RESEARCH ARTICLE

A Polymorphism Located Near *PMAIP1/Noxa* Gene Influences Susceptibility to Hodgkin Lymphoma Development in South India

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Abstract

Background: Single nucleotide polymorphisms (SNPs) in DNA repair and Toll-like receptor (*TLR*) genes have been reported to be associated with Hodgkin Lymphoma (HL) risk. Since such associations may be ethnicity dependent, polymorphisms in *TLR4* rs1554973, Xeroderma pigmentosum C (*XPC*) rs2228000, rs2228001 and a variant near *PMAIP1/Noxa* gene rs8093763 were here investigated with regard to HL susceptibility in a south Indian population. Normative frequencies of SNPs were established and compared with data for 1000 genome populations. **Methods:** We conducted a case control study consisting of 200 healthy volunteers and 101 cases with HL. DNA samples were genotyped using real-time PCR. Linkage disequilibrium (LD) analysis between rs2228000 and rs2228001 was performed using HaploView (version 4.2). **Results:** Among the studied variants, we observed that a variant rs8093763 located near *PMAIP1/Noxa* gene was associated with HL risk (OR=1.72 and 95% CI=1.004-2.93). The major allele frequencies of *XPC* (rs2228000 and rs2228001), *TLR4* (rs1554973) and *PMAIP1/NOXA* (rs8093763) variants were 79%, 66%, 67% and 59% respectively. The studied frequencies were significantly different from 1000 genome populations. **Conclusion:** The results suggest that a variant rs8093763 located near the *PMAIP1/Noxa* gene may modify risk of HL. We found variation in distribution of polymorphic frequencies between the study population and 1000 genome populations. The results may help identify individual risk of development of HL in our south Indian population.

Keywords: Hodgkin lymphoma- polymorphisms- DNA Repair- *PMAIP1/Noxa- TLR4*

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Introduction

Hodgkin lymphoma (HL) is an uncommon B-cell derived lymphoma characterised by the presence of Hodgkin and Reed-Sternberg (HRS) cells that make up to 0.1 to 2% of total tumour mass (Küppers et al., 2012; Bräuninger et al., 2006). Based on its histopathology it is divided into four subgroups; i) mixed cellularity (MC), ii) nodular sclerosis (NS), iii) lymphocyte rich (LR) and iv) lymphocyte depleted (LD) (Eberle et al., 2009). HL incidence is more common in males than in females. The American Cancer Society predicted that in 2017, 8260 new cases would be diagnosed with HL among which 4,650 would be males and 3,610 would be females with about 1,070 (630 males and 440 females) deaths (Siegel et al., 2017). In India, it was predicted that 7,912 males and 4,185 females would be diagnosed with HL by 2020 (Takiar et al., 2010). HL shows incidence peaks in young adults between the ages of 20-25 and in old individuals after the age of 60 (D'Amelio et al., 2012). The exact aetiology of HL is unclear but genetic and environmental factors are thought to play a role in pathophysiology of the disease. Previous studies have shown that polymorphisms in DNA repair and Toll-like receptor (*TLR*) genes are the factors involved in susceptibility to HL (El-Zein et al., 2009; Monroy et al., 2011a; Monroy et al., 2011b; Kushekhar et al., 2014; Sud et al., 2017). It is observed that associations between genetic polymorphisms and cancer risk studied in one population cannot be reproduced in new ethnic populations due to variation in genetic and environmental factors among populations (Jing et al., 2014).

