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Association of Interleukin-13 and Toll-like Receptor-2 Polymorphisms with Lymphoma Susceptibility: A Case-Control Study from Islamabad Pakistan

Bibi Khadija[1], Rani Faryal[2]

[1]National Skills University, Islamabad, Pakistan .
[2]Quaid-i-Azam University, Islamabad, Pakistan.

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Corresponding author: Bibi Khadija
bibi.khadija@nsu.edu.pk

ABSTRACT

Background: Interleukin-13 (IL-13) is a T helper 2 (Th2) cytokine commonly associated with allergic disorders. Toll-like Receptor-2 (TLR-2) provides first line of defense against pathogens. IL-13 and TLR-2 are known to play roles in tumorigenesis and progression.
Objectives: To investigate clinicopathological features of lymphomas and find the association of IL-13 2044G/A and TLR-2 Arg677Trp polymorphisms with lymphoma susceptibility.
Methods: Total 85 lymphoma patients from Nuclear Medicine Oncology and Radiotherapy Institute (NORI) Islamabad, and 90 controls were included in the study. Restriction fragment length polymorphism (RFLP) for the IL-13 gene after polymerase chain reaction (PCR), whereas Tetra-primer amplification refractory mutation system (Tetra-ARMS) PCR for TLR-2 gene were performed on purified DNA extracted from blood.
Results: Out of 85 lymphoma patients, 70.58% of cases were of non-Hodgkin lymphoma (NHL) and 29.42% of Hodgkin lymphoma (HL) type. Among NHL, diffuse large B cell lymphoma (DLBCL) was the prevalent subtype (80%), while Mix cellularity (MC) was the most prevailing HL type (88%). Genotype analysis of IL-13 2044G/A polymorphism demonstrated no association with lymphoma [χ^2=2.86, *P*-value=0.23] as well as in the DLBCL group [χ^2=3.141, *P*-value=0.201]. However, the analysis of allelic frequencies in DLBCL patients regarding IL-13 2044G/A polymorphism showed a significant association of A allele [χ^2=4.6, p-value=0.03]. Similarly, no association of TLR-2 Arg677Trp polymorphism was found in lymphoma patients [χ^2=0.51, *P*-value=0.43] and in DLBCL patients [χ^2=0.02, *P*-value=0.87].
Conclusion: IL-13 and TLR-2 polymorphisms were not associated with lymphoma susceptibility. However, IL-13 polymorphism showed a one-fold risk for lymphoma.

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Introduction

Lymphomas, comprising of Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), and its subtypes, are a group of lymphoid neoplasms [1], originating in lymphocytes and comprising of B cell lineage, T cell lineage, and natural killer cell lineage [2]. NHL makes up about 90% of all cases of malignant lymphomas. The incidence of NHL is high in developed countries, while

the lowest rate is found in Asia [3]. Diffuse large B cell lymphoma (DLBCL) is the common subgroup of NHL, representing almost one-third of all NHL worldwide. HL is identified by the presence of special cells called Reed-Stenberg (RS) cells, which are B-cells multinucleated giant cells. HL does not occur commonly in Asians [4]. HL accounts for 30% of cases of all lymphoid cancers found worldwide [5].

Interleukin-13 (IL-13) is a T helper 2 (Th2) cytokine [6]. IL-13 gene is present on chromosomal location 5q31, which is a region commonly associated with allergic disorders [7][8][9]. However, IL-13 receptors are also expressed in tumor cells and exist in two different forms [6]. In lymphomas, RS cells of classical HL produce several cytokines, including IL-13 and IL-13R α 1 [10], which are thought to be responsible for this disease's clinical and pathological characteristics [11]. Toll-like Receptor-2 (TLR-2) provides the first line of defense against harmful pathogens. It is also reported that wide varieties of tumor cells have TLR expressions, suggesting their roles in tumorigenesis and tumor progression [12][13].

