Polymorphisms in DNA repair genes and risk of non-Hodgkin's lymphoma in New South Wales, Australia

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ABSTRACT

Background and Objectives

A number of occupational and environmental exposures that can directly or indirectly cause DNA damage have been proposed as risk factors for non-Hodgkin's lymphoma (NHL). The human DNA damage repair system can recognize and repair such damage and maintain genomic stability. We investigated whether putatively functional single-nucleotide polymorphisms (SNP) in DNA repair genes influence susceptibility to NHL in a population-based case-control study conducted in Australia.

Design

A total of 561 cases and 506 controls were included in the analysis. Twenty-two SNP in 14 DNA repair genes were genotyped by a TaqMan-based assay. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI), adjusting for age, sex, residence, and ethnicity.

Results

Two SNP in *MGMT* (Ile143Val and Lys178Arg) were in complete linkage disequilibrium and associated with increased risk of NHL (Ile143Val, Ile/Val vs. Ile/Ile, OR: 1.26; 95% CI: 0.93-1.70; Val/Val vs. Ile/Ile, OR: 2.55; 95% CI: 0.98-6.63; *p* trend: 0.024). These SNP were associated with increased risk of several NHL subtypes. In addition, the *XRCC1* Arg194Trp polymorphism was associated with decreased NHL risk (Arg/Trp vs. Arg/Arg, OR: 0.72; 95% CI: 0.49-1.07; Trp/Trp vs. Arg/Arg, OR: 0.45; 95% CI: 0.10-1.99; *p* trend: 0.059), mainly in diffuse large B-cell lymphoma.

Interpretation and Conclusions

The association of genetic variants in *MGMT* with increased risk of NHL suggests that alkyl adducts may contribute to lymphomagenesis, and points to environmental and endogenous alkylating agents as possible risk factors for NHL. However, given that these results were based on a small number of variant carriers and the possibility that these results may have arisen due to chance, replication in other studies is needed.

Key words: non-Hodgkin's lymphoma, case-control study, DNA repair, single nucleotide polymorphism, MGMT.

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The incidence of non-Hodgkin's lymphoma (NHL) has increased steadily[1] in the past 50 years. Besides well-known risk factors, including family history, immune dysfunction (e.g., autoimmune diseases, immune deficiency syndromes, and iatrogenic immune suppression after organ transplant), immune stimulation, and infections (e.g., human T-lymphotrophic virus type I, human immunodeficiency virus), a number of occupational and environmental exposures have been proposed as risk factors for NHL. Associations with exposure to herbicides and pesticides, benzene and other solvents, dioxins and other potentially DNA-damaging agents have been reported, although the findings have been inconsistent.[1]

The human DNA repair system recognizes different types of damage and activates specific mechanisms to repair the damaged DNA and maintain genomic stability. Given that chromosome aberrations are a hallmark of lymphomas and defects in DNA repair and genomic maintenance can cause chromosomal aberrations,[2] it is plausible that genetic variation in DNA repair genes may influence risk of lymphoma.

Recently, studies have reported associations of certain DNA repair gene polymorphisms with NHL risk.[3,4] To study the effect of DNA repair gene polymorphisms in a different population, we explored associations between several genetic polymorphisms and lymphoma risk within a case-control study conducted in Australia. Genes and single-nucleotide polymorphisms (SNP) were selected based on experimental evidence of functional relevance and findings from previous association studies of lymphoma, related malignancies, and other tumor sites. These genes are involved in several DNA repair pathways, including direct repair (*MGMT*), base excision repair (*XRCC1, OGG1, PARP4*), nucleotide excision repair (*ERCC1, ERCC2, ERCC5*), double strand break repair (*BRCA1, BRCA2, LIG4, WRN, XRCC3, RAG1*), and mismatch repair (*MSH2*).

Design and Methods

Study subjects and data collection

The study methods have been described elsewhere in detail.[5] In brief, patients notified to the New South Wales (NSW) Central Cancer Registry with newly diagnosed NHL between 1 January 2000 and 31 August 2001 who were 20-74 years of age and resident in NSW or the Australian Capital Territory (ACT) were potentially eligible to be cases in this case-control study. Patients who had a history of transplantation or human immunodeficiency virus (HIV) infection were excluded. Pathology reports and slides for consenting cases were reviewed retrospectively by an anatomical pathologist to assess confidence in the diagnosis of NHL and to assign a cell phenotype and code of the World Health Organization International Classification of Diseases for Oncology, 3rd edition.[6]

Table 1. Genes and single nucleotide polymorphisms examined in this analysis.

