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Original scientific paper

GLUTATHIONE S-TRANSFERASE M1 - T1 NULL GENOTYPES AND SUSCEPTIBILITY TO HODGKIN'S LYMPHOMA

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Hodgkin's Lymphoma (HL) is a heterogeneous malignant disease of lymph node. The glutathione S-transferases (GSTs) have an important role in the detoxification of a wide variety of toxins and carcinogens. Studies have been indicated that genetic variation in the *GST* gene family may lead to susceptibility in HL. Hereby, we investigated the association of *GSTT1* and *GSTM1* null genotypes with HL in the Iranian population. This case-control study consisted of 76 patients suffering from HL and 120 healthy individuals as a control group. Genomic DNA was extracted and genotyping of *GSTT1* and *GSTM1* genes for the identification of their null genotypes was carried out using multiplex PCR method. Our findings indicated that *GSTM1* null genotype is associated with risk of developing HL in our population (P=0.025; OR=2.00; 95%CI=1.110-3.602); however, no association was found for *GSTT1* null genotype. Our study also showed that the *GSTM1* null genotype increased the risk of disease in the individuals younger than 45 years, and it had a positive association with low ESR. *GSTM1* null genotype may have the key role in increasing the risk of HL in the Iranian population.

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INTRODUCTION

Hodgkin's Lymphoma (HL) is a type of lymph node cancer that is originated from abnormal germinal center B-cell. It is characterized by Hodgkin and Reed Sternberg (HRS) cells, lymphocyte predominant HL (LPHL) cells, and other reactive inflammatory cells (KÜPPERS, 2009). Although the main etiology of the disease is unknown, besides environmental factors, several studies have been indicated that genetic factors can be important in susceptibility to the HL. Epstein–Barr virus (EBV) infection and abnormal immune reaction are also considered as a pathogenic factor for HL, however; infection with EBV seems not to be important in familial cases (CHAPMAN and RICKINSON, 1998). Clinical results demonstrate that frequency of HL especially among young adults has been arisen since the 1970s, suggesting changes in the exposure to carcinogens (CHEN *et al*., 1997). Some studies also revealed an increased risk of HL in sibling and twins. Risk of HL in sibling younger than 45 years is seven-fold higher than older cases (GRUFFERMAN *et al*., 1977; MACK *et al*., 1995). The genetic aberration of the HL same as other cancers can be categorized into four categories: subtle changes in DNA sequences, including microsatellite, gene amplifications, chromosomal translocations, and instability (LENGAUER *et al*., 1998). Studying genetic susceptibility to the HL can lead to clarifying of its mechanism and risk estimation among the population. Several studies have examined polymorphisms in some genes and cancer risk especially HL, such as cytokines genes (*IL6*, *TNFA*, *IL10*, *L1RN*, *INFG*, *CCL17* and *TGFB*) (DOMINGO-DOMÈNECH *et al*., 2007; CORDANO *et al*., 2005; HOHAUS *et al*., 2007; SCHOOF *et al*., 2013; GHESQUIÈRES *et al*., 2013; DEHGHAN TEZERJANI *et al*., 2015) and *HLA* genes (HUANG *et al*., 2012). The associations between *GST* genes variants and HL has also investigated (HOHAUS *et al*., 2003).