Polymorphisms in various parts of the IL-13 and TLR-2 genes have been identified. IL-13 2044G/A polymorphism is one of the most common polymorphisms found in the IL-13 gene. It is located in exon 4 at position 2044, which is caused by an amino acid change of arginine in place of glutamine at codon 130 [7]. TLR-2 Arg677Trp is due to single nucleotide polymorphism (SNP) found in the start codon of TLR-2 in exon 3, which causes a C/T substitution at nucleotide 2029 [14]. The present study was carried out in the local Pakistani population to investigate demographic and clinicopathological features of lymphoma and to detect SNPs in IL-13 (2044G/A [R130Q]) and TLR-2 (Arg677Trp [C2029T]) gene in lymphoma patients to assess their association with lymphomas. Until now, no such data is available which shows the association of these polymorphisms with lymphomas.

Methods

Sample Collection: In the present case-control study, blood samples were collected from 85 lymphoma patients, representing 34 females and 51 males, at Nuclear Medicine Oncology and Radiotherapy Institute (NORI) Islamabad, from January 2016 to October 2017. Of these 48 were of the DLBCL subtype comprising 30 males and 18 females. Samples of 90 healthy individuals (51 females and 39 males) were collected from the general population as a control. Both patient and control samples were analyzed in the Molecular Biology Laboratory at the Department of Microbiology, Quaid-i-Azam University (QAU) Islamabad. The patients' history was recorded using an in-person interview method through a structured questionnaire.

Inclusion and Exclusion Criteria: All the patients suffering from lymphoma were included in the present study, while patients suffering from other myelo-proliferative disorders, allergies, metabolic disorders, and cardiovascular diseases were excluded from the present study.

Genotyping of IL-13 and TLR-2: After DNA extraction from the blood by the phenol-chloroform method, samples were genotyped for polymorphisms through polymerase chain reaction (PCR) using designated primers. For IL-13 2044 G/A polymorphism forward primer 5'CTTCCGTGAGGACTGAATGAGACGGTC3' and reverse primer 5'GCAAATAATGATGCTTTCGAAGTTTCAGTGGA3' were used. Restriction fragment length polymorphism (RFLP) with restriction enzyme *Nla* IV (Thermo scientific) was carried out after PCR amplification. PCR reaction mixture of 20 µL was used containing 2µL DNA, 2µL 10X Taq-Buffer $(NH_4)_2$ SO_4 (Thermo scientific), 2µL 25mM $MgCl_2$ (Thermo scientific), 0.3 µL each primer (e-Oligos), 0.2µL Taq polymerase (Thermo scientific), 0.2µL deoxyribonucleotides (Thermo scientific) and 12.8µL PCR water. Thermocycler conditions included: denaturation at 95 ºC for 5 minutes, annealing at 59.6 ºC for 2 minutes, extension at 72 ºC for 45 seconds (35 cycles), and final extension at 72 ºC for 10 minutes. PCR amplified product size was 235bp. RFLP of IL-13 PCR products was carried out using 0.5 µL enzyme, 1µL Tango buffer, 7 µL PCR products, 9 µL PCR water and incubated for overnight at 37 ºC. After RFLP, a 178/26/32bp bands for GG, 210bp/26bp bands for AA, and bands of 178bp/

210bp/ 28bp/ 32bp for GA genotype were visualized on 3% agarose gel. For TLR-2 Arg677Trp polymorphism Tetra-primer amplification refractory mutation system (Tetra-ARMS) PCR was used. In this method, two inner primers called allele specific primers forward inner 5'CCCTTCAAGTTGTGTCTTCAACGT3' and reverse inner primer 5'TTGCCAGGAATGAAGTCACG3' and two outer primers forward outer primer 5'CTGTGCTCTGTTCCTGCTGATC3 and reverse outer primer 5'TGAGAATGCAGCATCATTGTT3' were used. PCR reaction mixture of 15µL was used, consisting of 2µL DNA, 2µL 10X Taq-Buffer $(NH_4)_2SO_4$ (Thermo scientific), 2µL 25mM $MgCl_2$ (Thermo scientific), 0.3 µL each primer (e-Oligos), 0.2µL Taq polymerase (Thermo scientific), 0.2µL dNTPs (Thermo scientific) and 7.2µL PCR water. Thermocycler conditions were denaturation at 95 ºC for 5 minutes, annealing at 56.4 ºC for 45 seconds (40 cycles), extension at 72 ºC for 45 seconds, with a final extension at 72 ºC for 10 minutes. PCR amplified product size was 419bp and 264bp band for CC genotype, 419bp, 264bp, and 199bp band for CT genotype, 419bp and 199bp for TT.

