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No substantial difference in genotype frequencies of interleukin and myeloperoxidase polymorphisms between malignant lymphoma patients and non-cancer controls

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Background and Objectives. The functional polymorphisms regulating immunologic responses may influence the proliferation or suppression of malignant lymphoma. We examined the association between malignant lymphoma risk and the polymorphisms of the IL-1 gene family [*IL-1B* –31 C/T, *IL-1A* –889 C/T, and *IL-1RN* 86-bp variable number of terminal repeat (VNTR)] and myeloperoxidase (MPO –463 G/A).

Design and Methods. The hospital-based case-control study was conducted in Japan. Genotypes were examined in a total of 372 lymphoma cases and 241 non-cancer control subjects. The relative risks were estimated by unconditional logistic regression analysis.

Results. The overall allele distribution of these polymorphisms did not differ substantially between patients and controls; the odds ratios were 0.73 (95% confidence interval, 0.48-1.11) for the T allele carriers of *IL-1B* relative to the non-carriers, 1.01 (0.56-1.82) for the 2-repeat allele (allele 2) carriers of *IL-1RN*, 0.96 (0.62-1.48) for the T allele carriers of *IL-1A*, and 1.04 (0.70-1.57) for the A allele carriers of *MPO*. Subgroup analyses according to histology [diffuse large B-cell lymphoma (DLBL), follicular lymphoma, low-grade lymphoma of mucosa associated lymphoid tissue, and others] failed to illustrate differences except for DLBL which showed a possible association with *IL-1A* and *IL-1B* polymorphisms.

Interpretation and Conclusions. Our data show a limited association between these polymorphisms and malignant lymphoma risk in total. The possible association of the *IL-1A* and *IL-1B* polymorphisms with DLB-needs further clarification.

Key words: malignant lymphoma, genetic predisposition of disease, IL-1, myeloperoxidase, gene polymorphism

Cytokines play important roles in the hematopoietic and immune systems. Their functions include control of cellular and humoral immune responses, with an impact on inflammation, chemotaxis, tumor regression, hematopoiesis, and acute-phase responses.[1] Interleukin-1 (IL-1), which is a prototypic multifunctional cytokine synthesized by a variety of cell types, including activated macrophages and stimulated B-lymphocytes, is an essential mediator of inflammation and immunity. It can exert either inhibitory or promoting effects on neoplasms including hematologic malignancies.[2] Accumulated evidence indicates that the production and activity of IL-1, particularly IL-1β, one prominent member of the IL-1 family, may regulate the effects of IL-1. The allelic state of IL-1 genes has been suggested to determine basal production and inducible responses of IL-1.

The IL-1 gene cluster, comprising the *IL-1A*, *IL1-B* and IL-1 receptor antagonist (*IL-1RN*), is located on human chromosome 2q.[3] These genes code for three ligands of the IL-1 family: the first two (*IL-1α* and IL-1β) with agonist properties towards membrane IL-1 receptors, also located on 2q and the third (IL-IRa) a competitive antagonist. *IL-1B* has three polymorphisms at -511, -31, and +3954, the former two being tightly linked.[4] The T allele at -31 makes a TATA box, which may enhance gene expression. An association between *IL-1B* polymorphism and risk of gastric cancer was reported,[4] and several other studies showed that this polymorphism is associated with various diseases.[5,6] The 2-repeat type (allele 2) of *IL-1RN* variable number of terminal repeat (VNTR) enhances the production of IL-1β,[7] and is associated with several diseases.[4,8,9] IL-1β is a primarily

cytosolic cytokine. Approximately 10% to 15% of IL-1α is myristaylated and transported to the cell surface (membrane IL-1), but IL-1α is not detected in the serum under normal conditions.[2] *IL-1A* is reported to have three polymorphisms; C-899T, 46bp VNTR at intron 6, and G4845T. One study showed that the combination of T/T of *IL-1A* –889 and T/- of *IL-1B* –511 was related to high plasma levels of IL-1β.[10]

Myeloperoxidase (MPO) is another enzyme which has an impact on inflammation. Its gene has a polymorphism –463 G/A. The A allele of this polymorphism reduces mRNA expression,[11] and subsequently reduces tissue damage accompanying local inflammation.[12] Several studies with chronic granulomatous disease,[12] malignancies such as lung[13] and pharyngeal cancer[14] and Alzheimer's disease,[15] showed that this *MPO* gene polymorphism had a pathogenic effect.