DNA repair pathways rectify the DNA damage caused by environmental exposures and metabolic activities thereby maintaining the structural integrity of a human genome (Köberle et al., 2016). There exists considerable inter-individual variability in the ability to repair DNA damage which can be attributed to polymorphisms in DNA repair genes *XPC* (xeroderma pigmentosum C) one of the key protein in NER (nucleotide-excision repair) pathway, is involved in correcting bulky DNA adducts

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and is reported to be repairing bleomycin -induced DNA damage (Laczmanska et al., 2007). Any mutation in coding region of *XPC* gene may lead to altered function of *XPC* protein thereby modifying DNA repair capacity (DRC) (Zhu et al., 2008). The two most common variants of *XPC* rs2228001 A > C and rs2228000 C > T have been found to be associated with bladder, lung, colorectal and breast cancer (He et al., 2013). Individuals with *XPC* rs2228001 A > C variant had higher DRC and individuals with rs2228000 C > T had reduced DRC. These polymorphisms were also found to increase the risk of HL (Monroy et al., 2011). Another DNA repair polymorphism rs8093763 located near *PMAIP1/Noxa* gene on chromosome 18q21 was found to be associated with increased mutagen sensitivity thereby reducing DNA repair capacity and increasing susceptibility to cancer (Gu et al., 2011).

Inflammation plays a critical role in cancer development. In HL many cytokines are released by HRS cells due to the abnormal immune response (Küppers et al., 2012; Bräuninger et al., 2006). Based on their function, cytokines are divided into anti- and pro-inflammatory, which mediates inflammation. A polymorphism in this pathway could influence the inflammatory response by uncontrolled production of cytokines that leads to the production of reactive oxygen species and DNA damage. Nuclear factor-κB (NFκB) is a transcriptional factor that controls cytokine production which is activated by *TLRs* (anti-inflammatory) (Zhang and Ghosh, 2001). In mouse model, *TLR 4* was found to promote bleomycin-induced lung fibrosis (Li et al., 2015). Genetic variants of *TLR4* have been found to be associated with prostate cancer and gastric cancer (Weng et al., 2014; El-Omar et al., 2008). Polymorphism in *TLR4* rs1554973 was reported to have a protective effect in HL (Monroy et al., 2011).

Hence, polymorphisms in *XPC* increased risk to HL while polymorphism in *TLR4* had protective effect in HL and the role of a variant located near *PMAIP1/Noxa* gene as a risk factor has never been studied. These polymorphisms were also found to increase sensitivity to bleomycin, as HL patients are treated with bleomycin, these SNPs could also alter their response and toxicity profile. In this preliminary study, we assessed if these polymorphisms were associated with the risk of HL in south Indian population.

As allelic and genotypic frequencies vary from population to population, it could affect the results of genotype-phenotype association studies. Therefore, it is imperative to establish these frequencies in normal healthy volunteers in the study population (Majumder, 2010). Therefore, this study aimed to establish the allelic and genotypic frequencies of *XPC* rs2228001 A > C and rs2228000 C > T, *PMAIP1/Noxa* rs8093763 A > G, and *TLR4* rs1554973 C > T polymorphisms in south Indian healthy population. The same was compared with the other 1000 genome populations.

Materials and Methods

A case-control study was started after obtaining JIPMER (Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India) institutional ethics committee approval (ECR/342/Inst/PY/2013). The written informed consent was obtained from the study participants, from the legally accepted guardian in case of child participants and also assent form was collected from children above age 7.

Patients and controls

Unrelated controls (200 healthy volunteers) were recruited with no family history of HL. Hundred and one patients diagnosed with HL at the Regional Cancer Centre (RCC), JIPMER were recruited during July 2015 to January 2017. All the study participants were of south Indian origin i.e., residing in one of the south Indian states for 3 consecutive generations and speaking one of the south Indian languages. Baseline characteristics such as age at diagnosis, gender, ethnicity, presence of B symptoms, histologic subtypes and Ann Arbor stage were obtained from the medical records.

Sample collection and processing

Five ml of venous blood was collected from all the participants (cases and controls) in tubes containing 100 µL of 10 % EDTA (ethylenediamine tetra-acetic acid). The samples were centrifuged at 2500rpm for 10 min and plasma was separated and the cells were stored at -20 °C until DNA isolation. Genomic DNA was isolated using phenol–chloroform method and was quantified using multi-analyser (Infinite 200; Tecan, Austria). DNA was diluted to 50 ng/µL concentration and was stored at 4 °C until genotyping.