Glutathione-S-transferases (GSTs) are belonged to the phase II XMEs (xenobiotic metabolizing enzymes) with the key roles in the elimination and detoxification of the xenobiotics or exogenous molecules such as toxins and carcinogens in the human body (OMIECINSKI *et al*., 2011). There are eight isoenzymes classes of GSTs in mammals including: alpha (GSTA), mu (GSTM), theta (GSTT), Pi (GSTP), zeta (GSTZ), sigma (GSTS), kappa (GSTK), and omega (GSTO) (Mannervik et al. 1992) among which GSTM1 and GSTT1 polymorphisms are studied more than others. *GSTM1* gene locus is located on the chromosome 1 region 1p13.3 and it is considered as a key factor in eliminating detoxifications of mutagens such as polycyclic aromatic hydrocarbons. *GSTT1* gene maps on chromosome 22 region 22q11.23 and it has an important role in metabolism and detoxification of small compounds such as mono halo methanes and ethylene oxide (HAYES and PULFORD, 1995). The null genotypes of both *GSTM1* and *GSTT1* which encode deficient or no glutathione-S-transferase can lead to insufficient detoxification, genetic damage, and the increased risk of tumor formations (COUGHLIN and HALL, 2002). The association of *GSTs* genes variants have been evaluated in various cancers such as cervical cancer, esophageal cancer, colorectal cancer, and Hodgkin and non-Hodgkin lymphoma (ZHANG *et al*., 2012, YI and LI, 2012; WANG *et al*., 2012; BIN and LUO, 2013).

In this study, we hypothesized that *GSTM1* and *GSTT1* genes variation might be associated with the risk of Hodgkin's Lymphoma in Iranian population. Therefore, we investigated the association of these genotypes with HL disease.

MATERIALS AND METHOD

Patients and Control

This case-control study included 76 Iranian patients with Hodgkin's Lymphoma (28 females and 48 males) and 120 healthy individuals (43 females and 77 males) who were age-matched as a control group. The samples were recruited from Shahid Sadoughi hospital from September 2014 to August 2015. The patient's median age was 34.97±15.89 ranging from 8 to 82 years. The clinical characteristic of the patients is shown in Table 1. The study was approved by the ethics committee of the Shahid Sadoughi University of Medical Sciences, Yazd, Iran and the written informed consents were obtained from all patients. No history of cancer, autoimmune, and known genetic diseases or hereditary predisposition were considered as the inclusion criteria for the control group.

Table 1. The clinical characteristics of the patients

Characteristics		**n**
Age	Average/Range	**34.97±15.89/8-82**
	<45	**56**
	>45	**20**
Sex	Male	**48**
	Female	**28**
Stage	I	**13**
	II	**29**
	III	**23**
	IV	**11**
Histotype	Nodular sclerosing HL	**37**
	Mixed-cellularity HL	**30**
	Lymphocyte depleted HL	**3**
	Lymphocyte-rich HL	**6**
	Unclassifiable classic HL	**-**
B-symptoms	Yes	**41**
	No	**35**
Bulky disease	Yes	**37**
	No	**39**
ESR	<50 mm/h	**42**
	>50 mm/h	**34**
Hb	<12 grams/dl	**31**
	>12 grams/dl	**45**

HL, Hodgkin's Lymphoma.

DNA extraction and Genotyping

Genomic DNA was extracted from anticoagulated whole blood of each sample using DNA extraction kit (Qiagen, Hilden, Germany). The multiplex PCR method was used for the

identification of *GSTM1* and *GSTT1* genotypes (ARAND *et al*., 1996). The set of primers used for *GSTM1* were F 5'-GAA CTC CCT GAA AAG CTA AAG C-3', R 5'- GTT GGG CTC AAA TAT ACG GTG G-3'; and for *GSTT1* were F 5'-TTC CTT ACT GGT CCT CAC ATC TC-3', R 5'-TCA CCG GAT CAT GGC CAG CA-3'. The set of primers including F 5'-CAA CTT CAT CCA CGT TCA CC-3' and R 5'-GAA GAG CCA AGG ACA GGT AC-3' were used for amplification of the limited region of *β-globin* gene in all samples as a positive control. DNA contamination also was checked by negative control. DNA amplification was performed in a total volume of 25 µl containing 3–5 µl genomic DNA, 1 µl of each three sets of primers and 12.5 µl of PCR Master Mix (Bioneer) and H_2O. The PCR reaction was carried out under the following conditions: an initial denaturation step at 94°C for 5 min followed by 35 cycles of 94°C for 1 min, 62°C for 1 min, 72°C for 1 min, and a final extension step at 72°C for 10 min and holding at 4°C. The PCR products were identified using 2% agarose gel electrophoresis in 1X TBE buffer and under UV light. The absence of each product indicated null genotype in target gene. Some experiments repeated three times by different observer to confirm our results.