The present hospital-based, case-control study was conducted in Aichi Cancer Center to evaluate the effects of polymorphisms in the IL-1 family (*IL-1A* -889 C/T, *IL-1B* –31 C/T, and *IL-1RN* 86-bp VNTR at intron 2) and *MPO* –463 G/A on the susceptibility to various histologic subtypes of malignant lymphoma.

Design and Methods

The study population

The cases were recruited from patients who were diagnosed histologically as having malignant lymphomas in Aichi Cancer Center. The 383 cases comprised two groups: 109 prevalent cases who visited outpatient clinics and provided a venous blood sample; and 274 incident cases diagnosed between 1993 and 2000 whose lymphoma tissue DNAs were available. Because eleven cases overlapped between the two groups, 372 cases were eligible for analysis. Controls (n=241) were outpatients without any history of cancer who visited ACC during March to December 1999 for gastroscopy.[16,17] Of the 241 controls, 97 (40.2%) stated they were receiving medication for a total of 107 diseases (not confirmed by their medical records); 23 with gastric/duodenal ulcer, another 23 with so-called gastritis, 16 with hypertension, 8 for pain including arthritis and lumbago, 7 with diabetes mellitus, 7 with hyperlipidemia, and the other 23 with miscellaneous diseases. Patients with autoimmune diseases were not included in the control group. All cases and controls were Japanese. Written informed consent for analyzing DNA polymorphisms was obtained from all the prevalent cases and controls. The samples from prevalent cases and controls were obtained from peripheral blood. The use of all samples was approved by Ethical Committee of Aichi Cancer Center. The stocked tissue DNA samples with information such as age, sex, and histologic subtype were made anonymous after checking for overlapping cases. Matched case sampling was not conducted to avoid the reduction of power.[18]

Genotyping

The gene polymorphisms evaluated in this study were *IL-1B* -31C/T, *IL-1RN* VNTR at intron 2, *IL-1A* –899 C/T and *MPO* -463 G/A. Typing was accomplished according to previously described methods for *IL-1RN* VNTR at intron 2,[1,19] and *MPO* -463.[20] For IL-1B –31 C/T and IL-1A –889 C/T, a novel method named polymerase chain reaction with confronting two-pair primers (PCR-CTPP) was used, which does not require restriction enzyme digestion for genotyping.[21] Briefly, confronting two-pair primers (F1 and R1 for T allele, F2 and R2 for C allele, R1 including adenine at the end and F2 including cytosine at the end) contained in one tube produces allele-specific PCR products for the C allele and T allele, as well as a product between F1 and R2. Descriptions of typing of each polymorphism are shown in Table1.

Statistical analysis

All odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for sex as well as age as a continuous variable, instead of age-sex matching, using an unconditional logistic regression model. Accordance with the Hardy-Weinberg equilibrium, which indicates an absence of discrepancies between genotype and allele frequencies, was checked for in the control-subjects by using the χ^2 test. The genotype frequencies among cases and controls were also compared with the χ^2 test. Subgroup analyses according to histologic subtype were conducted for diffuse large B-cell lymphoma (DLBL), low-grade lymphoma of mucosa-associated lymphoid tissue type (MALT), follicular lymphoma, and the others. The statistical power for 241 controls and 341 cases was more than 95% for OR=2 or 0.5 under a two-side significance level of 0.05, with a genotype frequency among the controls being between 30% and 70%. All statistical analyses were performed using STATA version 6 software (STATA Corporation Inc., College Station, TX, USA).

Results

The characteristics of the 372 cases and 241 controls are shown in Table 2. The cases included 123 diffuse large B-cell lymphomas, 71 low-grade lymphomas of mucosa associated lymphoid tissue (MALT) type and 74 follicular lymphomas (FL), and 104 other lymphomas (22 Hodgkin's diseases, 16 marginal zone B-cell lymphomas, 15 diffuse lymphomas other than DLBL, 11 peripheral T-cell lymphomas, 9 mantle cell lymphomas, 5 lymphoblastic lymphomas, 5

Table 1. Gene polymorphisms and typing protocols for *IL-1B*, *Il-1RN*, *IL-1A*, and *MPO*.

