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Tumor necrosis factor alpha−308 and Lymphotoxin alpha+252 genetic polymorphisms and the susceptibility to non-Hodgkin lymphoma in Egypt

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ABSTRACT

Genetic polymorphism within the regulatory regions of tumor necrosis factor-alpha (TNF-α) and Lymphotoxin-alpha (LT-α) may be involved in the development of lymphoid malignancies. The aim of the current study was to investigate the effect of TNFα−308 and LTα+252 genetic polymorphism on susceptibility to non-Hodgkin lymphoma (NHL) in Egypt. Genotyping of the studied genes by restriction fragment length polymorphism polymerase chain reaction was conducted on 84 NHL and 100 healthy controls and revealed that TNFα−308 homotype (AA) was significantly higher in NHL patients and conferred sixfold increased risk of NHL (OR = 5.9, 95%CI = 2.3–16.1). Moreover, TNFα/LTα high-producer haplotypes were significantly higher in NHL patients and conferred increased risk of NHL (OR = 4.59, 95%CI = 2.19–9.42).

1. Introduction

Non-Hodgkin lymphomas (NHL) are closely related diseases, each involving the malignant transformation of lymphoid cells, but with distinctive morphologic, immunophenotypic, genetic, and clinical features [1]. B-cell lymphomas make up the majority of cases and, of these, diffuse large B-cell lymphoma and follicular lymphomas are the two major subtypes [2]. In Egypt, lymphoma represented 11.66% of all diagnosed cancer cases at the National Cancer Institute (NCI) during the period 2003–2004 according to the Cancer Pathology Registry, with non-Hodgkin's lymphoma constituting 76.5% of these cases [3]. Genetic susceptibility studies of lymphoma may serve to identify at risk populations and clarify important disease mechanisms. The majority of candidate genes that have been investigated to date can be categorized into functional groups based on their potential biologic relevance. One group of genes that alter B-cell survival and growth includes pro-inflammatory and regulatory cytokine genes [2].

Tumor necrosis factor (TNF) and Lymphotoxin (LT) are good candidate genes for the study of lymphomagenesis because they code for important immunoregulatory cytokines that are crucial mediators of inflammation, apoptosis, and T-helper cell type 1/2 (Th1/Th2) balance, and function as autocrine growth factors in lymphoid tumors [4,5]. TNF-α and LT-α cytokines are thought to influence lymphomagenesis through up-regulation of proinflammatory and anti-apoptotic signals, possibly via the nuclear transcription factor kappa B (NF-κB) pathway [5]. NF-κB acts in two ways that are relevant for lymphomagenesis. First, it has anti-apoptotic properties and prevents cell death among cells with malignant potential. Second, NF-κB stimulates the immune response, specifically the production of pro-inflammatory cytokines, which permits survival and proliferation of these cells [6]. A tightly regulated balance between proapoptotic and anti-apoptotic processes is of utmost importance and thus a slight imbalance towards increased cell survival could favor lymphomagenesis [7].

A single-base polymorphism within the promoter region of TNF-α gene at nucleotide position −308 results in 2 allelic forms, one with guanine, TNF-G allele (TNF1 allele) and the other, in which guanine is substituted by adenosine, TNF-A allele (TNF2 allele). TNF-A allele has been found to correlate with enhanced spontaneous or stimulated TNF-α production in vivo and in vitro [8]. As a major proinflammatory cytokine, TNF-α may function as a bridge between inflammation and cancer through its roles in promoting cell transformation, proliferation, survival, invasion and angiogenesis [9].

A polymorphism in the coding region at position +252 of the LT-α gene (A → G) leads to different alleles of LT-α, referred to as LT-α A allele for the wild-type allele, and LT-α G for the variant allele. Both the TNF-α and/or LT-α variant alleles have been shown to correlate

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with elevated TNF-α and LT-α plasma levels and have been associated with a more severe outcome of autoimmune and infectious diseases and lymphoid malignancies [10]. Several studies examined the association of TNFα−308 and LTα+252 polymorphisms with NHL. Nevertheless, the results are controversial. The aim of this study was to investigate the effect of genetic polymorphism at TNFα−308 (G → A) and LTα+252 (A → G) on susceptibility to NHL in Egypt.