Gene	*SNPs*
Direct reversal of damage	
MGMT	Ex2 -25 C>T (rs12917) Leu84Phe
	Ex4 +13 A>G (rs2308321) Ile143Val
	Ex4 +119 A>G (rs2308327) Lys178Arg
Base excision repair	
XRCC1	Ex9 +16 G>A (rs25489) Arg280His
	Ex6 -22 C>T (rs1799782) Arg194Trp
OGG1	Ex6 -315 C>G (rs1052133) Ser326Cys
PARP4	Ex31 +172 G>C (rs13428) Gly1280Arg
Nucleotide excision repair	
ERCC1	IVS5 +33 A>C (rs3212961)
ERCC2	Ex10 -16 C>T (rs1799793) Asp312Asn
	Ex23 +61 A>C (rs13181) Lys751Gln
ERCC5	Ex15 -344 G>C (rs17655) Asp1104His
Double strand break repair	
BRCA1	Ex12 -984 A>G (rs16941) Glu997Gly
	Ex17 -150 A>G (rs1799966) Ser1572Gly
	Ex17 -31 G>A (rs1799967) Met1611Ile
BRCA2	Ex10 +72 A>C (rs766173) Asn289His
	Ex10 +321 A>C (rs144848) Asn372His
LIG4	Ex2 +54 C>T (rs1805388) Thr9Ile
WRN	Ex4 -16 G>A (rs2230009) Val114Ile
	Ex34 -93 T>C (rs1346044) Cys1367Arg
XRCC3	Ex8 -53 C>T (rs861539) Thr241Met
RAG1	Ex2 +2473 A>G (rs2227973) Lys820Arg
Mismatch repair	
MSH2	Ex6 +23 G>A (rs4987188) Gly322Asp

Controls were randomly selected from the NSW and ACT electoral rolls to match approximately the expected distributions of cases with respect to age, sex and residence (NSW or ACT). A telephone interview of up to 60-min duration was conducted. The interviewers were blinded to the case or control status of subjects.

Of all eligible and participating subjects (687 cases and 694 controls), 597 cases and 525 controls provided blood, and genomic DNA was extracted successfully from 584 cases and 518 controls. Among them, there were 564 B-cell lymphomas, which include 189 diffuse large B-cell lymphomas (DLBCL), 216 follicular lymphomas (FL), 19 small cell lymphocytic lymphomas/chronic lymphocytic leukemias, and 57 marginal zone (MZ) lymphomas (including 33 MALT), and 17 T-cell lymphomas.

Genotyping

The selected genes and SNP are listed in Table 1. DNA was extracted and genotyped by TaqMan-based real-time polymerase chain reaction (PCR) at the Core Genotyping Facility of the NCI as described on the SNP500 website (http://snp500cancer.nci.nih.gov). More than 95% of the DNA samples were successfully genotyped for all selected SNP. Quality control samples (95 study subjects) for all SNP showed concordance rates of 100% except for *WRN* Val114Ile (98%).

Statistical analysis

The analysis included only people of European or Asian ethnicity (561 cases, 506 controls; 97% of study subjects). Genotype data were analyzed with the homozygotes of the common allele as the reference group. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusting for age, sex, residence, and ethnicity. We also conducted analyses stratified by histology. A test of association assuming an additive model was also conducted by including the number of rare alleles (0, 1, 2) as a continuous variable in the logistic regression model. To control for multiple hypothesis testing, we assessed the robustness of our additive-model SNP findings by using the false discovery rate (FDR) method. The FDR is defined as the expected ratio of false positive findings to the total number of significant findings.[7] Although there is no strict agreement on what value the FDR test should have in order to afford strong protection against an observation being a false discovery, a value of 0.15 or even 0.20 is considered reasonable. Haplotype block structure was examined and individual haplotypes were estimated. Overall differences in the frequency distribution of haplotypes between cases and controls (omnibus test) and associations with specific haplotypes were tested in Europeans only. Data were analyzed using the Statistical Analysis Software 9.1.3 (SAS Institute Inc, 1996).