Statistical Analysis

SPSS statistical software (version 20, SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analysis. The genotypes of *GSTM1* and *GSTT1* were compared with a 2×2 contingency table using Fischer's exact test and chi-squared (Two-tail) test. Odds ratios (OR) were calculated by considering 95% confidence interval (CI).

RESULTS

In this study, we investigated *GSTT1* and *GSTM1* null genotypes in 76 patients with Hodgkin's Lymphoma and 120 healthy individuals as control group. The specific bands of PCR products were analyzed and counted (figure 1). The prevalence and frequency of *GSTT1* and *GSTM1* null genotypes in both patient and control group are demonstrated in Table 2. Both null genotypes are more frequent in patients in comparison with control group (23.7% versus 21.7% for *GSTT1* and 50% versus 33.3% for *GSTM1*). There was a significant association between *GSTM1* null genotype and HL disease (P=0.025; OR=2.00; 95%CI=1.110- 3.602). The calculated odds ratio revealed the fact that *GSTM1* null genotype conferred two fold increased risk of HL. However, GSTT1 null genotype, dual null genotype and dual-non genotype are not associated with HL disease in our population.

Table 2. Frequency of genotypes in both Hodgkin's Lymphoma (HL) patients and control group

Genotype	**HL patients n(%) n=76**	**Control group (n/%) n=120**	**P value**	**OR (95%CI)**
GSTT1 null genotype	18 (23.7%)	26 (21.7%)	0.861	**1.12(0.56-2.22)**
GSTM1 null genotype	38(50%)	40(33.3%)	**0.025**	**2.00(1.110-3.602)**
Dual null genotype	8(10.5%)	6(5%)	0.163	**2.235(0.744-6.717)**
Dual non-null genotype	28(36.8%)	60(50%)	0.078	**0.583(0.324-1.050)**

The bold value is statistically significant, OR: odd ratio, CI: confidence interval, P value < 0.05 is considered as significant. N total= n (*GSTT1* null genotype) +n (*GSTM1* null genotype) + n (dual non-null genotype) – n (dual null genotype).

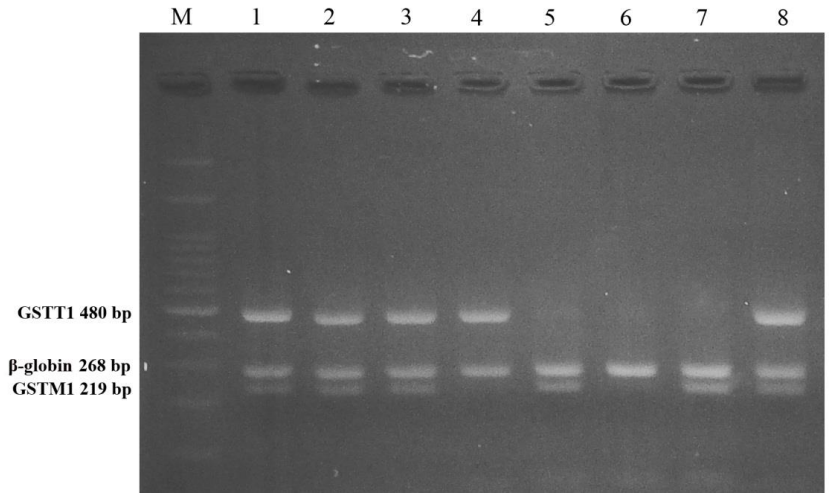

Fig. 1. The results of multiplex PCR analysis of *GSTT1* and *GSTM1* null genotypes. Lane M shows molecular weight marker, Specific band indicates at least one non-null genotypes of the related gene. A 268 bp band in all lanes is a part of *β-globin* gene as a positive control. Lane 5 and 7 show GSTT1 null genotype. Lane 4 indicates *GSTM1* null genotype. Lane 6 show dual null genotype, and Lane 1, 2, 3, and 8 indicate dual non-null genotype.