2. Materials and methods

The current study was carried out on 84 Egyptian patients with NHL. Patients were chosen during the period between May 2009 and June 2010 among cases referred to the Department of Medical Oncology, National Cancer institute (NCI), Cairo University, after taking their written informed consents. Patients were either newly diagnosed or attending the NCI for follow up. They were 43 males and 41 females. Their ages ranged between 16 and 85 years. Hundred unrelated age-gender-ethnic matched healthy blood donors without previous history of malignancy were included in the current study as a control group. The research protocol was approved by the research Ethics committee of the Department of Clinical Pathology, Cairo University. Diagnosis of B-cell NHL was based on lymph node excision biopsy from the affected group of lymph nodes. Histopathological and immunohistochemical studies were done to confirm the diagnosis and for proper NHL sub-typing. Exclusion criteria included T-cell NHL cases, pediatric age group, non-Egyptians and patients with double malignancy.

All patients were subjected to full history taking with special attention to B symptoms, symptoms denoting site of affection, or family history of similar condition. Thorough clinical examination according to the standard sheet of haematological malignant disorders of the NCI was done with careful notation and assessment of clinical signs relevant to NHL as nodal areas affected all over the body, liver and splenic affection.

Radiological assessment in the form of computerized tomography (CT) abdomen and pelvis was done for all patients for proper diagnosis and staging. Other radiological procedures were chosen according to the site affected by lymphoma. Laboratory investigations included complete blood count, liver and kidney functions, serum uric acid, LDH and beta 2 microglobulin, cytological examination of any effusion and CSF cytology (if needed). Bone marrow biopsy for staging. The extent of the disease was categorized according to the Ann Arbor classification and the Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) criteria [11].

2.1. Detection of TNFα−308 and LTα+252 genetic polymorphism by restriction fragment length polymerase chain reaction

Five milliliter venous blood were withdrawn under complete aseptic conditions from all participants on EDTA. Samples were either stored in the same vacutainer at −20 °C or used directly within 24 h for DNA extraction. DNA was extracted from whole blood using AxyPrep Blood Genomic DNA Miniprep Kit (Axygen Biosciences, USA). Genotyping was based upon the methods described by Jrad et al. [12] and Warzocha et al. [13] as the target genes were amplified by PCR then restriction with the endonuclease NcoI. All PCR reactions were performed in a total volume of 25 μl containing 12.5 μl Master mix (Bioron GmbH, Germany), 1 μl forward primer (25 pmol), 1 μl reverse primer (25 pmol), 5.5 μl nuclease-free water and 5 μl Genomic extracted DNA.

For TNF-α−308 genotyping, the following primers were used, Forward primer 5′-AGGCAATAGGTTTTGAGGGCCAT-3′, and reverse primer 5′-TCCTCCCTGCTCCGATTCCG-3′ (Fermentas™–Lithuania). The thermocycler program applied was heating at 95 °C for 5 min, followed by 29 cycles of denaturation at 95 °C for 30 s, annealing at 60 °C for 30 s, and extension at 72 °C for 45 s. A final extension step was carried out at 72 °C for 10 min. The PCR product (107 bp) was digested with NcoI (Fermentas, Cat. No. #ER0571). The product was visualized by 2% agarose gel electrophoresis stained with ethidium bromide under UV light. A DNA molecular weight marker was also run to identify the site of bands. The presence of a NcoI restriction site in the mutant allele of TNF-α (A allele) was indicated by the cleavage of the 107 bp amplicon to yield two fragments of 87 and 20 bp (Fig. 1).

LT-α+252 genotyping was performed by using the following primers: forward primer 5′-CTCCTGCACCTGCTGCCTGGATC-3′ and reverse primer 5′-GAAGAGACGTTCAGGTGGTGTCAT-3′ (Fermentas™–Lithuania). The reaction conditions was initial heating at 95 °C for 10 min, followed by 31 cycles of denaturation at 96 °C for 60 s, annealing at 65 °C for 60 s, and extension at 72 °C for 120 s. A substitution of A to G at the nucleotide position 1252 of LT-α gene creates a NcoI restriction site. The 368-bp PCR product cleaved with NcoI (133- and 235-bp fragments) represented the mutant LT-α A allele (Fig. 2).