IL-1B –31 C/T (PCR-CTPP)
Primers: IL1b-31F1:5'-AAT GTG GAC ATC AAC TGC A-3'
IL1b-31R1:5'-CTC CCT CGC TGT TTT TAT A-3'
IL1B-31F2:5'-ACT TCT GCT TTT GAA GGC C-3'
IL1B-31R2:5'-TCA GCT GTT AGA TAA GCA G-3'
PCR: Denaturing 5-min at 94˚C
(94˚C 1-min, 56˚C 1-min, 72˚C 1-min) 30 cycles
Extension 5-min at 72˚C
Genotyping: 574-, and 345-bp for C-allele, 574-, and 266-bp for T allele.

IL-1RN 86-bp VNTR at intron 2
Primers: IL1RAF:5'-CTC AGC AAC ACT CCT AT-3'
IL1RAR:5'-TCC TGG TCT GCA GGT AA-3'
PCR: Denaturing 5-min at 94˚C
(94˚C 1-min, 60˚C 1-min, 72˚C 1-min) 30 cycles
Extension 5-min at 72˚C
Genotyping: 4 repeats 412-bp (allele 1), 2 repeats 240-bp (allele 2),
3repeats 326-bp (allele 3), and 5 repeats 498-bp (allele 4).

IL-1A –889 C/T (PCR-CTPP)
Primers: IL1A-F1:5'-ATC ACA CCT AGT TCA TTT CC-3'
IL1A-R1:5'-TAC ATA TGA GCC TTC AAT GA-3'
IL1A-F2:5'-TAA TAG TAA CCA GGC AAC AC-3'
IL1A-R2:5'-CAA CAC ATT TCC TAT AGA GG-3'
PCR : Denaturing 10-min at 95˚C
(95˚C 1-min, 48˚C 1-min, 72˚C 1-min) 30 cycles
Extension 5-min at 72˚C
Genotyping: 279-, and 428-bp for C allele, 186-, and 428-bp for T allele.

MPO –463 G/A (PCR-RFLP)
Primers: F: 5'-CGG TAT AGG CAC ACA ATG GTG AG -3'
R: 5'-GCA ATG GTT CAA GCG ATT CTT C-3'
PCR : Denaturing 2-min at 94˚C
(94˚C 30sec, 56˚C 30sec, 72˚C 30sec) 32 cycles
Extension 7-min at 72˚C.
Digestion: restriction enzyme AciI
Genotyping: 169-, 120-, and 61-bp for G allele, 289-, and 61-bp for A allele

Abbreviations: IL-1, interleukin-1; VNTR, variable number of terminal repeat; MPO, myeloperoxidase; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; OR, odds ratio; CI, confidence interval; DLB lymphoma, diffuse large B-cell lymphoma; MALT lymphoma, low-grade lymphoma of mucosa-associated lymphoid tissue lymphoma.

Table 2. Characteristics of study subjects.

Characteristics	*Cases*	*Controls*
Number	372	241
Age (years) (median)	5-89 (57)	39-69 (58)
Sex (male/female)	202/170	118/123
Histologic type* of lymphoma		
DLB	123	-
FL	74	-
MALT (total)	71	-
Gastric	24	-
Non-gastric	47	-
Others	104	-

**Abbreviations: DLB, diffuse large B-cell lymphoma; MALT, low-grade lymphoma of mucosa associated lymphoid tissue; FL, follicular center lymphoma.*

anaplastic large cell lymphomas, 5 Lennert's lymphomas, 4 Burkitt's lymphomas, 3 angioimmunoblastic lymphomas, and 9 other miscellaneous lymphomas).