Genotyping

Genotyping of *XPC* rs2228001 A > C and rs2228000 C > T, *PMAIP1/Noxa* rs8093763 A > G and *TLR4* rs1554973 C > T variants was performed by real-time PCR (AB7300; Applied Biosystems) using TaqMan SNP genotyping assay kits. To reconfirm, 10% of the samples were randomly selected and reanalysed. Linkage disequilibrium (LD) analysis between rs2228000 and rs2228001 was done using HaploView version 4.2.

Statistical analysis

Statistical analysis was done using GraphPad Instat version 3 (GraphPad Software Inc., San Diego, CA, USA). The control genotype frequency data was checked for Hardy-Weinberg equilibrium using chi-square test. Chi-square test was used to test for the differences in distribution of age, gender and genotype between cases and controls. The allelic and genotypic frequencies of south Indian population were compared with 1000 genome project data using chi-square test. Two sided P value <0.05 was considered statistically significant.

Results

A total of 101 HL patients and 200 age and gender matched controls were evaluated in this study. The demographic characteristics of cases and controls are summarized in table 1. The mean age of the cases was 27.8 ±18.5 years with 76.2% of the cases under the age 40 years and 23.8% above age 40 years. The mean age of the

Table 1. Demographic Characteristics of Cases and Controls

	Cases N (%)	Controls N (%)	P value
Subjects analysed	101(100)	200 (100)	
Age (mean ± SD) in years	27.8 (±18.5)	24.5 (±5.6)	0.99
Gender			
Males	69 (68.3)	114 (57)	
Females	32 (31.7)	86 (43)	0.08
B symptoms			
Yes	53 (52.5)		
No	48 (47.5)		
Ann Arbor stage			
I	24 (23.7)		
II	25 (24.8)		
III	35 (34.7)		
IV	17 (16.8)		
Histologic subtypes			
Mixed cellularity	49 (48.5)		
Nodular sclerosis	27 (26.7)		
Lymphocyte rich	10 (9.9)		
Lymphocyte depleted	3 (2.9)		
Lymphocyte predominant	12 (11.9)		

control was 24.5 ±5.6 years. There were 69 males and 32 females in case group whereas 114 males and 86 females in control group. There was no significant difference in demographic characteristics such as age, gender and ethnicity between cases and controls. Among the cases, 52.5% of the patients had B symptoms.

Association of genotypes with HL risk

Details of the SNPs with rs ID and chromosomal position are shown in table 2. All the genotype frequencies were found to be in consistent with Hardy-Weinberg equilibrium. The distribution of genotypic and allelic frequencies of the studied polymorphisms in cases and controls is presented in table 3. Statistically significant difference was observed in distribution of genotypic frequencies in *PMAIP1/Noxa* rs8093763 between cases and controls. Presence of GG genotype in rs8093763 was associated with 1.72 fold higher risk to HL (OR=1.72 and 95% CI=1.004 to 2.93) as compared to AG genotype. We did not find any significant difference in distribution of allelic and genotypic frequencies of *XPC* rs2228001, rs2228000, and *TLR4* rs1554973 variants between cases and controls. No significant difference was found in genotype frequencies based on gender, age at diagnosis, HL stage and B symptoms presence among cases.

Comparison of allelic and genotypic frequencies of studied polymorphisms with 1000 genome populations

The allele and genotype frequencies of SNP TLR rs1554973 were significantly different from 1000 genome population except for South Asian (SAS) population. The frequency distribution of variant *XPC* rs2228000 was similar to American (AMR) and SAS population. Genotype frequency of *XPC* rs2228001 was similar to all population except African (AFR) whereas allele frequency was significantly different from those observed in Europeans (EUR) and AFR. In case of *NOXA*-rs8093763 allele and genotype frequencies were significantly different from AMR, EUR and East Asian (EAS) populations while similar to AFR and SAS (Table 4).