A meta-analysis was carried out to summarize our findings on *MGMT* with those of two other studies.[3,4] A random-effects model in STATA was applied to estimate summary OR and 95% CI by weighting each study result by a factor of within- and between-study variance.[8] Homogeneity of study results in different groups was assessed by the Q test.

Results

Characteristics of the study population

Cases and controls had a similar distribution by age, sex, and ethnicity. Most participants were of British/Irish ethnicity (76% of cases and 83% of controls) and any other single ethnic group (Western/Northern European, Southern European, and Asian) accounted for less than 5% of the study group.

The distribution of all genotypes in controls was consistent with the Hardy-Weinberg equilibrium in Europeans with the exception of *PARP4* Ex31 +172 G>C (p=0.02), but the concordance rate of quality control samples for this SNP was 100%. The allele frequencies in controls were similar to those in other studies conducted among Caucasians.[3,4]

Comparison of genotypes

Genotype frequencies between cases and controls were comparable for all SNP in the genes except variants in *MGMT* and *XRCC1* (Table 2 and Onlne Supplementary Table). Two SNP in *MGMT* (Ile143Val and Lys178Arg) were in linkage disequilibrium (R^2=1) and associated with a 2.5-fold increased risk of NHL in homozygous variant carriers and a statistically significant linear trend (Table 2). Furthermore, there was evidence of this association for several subtypes including DLBCL and FL (Table 2) and MZ lymphomas (Ile143Val, Ile/Val or Val/Val vs. Ile/Ile, OR: 1.51; 95% CI: 0.76-3.03; p trend: 0.08), MALT (a subgroup of MZ lymphoma) (Ile143Val, Ile/Val or Val/Val vs. Ile/Ile, OR: 1.92; 95% CI: 0.82-4.48; p trend: 0.021), and T-cell lymphomas (Ile143Val, Ile/Val or Val/Val vs. Ile/Ile, OR: 2.22; 95% CI: 0.80-6.20; p trend: 0.071), although they were not statistically significant in most instances. The FDR value of the *MGMT* Ile143Val polymorphism was 0.31, which means there is a probability of 0.31 that this significant finding is a false positive finding.

The *XRCC1* Arg194Trp polymorphism was associated with a reduced risk of NHL (OR for CT/TT vs. CC: 0.70; 95% CI: 0.48-1.03; p trend: 0.059) and the major B-cell subtype DLBCL (OR for CT/TT vs. CC: 0.50; 95% CI: 0.27-0.93; p trend: 0.028). Haplotype analyses of SNP in linkage disequilibrium within each gene were not informative beyond the results obtained from the analysis of individual SNP.

Discussion

In our study, we found SNP in *MGMT* to be positively associated with NHL risk. A larger population-based case-control study carried out in Los Angeles, Seattle, Detroit and Iowa observed a non-significant positive association between the *MGMT* Ile143Val polymorphism and NHL but a significant positive association with the FL subtype.[4] A study of NHL among women in Connecticut did not find evidence of this association.[3] We carried out a meta-analysis of data from these two studies and the current report, and found an overall positive association (Ile143Val, Ile/Val vs. Ile/Ile, OR: 1.30; 95% CI: 1.03-1.64; Val/Val vs. Ile/Ile, OR: 1.65; 95% CI: 0.72-3.76) with FL (573 FL cases and 1959 controls) without evidence of heterogeneity among the studies. This association was not evident for DLBCL (667 cases, *data not shown*), the only other lymphoma subtype for which all three studies reported results. This suggests that genetic variation in *MGMT* is associated with at least one subtype of NHL. Given the relatively high FDR value for this finding in our data, our results should be examined in larger studies and in pooled analyses with larger sample sizes. According to a data simulation based on the parameters and distribution of covariates observed in this study, a two- or three-fold increase in the number of cases and controls would be required to produce a highly statistically significant OR. For example, the p-values for the additive-model OR for MGMT Ile143val would be 1×10^{-4} for a two-fold increase in sample size and 7×10^{-6} for a three-

Table 2. Logistic regression analysis for *MGMT* and *XRCC1* on the risk of NHL.