Statistical Analysis: Using IBM SPSS version 25, $\chi 2$ contingency table analysis was used for genotype and allelic frequencies and to determine the association of polymorphisms with lymphoma and DLBCL. Odds ratios with 95% confidence intervals were calculated to assess the degree of association. Statistical significance was defined as $p<0.05$.

Results

Mean age of lymphoma patients was 42.21±16.85 years, while it was 38.75±14.88 for healthy controls.

Clinicopathological and Biochemical Characteristics: Out of 85 patients, 60 (70.58%) represented NHL, while 25 (29.42%) were HL patients. Among NHL, most cases were presented with DLBCL (80%), and mixed cellularity was more prevalent in HL (88%). NHL was highly prevalent at age of 41-50 years, while HL peak age ranged between 11-20 years. A high prevalence of lymphoma was seen among patients of low socio-economic status and was more common among males than females. Among NHL, 90% of the patients received CHOP treatment (cyclophosphamide, doxorubicin, vincristine, and prednisone), and for HL 83.33% cases received ABVD treatment (Adriamycin, bleomycin, vinblastine, and dacarbazine).

Comparison of extra-nodal (EN) and nodal (N) involvement: Nodal involvement was present in 74.11% of cases with 63.49% cases of NHL and 36.50% cases of HL (Table 1). EN involvement was recorded in 25.88% of cases. In both NHL and HL subjects, the most frequent site of nodal involvement was cervical. While the most frequent EN site of involvement amongst NHL cases were stomach and tonsils. In NHL patients, both nodal and EN involvement was more common among males. Among HL cases, nodal involvement was also dominant among males with a one-fold risk. Among studied NHL subjects, with nodal involvement, the maximum number was either in stage I or II, while for EN cases, 80% were categorized in stage I. On the other hand, among HL patients, only two were having EN involvement, with first being in stage II and the second in stage III. No association of symptom B (fever, weight loss, and night sweats) and symptom A (absence of symptom B) with nodal or EN involvement in both lymphomas was observed. Bone marrow involvement was observed in only one case of NHL.

Distribution of IL-13 2044 G/A genotype: The frequency of wild-type genotype GG was highest among lymphoma patients and controls. However, among lymphoma patients with subtype DLBCL, the variant genotype (AA) was more predominated (Table 2). The frequency of GG and GA genotypes were higher in controls than DLBCL patients. Allelic frequency of normal allele G was higher in both controls and lymphoma patients while in the case of patients with DLBCL allelic frequency of variant A allele was higher. Genotype and phenotype analysis showed no significant association of polymorphism in all lymphoma patients and among patients with subtype DLBCL. However, odd ratios indicate that patients having IL-13 2044G/A polymorphism exhibit a one-fold risk for lymphoma [OR=1.045(95%Cl)]. DLBCL analysis of allelic frequencies demonstrated a significant association of A allele with the DLBCL patients [χ^2=4.616, p-value=0.031] (Table 3).

Distribution of IL-13 2044 G/A genotype: For TLR-2 Arg677Trp polymorphism, wild-type genotype CC was observed in 50.58% of the lymphoma patients, and in the case of DLBCL patients, it was observed in 54.16% of the cases (Table 2). In the control group, the frequency of wild-type genotype was 55.55%. No study subject in either group was found to be homozygous for the variant genotype TT. The frequency of normal genotype CC was highest in healthy controls followed by lymphoma and DLBCL patients. Allelic frequency of normal allele C was the least among lymphoma patients. In the case of DLBCL patient's allelic frequency of normal allele C was 77.08 % [OR=0.96(95%Cl)]. Analysis of genotype frequency showed no significant association of polymorphism in lymphoma patients [$\chi^{2=}$0.51, p-value=0.433] and in DLBCL patients [$\chi^{2=}$0.024, p-value=0.875] (Table 3).