Linkage disequilibrium

There was no linkage disequilibrium (D' value = 0.52) observed between rs2228000 and rs2228001 on chromosome 3 therefore, haplotype analysis was not done.

Discussion

This study established the normative frequencies of four polymorphisms in *XPC* (rs2228000 and rs2228001), *TLR4* (rs1554973) and *NOXA* (rs8093763) in south Indian population. We also report for the first time that the variant rs8093763 located near *PMAIP1/Noxa* gene is associated with HL risk whereas other studied polymorphisms did not alter the risk to HL in south Indian population.

About 49% of the cases were of histological subtype mixed cellularity and 51% of the cases were at advanced stage (III or IV). About 53% patients reported to have B symptoms. Nodular sclerosis is the most common type of HL in western world that accounts for 60-70% of the cases. Nodular sclerosis shows female predominance in incidence and 40% of the patients experience B symptoms. Mixed cellularity accounts for 10-20% of the cases, is more common in males and B symptoms are frequently seen (Eberle et al., 2009). In the present study however, mixed cellularity subtype was more prevalent that could explain the higher incidence of males and presence of B symptoms in the study. This shows that south Indian HL patients are histopathologically different from western world.

Previous studies have shown that SNPs in DNA repair genes alter the risk to many cancers (Grundy et al., 2016; Li et al., 2016; Farnebo et al., 2015). T allele frequency of *XPC* rs2228000 C > T was 21% in cases and controls in the studied population. In a study conducted in American

Table 2. List of SNPs with rs ID and Chromosome Location

GENE	Amino acid change	rs ID	Base pair change	SNP location	Chromosome
XPC	Ala499Val	rs2228000	C/T	Ex9−377C>T	3
XPC	Lys 939Gln	rs2228001	A/C	Ex16+211C>A	3
TLR4	Thr399Ile	rs1554973	C/T	3885 bp 30 of STPC>T	9
NOXA	-	rs8093763	A/G	64 kb apart from *PMAIP1/Noxa*	18

Table 3. Genotypic and Allelic Frequencies of Cases and Controls and Association with Risk of HL

SNP Allele/ Genotype	Patients with HL n(%) N=101	Healthy volunteers n(%) N=200	OR (95%CI)	p-value
TLR rs1554973 C>T				
TT	43 (42.6)	89 (44.5)		
CT	43 (42.6)	90 (45)	1.01 (0.60 to 1.69)	NS
CC	15 (14.8)	21 (10.5)	0.68 (0.31 to 1.44)	NS
TT vs CT+CC	43 (42.6) vs 58 (57.4)	89 (44.5) vs 111(55.5)	0.92 (0.57 to 1.49)	NS
Alleles				
T	129(64)	268 (67)		
C	73 (36)	132 (33)	0.87 (0.61 to 1.24)	NS
XPC- rs2228000 C>T				
CC	62 (61.4)	122 (61)		
CT	35 (34.6)	74 (37)	1.07 (0.64 to 1.78)	NS
TT	4 (4)	4 (2)	0.51 (0.12 to 2.10)	NS
CC vs CT+TT	62 (61.4) vs 39 (38.6)	122 (61) vs 78 (39)	1.01 (0.62 to 1.66)	NS
Alleles				
C	159 (79)	318 (79)		
T	43 (21)	82 (21)	0.95 (0.62 to 1.44)	NS
XPC- rs2228001 A>C				
AA	48 (47.5)	85 (42.5)		
CA	41 (46.6)	94 (47)	1.29 (0.77 to 2.15)	NS
CC	12 (11.9)	21 (10.5)	0.99 (0.44 to 2.18)	NS
AA vs CA+CC	48 (47.5) vs 53	85 (42.5) 115	1.22 (0.75 to 1.98)	NS
Alleles				
A	137 (68)	264 (66)		
C	65 (32)	136 (34)	1.08 (0.75 to 1.55)	NS
NOXA-rs8093763 A>G				
GG	47 (46.5)	72 (36)		
AG	35 (34.7)	92 (46)	1.72 (1.004 to 2.93)	0.047
AA	19 (18.8)	36 (18)	1.24 (0.63 to 2.40)	NS
GG vs AG+AA	47 (46.5) vs 54(53.5)	72(36) vs 128(64)	1.54 (0.95 to 2.51)	NS
Alleles				
G	129 (64)	236 (59)		
A	73 (36)	164 (41)	1.23 (0.86 to 1.74)	NS