Since there were no differences in the genotype frequency between the incident cases and prevalent cases (Table 3), both groups were combined for the following analyses. The frequencies of *IL-1B* –31CC, CT, and TT were 22.3%, 46.8%, and 30.9% for cases and 17.0%, 55.2%, and 27.8% for controls (χ^2 test: p=0.102). For *IL-1RN* VNTR, 4-repeat allele carriers were dominant among both cases and controls. The frequencies of IL-1A –889 CC, CT, and TT were 83.3%, 16.4%, and 0.3% for cases and 83.0%, 16.6%, and 0.4% for controls (p=0.951). The distribution of *MPO* –463 GG, GA, and AA was similar among cases and controls (p=0.856). The distributions of genotype for all polymorphisms among controls were in accordance with the Hardy-Weinberg law of equilibrium with no significant χ^2 test value, as shown in Table 3.

The odds ratios (OR) for each polymorphism according to histologic type are shown in Table 4. For all subjects, T allele carrier status of the *IL-1B* –31 C/T polymorphism tended to confer risk reduction (OR for the CT/TT type compared with the CC type, 0.73: 0.48-1.11, p=0.138), but the difference was not statistically significant. The *IL-1RN* intron 4 VNTR, IL-1A –889 C/T and *MPO* –463 G/A polymorphism did not demonstrate any risk change.

As for the overall analysis, subgroup analyses according to histologic subtypes all failed to demonstrate statistically significant risk changes. Concerning diffuse large B-cell lymphoma, T allele carriers of *IL-1B* and *IL-1A* polymorphisms showed a reduction of risk of marginal significance (OR for the T allele carriers compared with the CC type, 0.61: 0.36-1.04, p=0.070; OR for the *IL-1A* –889 CT/TT type compared with the CC type, 0.53: 0.26-1.04, p=0.065). Similar trends of risk reduction were observed for other subtypes except MALT lymphoma, but none of the results was statistically significant. Risk reduction was not observed for the T allele of the *IL-1A* polymorphism among any of the subtypes other than DLBL. The *IL-RN* and *MPO* polymorphism did not change the risk in our analyses.

Discussion

In this study, we did not find any difference in genotype frequencies of inflammation-related gene polymorphisms between malignant lymphoma patients as a whole and control subjects. Subgroup analyses according to histologic subtypes showed a possible difference in DLBL. Since the genotype frequencies were similar between the incident cases and

Table 3. Allele frequencies of *IL-1B*, *IL-1RN*, *IL-1A*, and *MPO* gene polymorphism among cases and controls.

Polymorphism	Genotype	Cases		Controls
		Prevalent	Incident	
IL-1B –31 C/T				
	CC	23 (21.1%)	60 (22.8%)	41 (17.0%)
	CT	52 (47.7%)	122 (46.4%)	133 (55.2%)
	TT	34 (31.2%)	81 (30.8%)	67 (27.8%)
	T allele frequency among controls: 0.554 %			
	Hardy Weinberg equilibrium test: χ^2=3.28 *p*= 0.07			
IL-1RN 86-bp VNTR at intron 2				
	2/2	1 (0.3%)	0 (0.0%)	1 (0.4%)
	2/4	13 (11.9%)	17 (6.5%)	18 (7.5%)
	2/5	0 (0.0%)	0 (0.0%)	1 (0.4%)
	3/4	0 (0.0%)	2 (0.8%)	1 (0.4%)
	4/4	94 (86.2%)	242 (92.0%)	217 (90.0%)
	4/5	1 (0.9%)	2 (0.8%)	3 (1.2%)
	4- repeat allele frequency among controls: 0.946			
	Hardy Weinberg equilibrium test: χ^2=2.69 *p*= 0.10, where 4-repeat allele vs. the other alleles was examined.			
IL-1A –889 C/T				
	CC	93 (85.3%)	217 (82.5%)	200 (83.0%)
	CT	16 (14.7%)	45 (17.1%)	40 (16.6%)
	TT	0 (0.0%)	1 (0.4%)	1 (0.4%)
	T allele frequency among controls: 0.08			
	Hardy Weinberg equilibrium test: χ^2= *p* =0.26			
MPO –463 G/A				
	GG	90 (82.6%)	203 (77.2%)	192 (79.7%)
	GA	19 (17.4%)	58 (22.1%)	47 (19.5%)
	AA	0 (0.0%)	2 (0.8%)	2 (0.8%)
	A allele frequency among controls: 0.11			
	Hardy Weinberg equilibrium test: χ^2=1.66, *p*=0.20			

**Accordance with Hardy-Weinberg law of equilibrium was calculated by the χ^2 test.*

prevalent cases, the inclusion of the prevalent cases did not seem to introduce any influence due to long survivors.