2.2. Statistical analysis

Data was analyzed using SPSSwin statistical package version 15. Numerical data were expressed as mean, standard deviation and range. Qualitative data were expressed as frequency and percentage. Chi-square test (or Fisher's exact test) was used to examine the relation between qualitative variables. Odds ratio (OR) and 95% confidence interval (CI) were calculated for risk estimation. A p-value less than 0.05 was considered significant.

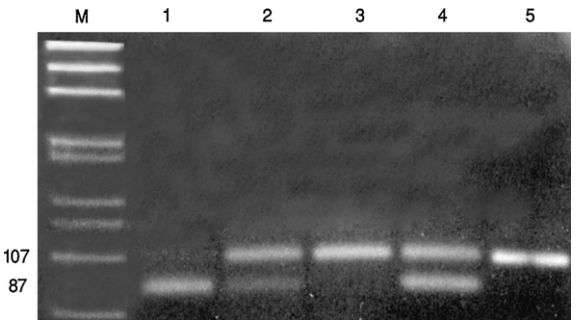

Fig. 1. TNFα−308 genotypes by agarose gel electrophoresis. M: 50–1000 ladder size marker. Lanes 3 and 5: TNF−308 GG genotype (wild type) showing a 107 bp band. Lane 1: TNF−308 AA homotype showing 87 bp band. Lanes 2 and 4: TNF−308 AG heterotype showing 87 and 107 bp bands.

3. Results

Clinical and laboratoty data of NHL patients are summarized in Table 1. TNFα−308 homomutant (AA) genotype was significantly higher among NHL patients and conferred almost sixfold increased risk of NHL. LTα+252 genotyping revealed that no statistical difference could be encountered between NHL patients and controls as regards the frequency of the three genotypes. Dual mutant genotype was detected in 22.6% of cases, while it was absent in the controls. Table 2 shows the results of TNFα−308 and LTα+252 genotyping by PCR-RFLP in patients and controls.

Statistical comparison between NHL patients with wild type alleles and those with mutant alleles of TNFα−308 gene revealed that the frequency of the mutant genotype was significantly lower in females and LDH level was significantly lower among NHL patients harboring the mutant allele of TNF-α (A allele). Otherwise, there was no statistically significant differences noticed between the two patients groups, as regards the presence of B-symptoms at presentation, hepatomegaly or splenomegaly, the groups of lymph nodes involved, extra-nodal involvement, clinical stage or their ECOG performance status.

Comparison between NHL patients with wild type alleles and those with mutant alleles of LTα+252 showed that there were no statistical differences between the two patients groups as regards their sex, B-symptoms, nodal involvement, extranodal involvement, hepatomegaly, clinical stage or their performance status. The involvement of inguinal lymph nodes was significantly higher among patients harboring the mutant genotype,

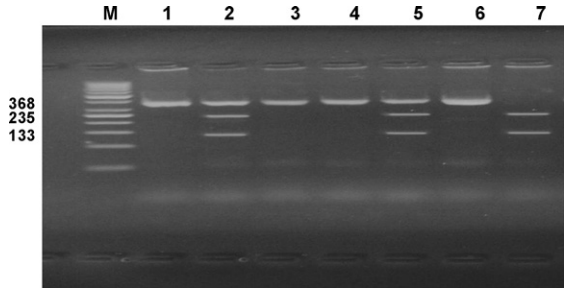

Fig. 2. LTα+252 genotypes by gel electrophoresis. M: 50–1000 Ladder size marker. Lanes 1, 3, 4 and 6: LT+252 AA genotype (wild type) showing a 368 bp band. Lane 7: LT+252 GG homotype showing 133 and 235 bp bands. Lanes 2 and 5: LT+252 GA heterotype showing 133, 235 and 368 bp bands.

Table 1
Clinical data of NHL patients at presentation.