OR, odds ratio; CI, confidence interval; NS, not significant

population by Monroy et al., (2011) they observed that heterozygote CT genotype of *XPC* rs2228000 C > T was associated with an increased HL risk (OR=1.77 and CI= 1.17–2.68). In this study, we found that polymorphism in DNA repair gene *XPC* rs2228000 was not associated with HL risk. This contradiction could be due to inter-individual variability in DNA repair capacity and variation in distribution of polymorphic frequencies within populations. The frequency of CT genotype was 47% and 33% in cases and controls respectively in Monroy et al., (2011) study. In our study frequency of CT genotype was 34.6 % and 37% in cases and controls. Hence, the frequency distribution in controls was similar to that of Monroy et al., (2011) study, but there was significant difference in genotype frequencies of cases that explains the contradictory results. The C allele frequency of *XPC* rs2228001 A > C was 32% and 34% in cases and controls respectively. Two other studies conducted by Monroy et al., (2011) and El-Zein et al., (2009) reported that *XPC* rs2228001 was not associated with an increased HL risk which is consistent with our finding. We also observed that haplotypes of SNPs rs2228000 and rs2228001 on *XPC* gene on chromosome 3 were not in linkage disequilibrium (D' value = 0.52) and did not alter the risk to HL. In contrast, D'Amelio et al., (2012) reported that haplotype CT rs2228000 and rs2228001, was associated with HL susceptibility.

The incidence of CC, CT and TT genotypes was 61%, 37% and 2% respectively in variant *XPC* rs2228000 which was significantly different from the north Indian population (34%, 43%, and 23%) (Sankhwar et al., 2016) with TT genotype frequency being lower in south Indian population. We found that TT genotype frequency was similar in AMR and SAS population. AFR had the

Table 4. Comparison of Allelic and Genotypic Frequencies with 1,000 Genome Populations

SNP Allele/ Genotype	South Indian N=200	AFR N=661	AMR N=347	EAS N=504	EUR N=503	SAS N=489
TLR rs1554973 C>T						
TT	44.5	4.5	65.4	74.0	58.4	49.1
CT	45.0	32.1	31.1	24.0	36.2	41.5
CC	10.5	63.4*	3.5*	2*.0	5.4*	9.4
Alleles						
T	67.0	20.6	81.0	86.0	76.5	69.8
C	33.0	79.4*	19*.0	14*.0	23.5*	30.2
XPC- rs2228000 C>T						
CC	61.0	81.8	56.5	36.5	55.1	63.4
CT	37.0	17.7	38.0	44.4	38.2	32.7
TT	2.0	0.5*	5.5	19*	6.8*	3.9
Alleles						
C	79.0	90.7	75.5	58.7	74.2	79.8
T	21.0	9.3*	24.5	41.3*	25.8*	20.2
XPC- rs2228001 A>C						
AA	42.5	56.1	50.4	45.4	35.8	45
CA	47.0	38.0	42.7	42.5	47.5	46.4
CC	10.5	5.9*	6.9	12.1	16.7	8.6
Alleles						
T	66.0	75.1	71.8	66.7	59.5	68.2
G	34.0	24.9*	21.2	33.3	40.5*	31.8
NOXA-rs8093763 A>G						
GG	36.0	37.0	66.0	57.0	55.0	38.0
AG	46.0	45.0	32.0	37.0	37.0	46.0
AA	18.0	18.0	2*.0	6*.0	8*.0	16.0
Alleles						
G	59.0	60.0	82.0	75.0	74.0	61.0
A	41.0	40.0	18*.0	25*.0	26*.0	39.0

N, total number of participants in each group is given in bold and the percentages of genotype frequencies are presented; AFR, African; AMR, American; EAS, East Asian; EUR, European; SAS, South Asian; *, Two sided P value < 0.05

lowest TT genotype frequency and it was highest in EAS. Genotype frequency of AA, CA and CC in *XPC* rs2228001 was 42%, 47% and 11% respectively which was similar to north Indian population (51%, 42% and 7%) (Mandal et al., 2010) and was also similar to other populations except AFR.

