (Kracht et al., 2004). The frequencies of *GSTT1* and *M1* deletions also differ among the ethnicities. The frequency of *GSTT1* deletion is significantly less frequent in Caucasians (allele frequency 0.197), and the frequency of *GSTM1* deletion is similar in Caucasians and less frequent in Africans (allele frequencies 0.531 and 0.267, respectively) (Garte et al., 2001). The frequencies of *NQO1* 609T allele, *GSTT1* deletion and *GSTM1* deletion in our control subjects were not significantly different from those of another report in Japanese (0.391, 0.540 and 0.513, respectively) (Naoe et al., 2000).

This study has several limitations. In this study, non-cancer outpatients (most were free from any kind of disease) were adopted as controls, thus, no selective mechanisms for a specific genotype of these polymorphisms are supposed to exist among the controls. However, the genotype distribution of *NQO1* C609T polymorphism was statistically significantly different from Hardy-Weinberg's equilibrium (P=0.0486). This might be attributable to the large number of the control subjects, or explained as a result of a random effect, type I error. In addition, we used relatively old stocked clinical samples for the cases, most of them are derived from CML cells, and age unknown samples are also included. Accordingly, we should be careful in interpreting the results of this study, and better-designed studies, i.e., incidence case-control studies with a large statistical power, are expected in the near future.

In conclusion, the present study revealed that the risk of chronic myelocytic leukemia was modulated little by *GSTT1* and *GSTM1* deletions, but statistically significant association between *NQO1* C609T polymorphism and risk of chronic myelocytic leukemia was observed for Japanese. Further examinations with sufficiently larger population and other ethnicities are required to confirm our findings.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture and Technology of Japan. The authors are grateful to Ms. Chika Wakamatsu and Ms. Mayumi Kato for their technical assistance.

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