Item		Patient group ($n=84$)	
		Number	Percentage
Sex	- Male	43/84	51.2%
	- Female	41/84	48.8%
B-symptoms: fever, night sweats, weight loss		43/84	51.2%
Lymphadenopathy		73/84	86.9%
Groups of lymph nodes involved	- Cervical L.N	35/84	41.7%
	- Axillary L.N	32/84	38.1%
	- Inguinal	21/84	25%
	- Submandibular	11/84	13.1%
	- Abdominal	13/84	15.5%
	- Mesenteric	7/84	8.3%
	- Para-aortic	16/84	19%
Extranodal involvement		20/84	23.8%
Splenomegaly		31/84	36.9%
Hepatomegaly		35/84	41.6%
Clinical stage			
- IA		13/84	15.5%
- IB		9/84	10.7%
- IIA		7/84	8.3%
- IIB		8/84	9.5%
- IIIA		7/84	8.3%
- IIIB		16/84	19%
- IVA		8/84	9.5%
- IVB		16/84	19%
ECOG performance status			
- I		37/84	44%
- II		37/84	44%
- III		8/84	9.5%
- IV		2/84	2.3%
NHL subtypes			
Diffuse large B-cell lymphoma		73/84	86.9%
Follicular lymphoma		5/84	5.9%
Small lymphocytic lymphoma (SLL/CLL)		2/84	3.5%
Splenic lymphoma		1/84	1.1%
Burkitt's lymphoma		1/84	1.1%
Anaplastic large cell lymphoma		2/84	2.3%
Treatment regimen			
Chemotherapy		67/84	79.7%
Chemotherapy + radiotherapy		7/84	8.33%
Prophase		2/84	2.3%
No treatment		15/84	17.86%
Response to therapy			
Complete remission		11/84	13.1%
Partial remission		19/84	22.6%
Progressive disease		4/84	4.8%
Relapse		13/84	15.5%
Not available		37/84	44%

while splenomegaly was significantly lower among patients with LTα+252 mutant genotype.

Analysis of TNFα/LTα polymorphic haplotype status revealed that TNFα-GG/LTα-AG combined genotype was significantly higher in the control group compared to NHL patients, and conferred decreased risk of NHL. No statistically significant difference could be encountered between the patients and the controls as regards the frequency of the combined genotypes; TNFα-GG/LTα-GG, TNFα-GA/LTα-AA and TNFα-AA/LTα-AA. The combined genotypes TNFα-GA/LTα-AG, TNFα-GA/LTα-GG, TNFα-AA/LTα-AG and TNFα-AA/LTα-GG were detected in NHL patients but not in the controls. This could be an evidence of increased risk of these combined genotypes as predictive risk factors for NHL.

According to Seidemann et al. [10], the low-producer haplotypes denoted the presence of less than two polymorphic alleles and are associated with decreased TNF-α production. The high-producer haplotypes denoted the presence of two or more polymorphic alleles associated with increased TNF-α production. More detailed analysis on the effects of low and high-producer haplotypes on NHL risk revealed that low-producers were significantly higher among the control subjects than NHL patients and conferred decreased risk of acquisition of NHL, while high-producer haplotypes were significantly higher in NHL patients and conferred nearly fivefold increased risk of NHL.

4. Discussion

Several studies examined the association of TNFα−308 and LTα+252 genetic polymorphisms with NHL. Nevertheless, the results were controversial. Previous studies have shown that single nucleotide polymorphisms of TNFα and LTα genes may be risk factors for NHL overall or for certain NHL subtypes [12–16]. The aim of this study was to investigate the effect of genetic polymorphism at TNFα−308 and LTα+252 on susceptibility to NHL in a cohort of Egyptians. To achieve this aim, TNFα−308 and LTα+252 genotyping was performed by PCR-RFLP technique.

TNF-α genotyping in NHL patients revealed that 25% of patients had TNFα-GA heterotype and 26.2% had the TNFα-AA homotype. This was in accordance with that reported in previous studies [5,10,12,13,15]. TNFα-GG wild genotype was significantly higher in the controls compared to NHL patients. However, the studies of Purdue et al. [5], Rothman et al. [7], Spink et al. [15] and Wang et al. [17] reported no significant difference in the frequency of TNFα-GG genotype between NHL patients and controls.