This is the first study to have assessed the role of genetic variant rs8093763 located near *PMAIP1/Noxa* gene on HL susceptibility. The frequency of homozygous mutant genotype GG was 47% in cases and 36% in controls. Homozygous mutant genotype GG of the gene seemed to increase the risk of HL by 1.72 fold (OR=1.72 and 95% CI=1.004 to 2.93). However, studies with larger sample size are required to validate this finding. Previous study has reported that rs8093763 is associated with increased bleomycin sensitivity and decreased DNA repair capacity which is a well-known risk factor for many cancers (Gu et al., 2011). A possible mechanism of our finding could be that mutant GG genotype of variant rs8093763 reduces DNA repair capacity and thereby increases risk to HL. Allele frequency of rs8093763 variant was comparable to AFR and SAS and AA genotype frequency was found to be lower in AMR, EAS and EUR. Frequency of GG genotype was highest in AMR.

Bleomycin is used as a mutagen to measure the DNA repair capacity of the gene. Variant *XPC* rs2228000 and *PMAIP1/Noxa* rs8093763 were found to increase bleomycin-induced chromosomal aberrations. This, in turn, can increase individual's risk to develop various cancers (Laczmanska et al., 2007; Gu et al., 2011). These DNA repair genes can also alter the treatment response in HL patients as they are treated with genotoxic agents such as bleomycin and dacarbazine (Kyrtopoulos, 1995).

Polymorphisms in Toll-like receptor genes have been extensively investigated for their association with various cancers (Weng et al., 2014; Pimentel-Nunes et al., 2013). Here we have established the normative frequency of *TLR4* rs1554973 variant in south Indian population. The minor allele frequency of *TLR4* rs1554973 was 36% and 33% in cases and control in study population. In a study by Monroy et al, (2011) it was reported that genotypes CT and TT of *TLR4* rs1554973 had protective

effects thereby reducing the risk to HL (OR= 0.43 and CI=0.25–0.75). However, we did not find any significant difference. The frequency of TT, CT and CC genotypes of *TLR4* rs1554973 was 44%, 45% and 11% respectively. We observed that genotype frequency of *TLR4* rs1554973 deviates from north Indian population (82.4%, 17.2 and 0.4%) (Najmi et al., 2010) and other 1000 genome populations except SAS.

Limitations of this study are, we did not examine the role of other DNA repair and TLR gene polymorphisms (XRCC1 rs1799782 and rs25487; *TLR4* rs4986790, TLR7 rs179008, TLR9 rs5743836 and rs352140) which have shown association with HL in previous studies (Monroy et al., 2011; Nieters et al., 2006; Monroy et al., 2011; Mollaki et al., 2009). We could not analyse the association of the studied polymorphisms with histological subtypes of HL due to insufficient sample size.

In conclusion, we have established the normative frequencies of *XPC*, *TLR* and *NOXA* gene polymorphisms in south Indian population. There was a significant difference in the distribution of concerned polymorphic frequencies between the study population and 1000 genome populations. We found that a genetic variant rs8093763 located near *PMAIP1/Noxa* gene was associated with HL risk in south Indian population although we did not find any significant association with *XPC* and *TLR4* gene polymorphisms. Studies with larger sample size are needed to validate this finding. The study results can be used to identify the individual's risk to develop HL and further to investigate the role of studied polymorphisms in treatment response in HL patients of south Indian origin.

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