IL-1 is the prototypic multifunctional cytokine, and its biological functions on hematologic malignancies have therefore already been pointed out.[2] An autocrine effect was reported for acute myelogenous leukemia (AML),[22,23] chronic myelogenous leukemia (CML),[22] and multiple myeloma (MM).[24,25] IL-1β has anti-neoplastic activity through activation of the immune system.[2] The higher incidence of hematologic malignancies among immune deficiency individuals suggests that differences in the status of immune activation may change the predisposition to hematologic malignancies. Several studies have demonstrated that IL-1β shows an anti-proliferation effect on tumor cells *in vitro*.[26,27] Studies concerning the mechanism of cell death have shown that Fas-mediated apoptosis is associated with IL-1β or converting enzyme like protease.[28,29] Regarding IL-1 gene family polymorphisms, *IL-1B* –31 *C/T*, *IL-1A* –889 C/T and *IL-1RN* VNTR at intron 4 were reported to influence the serum concentration of IL-1β.[7,10,30] Several studies have evaluated the pathogenic significance of this in terms of hematologic malignancies (including chronic lymphocytic leukemia, hairy cell leukemia, multiple myeloma, primary and secondary AML, CML and Hodgkin's disease), but could not identify any significant correlations.[31-34] Our result with malignant lymphoma was consistent with the literature, suggesting that the effects of IL-1 family gene polymor-

Table 4. Adjusted*odds ratios and 95% CIs for *IL-1B*, *IL-1RN*, *IL-1A* and *MPO* polymorphisms according to histologic type.

Subjects (n=241)	Controls (n=372)	All (n=123)	DLB (n=71)	MALT (n=74)	FL (n=104)	Others
IL-1B -31						
CC	41	1.00 (83)	1.00 (31)	1.00 (11)	1.00 (18)	1.00 (23)
CT/TT	200	0.73 (289)	0.61 (92)	1.10 (60)	0.68 (56)	0.85 (81)
(95%CI)		(0.48-1.11)	(0.36-1.04)	(0.53-2.28)	(0.36-1.28)	(0.47-1.54)
		p=0.138	*p*=0.070	*p*=0.794	*p*=0.228	*p*=0.592
IL-1RN						
Allele 2(-)	221	1.00 (341)	1.00 (113)	1.00 (68)	1.00 (66)	1.00 (94)
Allele 2(+)	20	1.01 (31)	0.97(10)	0.48 (3)	1.34 (8)	1.18 (10)
(95%CI)		(0.56-1.82)	(0.44-2.15)	(0.14-1.67)	(0.56-3.21)	(0.53-2.66)
		p=0.971	*p*=0.945	*p*=0.249	*p*=0.507	*p*=0.763
IL-1A -889						
CC	200	1.00 (310)	1.00 (111)	1.00 (58)	1.00 (59)	1.00 (82)
CT/TT	41	0.96 (62)	0.53 (12)	1.12 (13)	1.29 (15)	1.21 (22)
(95%CI)		(0.62-1.48)	(0.26-1.04)	(0.56-2.24)	(0.66-2.51)	(0.67-2.18)
		p=0.854	p=0.065	p=0.748	*p*=0.452	*p*=0.536
MPO -463						
GG	192	1.00 (293)	1.00 (95)	1.00 (62)	1.00 (55)	1.00 (81)
GA/AA	49	1.04(79)	1.15(28)	0.57(9)	1.35(19)	1.10 (23)
(95%CI)		(0.70-1.57)	(0.68-1.95)	(0.27-1.24)	(0.74-2.52)	(0.63-1.95)
		p=0.813	*p*=0.603	*p*=0.157	*p*=0.334	*p*=0.732

**Adjusted for age and sex.*

phisms in lymphoid malignancies seem to be limited, except DLB lymphomas in which a possible risk reduction was observed in the logistic regression model for T allele carriers of the IL-1A and IL-1B polymorphism. The biological mechanism of this difference is unclear; the observation implies that the change of the immunologic status by IL-1A and IL-1B polymorphisms is affected more dominantly than other histologic subtypes.