The Interlymph pooled analysis representing 8 studies reported the influence of genetic variation in TNFα−308 and LTα+252 on susceptibility to NHL [7]. In the present study, TNFα-AA genotype conferred as almost sixfold increased risk of NHL. This was in accordance with the results of Jrad et al. [12] and Wang et al. [18]. Similarly, Skibola et al. [9] found that TNFα-A allele conferred increased risk of B-cell NHL, especially DLBCL in Caucasians, suggesting a potentially common proinflammatory etiology. This was explained by their findings of enhanced transcriptional activation of TNFα and its overproduction by the A allele which provide a T-cell fueled proinflammatory milieu that may be involved in the pathogenesis of DLBCL. Although the frequency of TNFα-AA homotype was higher in NHL patients in the studies of Cerhan et al. [14] and Jevtovic-Steimenov et al. [19], it did not reach a statistically significant level. Oppositely, Rothman et al. [15] stated that TNFα−308 AA genotype was not associated with increased NHL risk ($p=0.16$), however, when restricted to DLBCL; the main histological subtype of NHL, the risk estimates revealed increased risk of DLBCL.

TNFα-GA heterotype, was detected in 25% of cases and 27% of the controls with no statistically significant difference between the two groups. This agreed with the studies of Purdue et al. [5] and Jrad et al. [12]. However, Rothman et al. [15] and Skibola et al. [9] reported that TNFα−308 GA heterotype was associated with increased risk of NHL. In agreement with the studies of Seidemann et al. [10] and Wang et al. [17], we found no statistically significant difference between NHL patients with TNFα−308 normal or mutant genotypes as regards the presence of B-symptoms at presentation, hepatomegaly or splenomegaly, nodal involvement, extranodal involvement, clinical stage or their performance status.

As regards the frequency of LTα+252 mutant genotypes, the heterotype and homotype were detected in 29.7% and 10.7% of patients respectively which agreed with other studies [13–15]. We did not encounter any statistically significant difference in the distribution of LTα+252 A → G polymorphism in NHL patients when compared to controls. This was in accordance with other studies [5,14,16]. On the other hand, Wang et al. [18] and Skibola et al. [9] reported that LTα+252 mutant genotypes were associated with increased risk of NHL and risk was particularly elevated for DLBCL.

TNFα-GG/LTα-AG combined genotype was significantly higher in the controls compared to NHL patients with decreased risk of NHL, thus it may have a protective role against the susceptibility to NHL. No statistically significant difference could be encountered

Table 2
The frequency of TNFα−308 and LTα+252 genotypes and haplotypes in NHL patients and controls.

Item	NHL patients No. (%)	Controls No. (%)	OR	95%CI	*p*-Value
Genotypes					
TNFα−308					
TNFα-G/G	41(48.8%)	67(67%)	0.469	0.258–0.853	0.01*
TNFα-G/A	21(25%)	27(27%)	1.3	0.63–2.5	0.49
TNFα-A/A	22(26.2%)	6(6%)	5.98	2.3–16.1	0.001*
LTα+252					
LTα-A/A	50(59.5%)	51(51%)	1.412	0.786–2.539	0.24
LTα-A/G	25(29.8%)	42(42%)	0.61	0.33–1.14	0.12
LTα-G/G	9(10.7%)	7(7%)	1.3	0.45–3.8	0.62
Combined genotypes					
TNFα-GG/LTα-AA	26(30.9%)	18(18%)	2.042	1.032–4.404	0.05
TNFα-GG/LTα-AG	10(11.9%)	42(42%)	0.188	0.086–0.403	0.0001*
TNFα-GG/LTα-GG	5(5.9%)	7(7%)	0.84	0.256–2.75	0.77
TNFα-GA/LTα-AA	14(16.7%)	27(27%)	0.541	0.2622–1.115	0.13
TNFα-GA/LTα-AG	5(5.9%)	0(0%)	ND	ND	ND
TNFα-GA/LTα-GG	2(2.4%)	0(0%)	ND	ND	ND
TNFα-AA/LTα-AA	10(11.9%)	6(6%)	2.117	0.735–6.0924	0.24
TNFα-AA/LTα-AG	10(11.9%)	0(0%)	ND	ND	ND
TNFα-AA/LTα-GG	2(2.4%)	0(0%)	ND	ND	ND
Low-producer haplotypes	50/84	87/100	0.219	0.106–0.454	0.001*
TNFα-GG/LTα-AA					
TNFα-GG/LTα-AG	(59.5%)	(87%)			
TNFα-GA/LTα-AA					
High-producer haplotypes	34/84	13/100			
TNFα-GG/LTα-GG			4.59	2.198–9.42	0.001*
TNFα-GA/LTα-AG	(40.5%)	(13%)			
TNFα-GA/LTα-GG					
TNFα-AA/LTα-AA					
TNFα-AA/LTα-AG					
TNFα-AA/LTα-GG					