Single nucleotide polymorphism	*Controls*	*NHL*				*DLBCL*				*Follicular lymphoma*			
		Cases	*OR a*	*95% CI*	*p*	*Cases*	*OR a*	*95% CI*	*p*	*Cases*	*OR a*	*95% CI*	*p*
MGMT													
Ex2 -25 C>T (rs12917)													
Leu84Phe													
CC	373	432	Ref.			136	Ref.			159	Ref.		
CT	110	112	0.88	0.65-1.18	0.38	40	1.02	0.67-1.55	0.91	45	0.92	0.61-1.37	0.67
TT	12	11	0.75	0.32-1.73	0.50	1				7	1.24	0.47-3.27	0.66
CT+TT	122	123	0.86	0.65-1.15	0.32	41	0.94	0.63-1.42	0.78	52	0.95	0.65-1.39	0.79
Trend			0.87	0.68-1.12	0.29		0.88	0.61-1.27	0.49		0.99	0.71-1.37	0.94
Ex4 +13 A>G (rs2308321)													
Ile143Val													
AA	367	388	Ref.			125	Ref.			146	Ref.		
AG	104	130	1.26	0.93-1.70	0.13	43	1.30	0.86-1.98	0.21	51	1.32	0.89-1.97	0.17
GG	6	16	2.55	0.98-6.63	0.055	6	2.63	0.81-8.52	0.11	4	1.64	0.44-6.08	0.46
AG + GG	110	146	1.33	1.00-1.78	0.053	49	1.38	0.93-2.07	0.11	55	1.34	0.91-1.97	0.14
Trend			1.34	1.04-1.74	0.024		1.40	0.98-1.99	0.064		1.31	0.93-1.86	0.13
Ex4 +119 A>G (rs2308327)													
Lys178Arg													
AA	384	398	Ref.			125	Ref.			151	Ref.		
AG	108	131	1.24	0.92-1.67	0.15	44	1.35	0.89-2.04	0.15	49	1.21	0.82-1.80	0.33
GG	6	16	2.56	0.98-6.66	0.054	5	2.21	0.64-7.62	0.21	4	1.62	0.44-5.99	0.47
AG+GG	114	147	1.31	0.99-1.75	0.062	49	1.40	0.94-2.09	0.10	53	1.24	0.84-1.82	0.28
Trend			1.33	1.03-1.72	0.028		1.39	0.97-1.98	0.072		1.23	0.87-1.74	0.25
Haplotype of *MGMT*[b]													
Leu84Phe-Ile143Val-Lys178Arg													
C-A-A	741	792	Ref.			250	Ref.			294	Ref.		
C-G-G	122	164	1.29	1.00-1.67	0.049	55	1.44	0.98-2.11	0.065	59	1.40	0.96-2.05	0.078
T-A-A	130	125	0.90	0.69-1.18	0.45	40	0.98	0.64-1.49	0.916	56	1.07	0.72-1.59	0.733
T-G-G	1	5				1				1			
Omnibus test					0.19				0.17				0.37
XRCC1													
Ex6 -22 C>T (rs1799782)													
Arg194Trp													
CC	430	498	Ref.			163	Ref.			189	Ref.		
CT	62	55	0.72	0.49-1.07	0.11	14	0.52	0.28-0.97	0.042	21	0.70	0.41-1.21	0.20
TT	5	3	0.45	0.10-1.99	0.30	1				1			
CT+TT	67	58	0.70	0.48-1.03	0.072	15	0.50	0.27-0.93	0.029	22	0.68	0.40-1.15	0.15
Trend			0.71	0.50-1.01	0.059		0.53	0.30-0.94	0.028		0.68	0.42-1.11	0.12
Ex9 +16 G>A (rs25489)													
Arg280His													
GG	450	490	Ref.			157	Ref.			190	Ref.		
GA	48	62	1.13	0.75-1.69	0.56	22	1.27	0.73-2.20	0.40	18	0.85	0.48-1.53	0.60
AA		1								1			
GA+AA	48	63	1.14	0.76-1.70	0.52	22				19	0.89	0.50-1.58	0.70
Trend			1.15	0.77-1.72	0.48						0.94	0.54-1.64	0.83

[a]*Adjusted for age, sex, residence and ethnicity.* [b]*Haplotype analysis in Europeans only, adjusted for age, sex, residence and ethnicity.*

fold increase, which suggest true positive findings.[9]