MPO is an enzyme that leads to generation of hydroxy radicals in the presence of superoxide.[35] MPO and its reactive by-products have been linked to DNA base modification,[36] DNA strand breakage,[37,38] inhibition of DNA repair,[39] and generation of carcinogens.[40,41] Association of *MPO* –463 polymorphism was reported for diseases closely related to local inflammation accompanied by phagocyte invasion.[15,20] Therefore, we hypothesized the link with MALT lymphoma, which is known to arise in association with local inflammations such as autoimmune disease or *Helicobacter gastritis*.[42] Nevertheless, our present results did not show any significant association.

Although this study was not a population-based, case-controlled study, the overall number of cases was large enough to examine hematologic malignancies. The statistical power in assessing the association between each of these polymorphisms and the risk of malignant lymphoma was more than 95% with a genotype frequency between 30 to 70%. While only *IL-1B* –31 C/T met with this criterion, the other polymorphisms had target genotype frequencies around 20%, with estimated powers of 94.5%, suggesting that all the results were statistically conclusive as overall analyses. Subgroup analyses according to histologic type could benefit from further clarification because of lower statistical power compared with overall analyses. The control subjects were non-cancer outpatients, and the distribution of each of their gene polymorphisms was in accordance with the Hardy-Weinberg law of equilibrium with no significant χ^2 value (Table 3) indicating appropriate sampling. For the IL-1B -31 C/T polymorphisms, the T allele frequency was here found to be higher than in an earlier study of Caucasians,[4] and for the *IL-1RN* VNTR polymorphism, the 4-repeat allele (allele 1) homozygous type was dominant. The T allele of IL-1A was less frequent in our Japanese subjects (8.7%: 42/482) than in Caucasians (33.1% in Finland,[10] 28.3% in England[9]). For *MPO* -463 G/A, the A allele was also more rare in Japanese than Caucasians.[13,20]

We used different sources of DNA in this study. In general, for studies examining the association between polymorphisms and disease risk, germ line DNA from peripheral blood is suitable if a sample is available. In this study, we used peripheral blood DNAs from controls and prevalent cases and tissue DNAs from incident cases. We evaluated both peripheral blood and tissue DNA from eleven of the same individuals to rule out that the evaluated polymorphisms were somatic mutations. The results of genotyping for each source were consistent to each other, and this fact warrants the use of tissue DNA as an alternative to peripheral blood DNA for the study of these polymorphisms.

In conclusion, the present study revealed that genotype frequencies of IL-1-related genes and MPO gene polymorphisms do not vary between malignant lymphoma patients and non-cancer controls in Japanese. This result shows that these polymorphisms had limited effect in lymphomagenesis with the possible exception of DLBL which showed a marginal statistically significant association with *IL-1B* and *IL-1A* polymorphisms. Although the study was not population based, the result provides useful information to explore the susceptibility to malignant lymphoma.

Contribution and Acknowledgments

All authors contributed to the design of the study. KM and HN contributed to collection of data and samples, and was responsible for the laboratory data, statistical analysis, and principally writing the article. RS and MS collected the clinical data and did the DNA extraction from incident cases. SN collected the clinical data and made the pathologic diagnoses. YM coordinated the study and revised it critically, and collected clinical data from prevalent cases. KT provided supervision of the study. All authors approved the final version of the paper. Authors are listed according to a criterion of decreasing individual contribution to the work with the following exceptions: the first two authors contributed equally to this article, while the last author had a major role as senior author in designing the study. The authors are grateful to Ms. Michiyo Tani, Ms. Keiko Asai and Ms. Hiroko Fujikura for their technical assistance.

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Disclosures

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Manuscript processing

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Potential implications for clinical practice

IL-1 family and MPO gene polymorphisms do not influence the occurrence of malignant lymphoma except, perhaps, diffuse large B-cell lymphoma.

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