OR = odds ratio, CI = confidence interval.
* *p*-Value < 0.05 = significant.

between the patients and the controls regarding the frequency of the combined genotypes; TNFα-GG/LTα-GG, TNFα-GA/LTα-AA and TNFα-AA/LTα-AA. This is in accordance with the study of Warzocha et al. [13], who reported that the distribution of the TNFα/LTα polymorphic haplotypes between the patients and controls was not statistically significant. On the contrary, the study of Skibola and colleagues [9] reported that the GA haplotype (variant alleles for LTα+252G and TNFα−308A) had an increased risk of DLBCL, whereas the AA haplotype (wild type for LTα+252 and variant for TNFα−308A) did not influence DLBCL risk as revealed in our study. This suggests an independent effect of the TNF−308G > A polymorphism on DLBCL risk. So, functional studies will be needed to dissect the effects of these variants.

The combined genotypes TNFα-GA/LTα-AG, TNFα-GA/LTα-GG, TNFα-AA/LTα-AG and TNFα-AA/LTα-GG were not detected in the controls, so the statistical difference between the two groups and the risk estimates for these combined genotypes were not determined. This could be an evidence of increased NHL risk of these combined genotypes.

The strong association between TNFα−308 and LTα+252 polymorphic alleles and the possible contribution of both polymorphic sites in increased production of TNF led Seidemann et al. [10] and Warzocha et al. [13] to analyze these genetic markers as haplotypes rather than as individual alleles. Our results are in accordance with that of Seidemann et al. [10], as the frequency of low-producer haplotypes was significantly higher in the controls conferring protective effect against the acquisition of NHL, while high-producer haplotypes were significantly higher among NHL patients and conferred nearly fivefold increased risk of NHL.

Only few data exist on the association of TNFα−308 and LTα+252 haplotypes and prognosis in B-cell malignancies, with conflicting results. Whereas some authors described worse prognosis with high producer haplotypes, others could not find such an association [10]. In the current study, there was no statistically significant difference noticed between patients with normal or mutant TNFα−308 or LT-α+252 genotypes as regards their response to therapy. On the contrary, Warzocha et al. [13] reported that TNFα−308 polymorphic alleles are associated with poor treatment outcome. However, the study of Seidemann et al. [10] reported that TNFα−308 is not a prognostic factor for pediatric and adolescent NHL cases. The limitation of our study was the relatively small sample size. The present study could have yielded more consistent results if included more patients and if treatment results were followed in relation to the genotyping.

In conclusion, our study provides further evidence of a role for genetic variation in the TNF G−308A single nucleotide polymorphism with risk of NHL as well as TNF/LT-α haplotypes in the Egyptian population. These findings provide additional clues to the etiology of this cancer and support identifying additional genes and environmental exposures that affect NF-κB signaling, with the ultimate goal of identifying novel prevention approaches. Additionally, TNFα−308 and LTα+252 polymorphic markers may be considered as targets for new therapeutic approaches, especially those based on immunomodulation or TNF inhibitors. Further exploration of additional variants in TNF-α and LT-α, in their receptors and other related genes, should provide further insight into the pathogenesis and ultimately the prevention and treatment of NHL, the incidence of which has risen steadily worldwide over the last half of the twentieth century and for which the factors governing development remain elusive.

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Conflict of interest

All authors have no conflict of interest to declare.