The risk assessment of HL and the subgroups of patients is shown in Tables 3 and 4. Based on our results, *GSTM1* null genotype in patients younger than 45 years shows a positive association (P=0.001; OR=3.261; 95% CI= 1.606- 6.622). No association was observed between the sex subgroup and HL risk. Regarding the patients' clinical characteristics, including histotype, stage, B-symptoms, Bulky disease, Erythrocyte Sedimentation Rate (ESR), and hemoglobin (Hb), only ESR showed a positive association with HL (P= 0.037).

Table 3. The frequency of null genotypes for age and sex subgroup

GSTM1 null		**Patients**	**Control group**	**P value; OR (95% CI)**
Age	<45	30/56- 53%	23/88- 25%	**0.001; 3.261(1.606-6.622)**
	>45	8/20- 40%	19/32- 59%	**0.255; 0.456(0.146-1.426)**
Sex	Male	28/48- 58%	26/61- 42%	**0.124; 1.885(0.876-4.054)**
	Female	10/28- 38%	16/59- 27%	**0.458; 1.493(0.57-3.91)**

45 years was considered as the cut point for Hodgkin's Lymphoma (HL).

Table 4. The frequency of GSTM1 null genotypes in the subgroup of patients' characteristics

		n/ntotal	%	P value	OR(95%)
Histotype	Nodular sclerosis	19/37	51	1.00	**1.111(0.452-2.733)**
	Other histotype	19/39	48		
Stage	I-IIA	10/24	41	0.46	**0.612(0.230-1.627)**
	IIB-IV	28/52	53		
B-symptoms	Yes	20/41	48	1.00	**0.899(0.365-2.218)**
	No	18/35	51		
Bulky disease	Yes	23/37	62	0.06	**2.629(1.041-6.636)**
	No	15/39	38		
ESR	<50 mm/h	26/42	61	**0.037**	**2.979(1.164-7.622)**
	>50 mm/h	12/34	35		
Hb	<12 grams/dl	14/31	45	0.641	**0.721(0.288-1.805)**
	>12 grams/dl	24/45	53		

DISCUSSION

HL is an uncommon and malignant disease of the lymphoid tissue with heterogeneous histologic characteristics and based on a study on Iranian population, it constitutes 8% of the total lymphoid malignancies in Iran (MOZAHEB *et al*.,2011). It is believed that genetic factors, especially the altered genes involved in Carcinogen metabolism may play an important role in susceptibility to the disease. Herein, using a case-control study, we studied the null genotypes of *GSTM1* and *GSTT1* genes, which may cause abnormality in the elimination of carcinogenic compounds and the increased risk of Hodgkin's Lymphoma in the Iranian population. To our knowledge, this is the first study on GST genotypes and susceptibility to development of HL disease in the Iranian population.

Several studies have also investigated the association between GST genotypes and the risk of lymphoid malignancy. A positive association was observed between *GSTP1* polymorphisms and DLBCL risk (AL-DAYEL *et al*. 2008; CHIU *et al*., 2005). Many studies also indicated the association between *GSTT1* null genotypes and Non-Hodgkin lymphoma (NHL), Diffuse large B-cell lymphoma (DLBCL), and Marginal zone B-cell lymphomas (MZBL) diseases (AL-DAYEL *et al*., 2008; KERRIDGE *et al*., 2002; ROLLINSON *et al*., 2003; WU *et al*., 2004). In a previous study from Egypt with a similar design to our study, a positive association was found between GSTT1 null genotype and the risk of DCLBL (OR = 3.9, 95% CI = 1.97–7.75) (RAHMAN *et al*., 2012). In addition, the study done by GUVEN *et al.* (2015) with the same method, revealed no association between GSTM1, GSTT1 null genotypes and risk of developing Childhood acute lymphoblastic leukemia (ALL) (GUVEN *et al*., 2015). There are only few reports investigating the association between GST genotypes and HL. HOHAUS *et al*. (2005) found an association between *GSTP1* Ile^{105}Val polymorphism and the survival rate in patients with HL (HOHAUS *et al*., 2005). In another study, a positive association was found between *GSTT1* null genotype and the risk of HL (HOHAUS *et al*., 2003). LOURECNCO *et al.* (2010) reported that *GSTM1+* genotypes and *GSTT1+* genotypes have a positive correlation with the advanced tumor stage and higher recurrence rate, respectively (LOURENCO *et al*., 2010). GSTM1 or GSTT1 deletion can increase the resistance to chemotherapy in patients with Acute myeloid leukemia