Table 1: Comparison of NHL and HL regarding demographic and clinicopathological features

Lymphoma subtype	Factors		Diagnosis		OR (95% Cl)	P-value (χ^2)
			EN *n* (%)	Nodal *n* (%)		
non-Hodgkin Lymphoma	Gender	Male	13(65)	25(62.5)	0.89(0.29-2.75)	0.849 (0.035)
		Female	7(35)	15(37.5)		
	Age	≤ 60	16(80)	35(87.5)	1.75(0.41-7.39)	0.443 (0.58)
		> 60	4(20)	5(12.5)		
	Stage	I	16(80)	13(32.5)	0.09(0.01-0.80)	0.005 (12.77)
		II	1(5)	9(22.5)		
		III	1(5)	12(30)	0.75(0.04-13.6)	
		IV	2(10)	6(15)	4(0.29-53.4)	
	Symptoms	A	15(75)	24(60)	0.5(0.15-1.64)	0.25 (1.31)
		B	5(25)	16(40)		
Hodgkin Lymphoma	Gender	Male	1(50)	12(52.17)	1.09(0.06-19.6)	0.95 (0.003)
		Female	1(50)	11(47.82)		
	Age	≤ 60	1(50)	22(95.66)	22(0.71-672.82)	0.022 (5.21)
		> 60	1(50)	1(4.34)		
	Stage	I	0	11(47.82)	-	0.20 (4.61)
		II	1(50)	3(13.04)		
		III	1(50)	3(13.04)	1(0.04-24.54)	
		IV	0	6(26.08)	-	
	Symptoms	A	2(100)	13(56.52)	-	0.228 (1.44)
		B	0	10(43.47)		

Table 2: Genomic frequencies of IL-13 and TLR-2 gene polymorphism in patients and controls

Polymorphism	Genotype	Controls *n* (%)	Lymphoma Patients *n* (%)	P-value (χ^2)	DLBCL Patients *n* (%)	P-value (χ^2)
IL-13 2044G/A	GG	48(53.33)	49(57.64)		20(41.66)	
	AA	33(36.66)	33(38.82)	0.23	25(52.08)	0.201
	GA	9(10)	3(3.52)	2.86	3(6.25)	3.141
TLR-2 Arg677Trp	CC	50(55.55)	43(50.58)		26(54.16)	
	TT	0	0	0.51	0	0.875
	CT	40(44.44)	42(49.41)	0.43	22(45.83)	0.024

Table 3: Allelic frequencies of IL-13 and TLR-2 gene polymorphism in patients and controls

Polymorphism	Allele	Controls (%)	Lymphoma Patients *n* (%)	OR (95% Cl)	P-value (χ^2)	DLBCL *n* (%)	OR (95% Cl)	P-value (χ^2)
IL-13 2044G/A	**G**	105 (58.33)	101 (59.41)	1.045 (0.68-1.60)	0.837 (0.042)	43 (44.79)	0.57 (0.35-0.95)	0.031 (4.616)
	A	75 (41.66)	69 (40.58)			53 (55.20)		
TLR-2 Arg677Trp	**C**	140 (77.77)	128 (75.29)	0.87 (0.53-1.42)	0.583 (0.300)	74 (77.08)	0.961 (0.53-1.73)	0.89 (0.017)
	T	40 (22.22)	42 (24.70)			22 (22.91)		

Discussion

Studies related to the association of the IL-13 2044G/A and TLR-2 Arg677Trp gene polymorphism with various types of cancers are available in the literature, however, there is a dearth of data related to their role in Lymphoma. IL-13 receptors are commonly expressed in tumor cells. IL-13Rα2 is overexpressed in pancreatic cancer, medulloblastoma, kidney cancer, glioblastoma, ovarian cancer, and head and neck cancer while type II IL-13R is expressed in prostate, breast, Kaposi sarcoma, head and neck, and in some ovarian cancers [6][15]. Tumors that exhibit elevated TLR expression include breast cancer, colorectal carcinoma, melanoma, lung cancer, prostate cancer, glioma, pancreatic carcinoma, liver cancer, and esophageal cancers [16]. In the present study, the impact of TLR-2 polymorphism Arg677Trp (C2029T) and IL-13 2044G/A polymorphism susceptibility to lymphoma in a sample of the Pakistani population along with their demographic and clinicopathological features, were investigated.