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References

[1] Morton LM, Purdue MP, Zheng T, Wang SS, Armstrong B, Zhang Y, et al. Risk of non-Hodgkin lymphoma associated with germline variation in genes that regulate the cell cycle, apoptosis, and lymphocyte development. Cancer Epidemiol Biomarkers Prev 2009;18(4):1259–70.
[2] Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. Haematologica 2007;92:960–9.
[3] Goldman L, Ezzat S, Mokhtar N, Abdel-Hamid A, Fowler N, Gouda I, et al. Viral and non-viral risk factors for non-Hodgkin's lymphoma in Egypt: heterogeneity by histological and immunological subtypes. Cancer Causes Control 2009;20(6):981–7.
[4] Kádár K, Kovács M, Karádi I, Melegh B, Pocsai Z, Mikala G, et al. Polymorphisms of TNF-alpha and LT-alpha genes in multiple myeloma. Leuk Res 2008;32(10):1499–504.
[5] Purdue MP, Lan Q, Kricker A, Grulich AE, Vajdic CM, Turner J, et al. Polymorphisms in immune function genes and risk of non-Hodgkin lymphoma: findings from the New South Wales non-Hodgkin lymphoma study. Carcinogenesis 2007;28:704–12.
[6] Wang SS, Purdue MP, Cerhan JR, Zheng T, Menashe I, Armstrong BK, et al. Common gene variants in the tumor necrosis factor (TNF) and TNF receptor superfamilies and NF-κB transcription factors and non-Hodgkin lymphoma risk. PLoS One 2009;4(4):e5360.
[7] Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the Inter-Lymph Consortium. Lancet Oncol 2006;7:27–38.
[8] Elahi MM, Asotra K, Matata BM, Mastana SS. Tumor necrosis factor alpha−308 gene locus promoter polymorphism: an analysis of association with health and disease. Biochim Biophys Acta 2009;1792(3):163–72.
[9] Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, de Sanjosé S, Hughes AM, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. Am J Epidemiol 2010;171(3):267–76.
[10] Seidemann K, Zimmermann M, Book M, Meyer U, Burkhardt B, Welte K, et al. Tumor necrosis factor and lymphotoxin alpha genetic polymorphisms and outcome in pediatric patients with non-Hodgkin's lymphoma. J Clin Oncol 2005;23(33):8414–21.
[11] Armitage JO. Staging non-Hodgkin lymphoma. CA Cancer J Clin 2005;55:368–76.
[12] Jrad BB, Chatti A, Laatiri A, Ben Ahmed S, Romdhane A, Ajimi S, et al. Tumor necrosis factor promoter gene polymorphism associated with increased susceptibility to non-Hodgkin's lymphomas. Eur J Haematol 2006;78:117–22.
[13] Warzocha K, Coiffier B, Salles G, Ribeiro P, Bienvenu J, Roy P, et al. Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin's lymphoma outcome. Blood 1998;91:3574–81.
[14] Cerhan JR, Wang SS, Maurer MJ, Ansell SM, Geyer SM, Cozen W, et al. Prognostic significance of host immune gene polymorphisms in follicular lymphoma survival. Blood 2007;109(12):5439–46.
[15] Spink CF, Keen LJ, Mensah FK, Law GR, Bidwell JL, Morgan GJ. Association between non-Hodgkin lymphoma and haplotypes in the TNF region. Br J Haematol 2006;133(3):293–300.
[16] Wang SS, Slager SL, Brennan P, Holly EA, De Sanjose S, Bernstein L, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). Blood 2007;109(8):3479–88.
[17] Wang SS, Davis S, Cerhan JR, Hartge P, Severson RK, Cozen W, et al. Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma. Carcinogenesis 2006;27(9):1828–34.
[18] Cerhan JR, Liu-Mares W, Fredericksen ZS, Novak AJ, Cunningham JM, Kay NE, et al. Genetic variation in tumor necrosis factor and the nuclear factor-kb canonical pathway and risk of non-Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prev 2008;17(11):3161–9.
[19] Jevtovic-Steimenov T, Kocic G, Pavlovic D, Macukanovic-Golubovic L, Marjanovic G, Djordjevic V, et al. Polymorphisms of tumor-necrosis factor-alpha−308 and lymphotoxin-alpha+250: possible modulation of susceptibility to apoptosis in chronic lymphocytic leukemia and non-Hodgkin lymphoma mononuclear cells. Leuk Lymphoma 2008;49(11):2163–9.