In this study, we did not find associations with NHL risk for several SNP found to be noteworthy in two other studies (e.g., *RAG1* Lys820Arg, *LIG4* Thr9Ile, *ERCC5* Asp1104His, and *WRN* Cys1367Arg).[3,4] A meta-analysis for these SNP using data from all three studies (in total 2,229 cases and 2,059 controls) provided evidence that the *LIG4* Thr9Ile was statistically significantly associated with NHL (Thr/Ile vs. Thr/Thr: OR: 0.98; 95% CI: 0.84-1.13; Ile/Ile vs. Thr/Thr, OR: 0.63; 95% CI: 0.43-0.93) without significant heterogeneity between the studies (p=0.64 for heterozygotes, p=0.41 for homozygotes). The meta-analysis of the other SNP did not find any additional statistically significant associations.

MGMT encodes the DNA repair protein O^6-methylguanine-DNA-methyltransferase (MGMT). This protein is unique among DNA repair proteins because it acts alone to remove alkyl DNA adducts at the O^6 position of guanine and, to a lesser extent, at O^4 of thymine to prevent G to A transitions, leaving a normal guanine or thymine behind.[10] Apart from repairing DNA, *MGMT* also interacts with a variety of proteins and may function

to link DNA damage and repair signals and ultimately maintain genomic stability.[11] Overexpression of *MGMT* prevents lymphomagenesis in mouse models.[10] The *MGMT* sequence and MGMT function are remarkably conserved through evolution and have several functional domains.[12] There is wide inter-individual variation of *MGMT* expression and this is partly influenced by the 143Val and the 178Arg polymorphisms.[13] The amino acid residue 143 is two residues from the conserved active site of alkyl group acceptor Cys 145. Hill *et al.* reported that the variant 143Val allele was associated with higher levels of nitrosamine-induced chromosome aberration.[14] This SNP was suggested to be a risk factor for lung cancer,[15] however, it was associated with reduced risk of colorectal in women[16] and head and neck cancer.[17] In our study, the two linked SNP had comparable effects as expected, and one haplotype of *MGMT* was associated with NHL risk, implying that the C-terminal domains are important.

MGMT protects against chromosome aberrations. A deficiency in MGMT leads to chromosomal instability induced by alkylating mutagens.[18] MGMT also prevents alkylation-induced mutations, sister chromatid exchanges, and chromosomal aberrations.[19] Some studies suggest that medical alkylating agents may increase the risk of NHL.[20] In view of the low exposure prevalence of medical alkylating agents in the general population, our results suggest the possibility that environmental and endogenous alkylating agents may increase the risk of NHL, e.g., N-nitroso compounds, chloromethane, and S-adenosylmethionine.[21] It may be worthwhile developing a composite exposure matrix to assess exposure to all classes of alkylating agents and investigating the effect of environmental alkylating agents on NHL and their interactions with *MGMT* and other relevant genes to clarify the impact of DNA alkylation on NHL risk. Directly studying biomarkers of DNA alkylation in case-control and prospective studies of NHL would also be of value.

The *XRCC1* gene encodes for a protein that plays an important role in repairing oxidative DNA damage. We found that the 194Trp variant, a conservative amino acid substitution, was associated with a reduced risk of NHL. This allele has been shown to be associated with lower bleomycin and benzo(a)pyrene diol epoxide sensitivity,[22] and has been found to be associated with a decreased risk of tobacco-related cancers.[23] However, it was not associated with NHL risk in two case-control studies in the United States and one case-control study in Sweden and Denmark.[3, 4, 24]

In summary, our study encourages further study of *MGMT* and exposure to alkylating agents, which may have contributed to the rise in NHL incidence in the recent past. Our results should be viewed as preliminary due to the limited number of variant carriers, and need to be replicated in additional studies. In particular, studies extending these findings to include tag SNP across the entire gene might offer additional insight into the relevance of *MGMT* to lymphomagenesis.

Author's contributions

MS conducted the statistical analysis and was the main author of the manuscript. MP, QL and NR were responsible for selecting the SNP to be studied and co-ordinating the transfer of specimens and data. AK, AG, CV, JT and BKA designed and conducted the case-control study in Australia. DNA extraction and genotyping were performed in the laboratories of DW and SC, respectively. All authors contributed to the preparation of the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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