In the present study, NHL was the common type of lymphoma accounting for 70.58% of cases of the study subjects while HL accounted for 29.41% of cases. NHL subtype DLBCL was most prevalent (80%) followed by follicular B-cell lymphoma (6.66%). In Karachi, Pakistan increasing trend in NHL incidence has been seen from 1995 to 2002 with almost double the rate (4.1/100,00 in 1995 to 8.4/100,00 in 2002). It was reported by Shaukat Khanam Memorial Hospital, Lahore as the 4th top cancer affecting all age groups and gender. DLBCL was reported as the most common type of NHL [17]. In the present study among HL, MC was the most prevailing condition, comprising 88% of all the cases of HL. Consistent to these findings in Yemen from 2004 to 2007, similar trends were seen with a predominance of subtype MC (72.3%) among HL [18]. It was also inferred in the study that lymphoma was most prevalent in males as compared to females. In terms of nodal involvement, cervical lymph node involvement was most frequent for both types of lymphoma, however, the most frequent EN sites of involvement were the stomach and tonsils for NHL. A study conducted at Karachi (Pakistan) in 2005 also exhibited the same findings in terms of socio-economic status and nodal involvement in lymphoma patients, as seen in the present study with one-fourth of the NHL cases presenting with EN involvement having predominantly gastrointestinal involvement. Similarly, the majority of the patients belonged to a group of lower socio-economic categories and had a marginally higher risk for oncogenesis [19].

In the present study, genotype analysis showed no association between IL-13 2044G/A polymorphism and susceptibility to lymphoma as well as DLBCL patients. However, allelic frequency analysis reveals a significant association of the A allele with DLBCL. Mostly this polymorphism is studied for its role in asthma, however, its association with this condition is inconsistent among the Asian population [20]. Sameni et al. conducted a study in Iranian lung cancer patients, found no significant difference in the frequency of genotype and allele regarding 2044 G/A polymorphism of IL-13 gene and hence concluded that it does not contribute to lung

cancer susceptibility [21]. Furthermore, in studies conducted on Iranian women with breast cancer, and in patients with squamous cell carcinoma of the head and neck, similar results of no association were reported [22][23]. Arg677Trp polymorphism of TLR-2 in the present study also shows no significant association with lymphoma and DLBCL.

In literature, there is a dearth of data related to the association of this polymorphism with lymphomas, however, similar to the present study finding no association between TLR-2 Arg677Trp gene polymorphism with end-stage renal disease, and in a meta-analysis of inflammatory bowel disease has also been reported in the literature [24][25]. TLR-2 Arg677Trp variant allele was not detected in any of the lymphoma patients involved in our study, exhibiting the same result as in the study conducted by Sanchez et al on autoimmune diseases [26].The present study was the first to find the association of lymphoma with IL-13 2044 G/A and TLR-2 Arg677Trp polymorphism. Although no association was found, however, the allelic frequency of DLBCL showed an association of the A allele with lymphoma regarding IL-13 2044G/A polymorphism. Since lymphoma is a polygenic disorder, further studies are needed to find the susceptibility of lymphoma with these and other SNPs by using larger population groups.

Authors' contributions

ICMJE criteria	Details	Author(s)
1. Substantial contributions	Conception, OR	1
	Design of the work, OR	1
	Data acquisition, analysis, or interpretation	1,2
2. Drafting or reviewing	Draft the work, OR	1
	Review critically for important intellectual content	1,2
3. Final approval	Approve the version to be published	1,2
4. Accountable	Agree to be accountable for all aspects of the work	1,2

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The QAU Ethics Review Committee approved the study. All participants gave their consent before enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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