(AML) (VOSO *et al*., 2002). In addition, at least one allele of GSTM1 can increase the efficiency of treatment in patients with non-HL (DIECKVOSS *et al*., 2002). However, there are inconsistent results due to the complexity of the role of these enzymes in detoxification of chemotherapy agent. Therefore, identification of GSTs genotypes might help to determine the best treatment and chemotherapy method.

In the current study, *GSTM1* null genotype is significantly associated with HL and calculated odds ratio of this genotype indicates 2-fold increase in the risk of HL. However, *GSTT1* null genotype does not have a positive association with HL in our population. On the contrary to our study, HOHAUS *et al*. (2003) reported a positive association of *GSTT1* null genotype and negative association of *GSTM1* null genotype in the Italian patients with HL (HOHAUS *et al.*, 2003). In the current study, the *GSTM1* null genotype was associated with ESR, suggesting prognostic factor for the disease. The genotypes also showed more association with the disease in the patients younger than 45 years, confirming the age under 45 years as an independent prognostic factor (HASENCLEVER *et al*., 1998). No association was found between the genotype and other clinical features.

The variation in the result of different studies can be ascribed to the different studied population, different number of studied individuals and different patterns of carcinogen exposure that can lead to developing HL disease with different rate in the target population.

CONCLUSION

In conclusion, our study showed a positive association between *GSTM1* null genotypes and the increased risk of HL, especially in patients younger than 45 years. This genotype also has a positive association with lower ESR in the studied patients. Our findings suggest that polymorphism in metabolic pathways genes may help to improve the prediction of HL patients survival and prognosis. In addition, further functional studies with larger sample size are greatly needed to confirm an association between the *GSTs* gene polymorphisms and risk of HL in the Iranian population.

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GLUTATION S-TRANSFERAZA KOD M1 - T1 GENOTIPOVA I OSETLJIVOST NA HODŽKINSOV LIMFOM

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Izvod

Hodžkinsov limfom (HL) je heterogena maligna bolest limfnih čvorova. Glutation S-transferaze (GSTs) imaju značajnu ulogu u detoksifikaciji brojnih toksina i kancerogena. Proučavanja ukazuju da genetičke varijacije u *GST* genskoj familiji mogu voditi ka povećanij osetljivosti prema HL. U radu smo proučavali vezu *GSTT1* i *GSTM1* genotipova sa HL u iranskoj populaciji. Obuhvaćeno je 76 pacijenata obolelih od HL i 120 zdravih individua, koji su predstavljali kontrolnu grupu. Genomska DNK je ekstahovana i urađena je identifikacija nultih genotipova za gene *GSTT1* i *GSTM1*, multipleks PCR metodom. Rezultati ukazuju da je *GSTM1* nulti genotip povezan sa rizikom od razvoja HL u populaciji (P=0.025; OR=2.00; 95%CI=1.110- 3.602). Međutim, za nulti genotip *GSTT1* nije pronađena nikakva povezanost. Takođe je utvrđeno da *GSTM1* nulti genotip ima i povećan rizik od pojave bolesti kod dela populacije koji je mlađi od 45 godina, što je u pozitivnoj korelaciji sa niskim ER. To ukazuje na moguću ključnu ulogu *GSTM1* u pojavi HL kod iranske populacije.

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