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No association between *GSTT1*, *GSTM1,* and *GSTP1* gene polymorphism and risk of non-Hodgkin lymphoma in a population from Romania

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ABSTRACT: Polymorphisms of the glutathione S-transferases (GSTs), which are involved in the cellular oxidative and antioxidant mechanisms of the xenobiotic substances and carcinogens, represents a factor that increases the risk of developing cancer. We aimed to determine in a case-control study (82 patients and 152 controls) a possible association between the *GSTT1*, *GSTM1* and *GSTP1* gene polymorphisms and susceptibility to non-Hodgkin lymphoma (NHL) in a Romanian population. *GTSs* genotypes were obtained using the multiplex polymerase chain reaction (PCR) and the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Increased frequencies of the *GSTM1* null genotype were observed in the patients (51.22%) with NHL and in controls (56.58%). No associations were observed between *GSTP1* Ile/Val + Val/Val and *GSTM1* null genotypes and risk of NHL, while an increased risk for *GSTT1* null genotype was noticed without statistical significance. We did not find differences for the combined *GST* gene polymorphisms and risk of NHL between patients and controls. Also, no differences between patients' demographic and clinical characteristics and GTSs genotypes were detected ($p>0.05$, for all comparisons). Therefore, our research suggests that *GSTM1*, *GSTT1*, and *GSTP1* genotypes do not contribute to the risk of developing NHL.

KEYWORDS: *GSTT1*, *GSTM1*, *GSTP1*, gene polymorphism, non-Hodgkin lymphoma.

1 INTRODUCTION

In Romania, approximately 1566 new cases of non-Hodgkin lymphoma (NHL) are diagnosed every year according to GLOBOCAN [1]. It has been suggested that xenobiotic substances and environmental carcinogen exposure, particularly exposure to nitrates, pesticides, herbicides and solvents, is a susceptibility factor for NHL [2]. Therefore, responsible for the biotransformation and the detoxification of many different xenobiotic substances and carcinogens are glutathione S-transferases (GTSs) [3].

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GTSs, a phase II xenobiotic-metabolizing enzymes, are a major group of multifunctional enzymes involved in the regulation of the cellular oxidative and antioxidant pathways by catalyzing conjugation to glutathione and neutralizing free radicals, respectively. In humans, were identified 8 main classes of GTSs, such as alpha, mu, kappa, omega, pi, sigma, theta, and zeta [3].

The most commonly reported polymorphisms in the genes that encoded GTSs associated with low or lack of enzyme activity are *GSTT1*, *GSTM1,* and *GSTP1* [4]. A deletion of *GSTT1* gene (located on chromosome 22q11.2) is associated with risk of malignant lymphomas and other types of cancer (cancer of bladder, lung, colon, stomach and skin). A similar deletion was found in the *GSTM1* gene, located on chromosome 1p13.3 and in the *GSTP1* gene, located on chromosome 11q13 responsible for inactivation of toxins and carcinogens [5]. Thus far, are only a few studies that associated GTSs polymorphisms with risk of NHL, and results are not consistent [6], [7], [8], [9], [10], [11].

The frequencies of GTSs polymorphisms is different among populations. Therefore *GSTT1* polymorphism is more frequent Asians and Caucasians, 35-52% and 13-26%, respectively, and is higher in Chinese (58.3%) and in French (43%) than in Nigerians (21.7%) in the case of the *GSTM1* polymorphism [12]. It is found that approximately 30% of the Caucasian population carries the GSTP1 polymorphism and it is less frequent in Asians [13].

The aim of the study was to determine if there is an association between the common *GST* gene polymorphisms and susceptibility to NHL in a Romanian population and to correlate the *GSTs* genotypes to patients' clinical characteristics.

2 MATERIALS AND METHODS

2.1 STUDY POPULATION

Our patients' group study involved 82 Caucasian adults with confirmed diagnoses of NHL according to WHO classification [14] admitted to the Hematology Clinic I from Emergency Clinical County Hospital, Tîrgu Mureș, Romania. Patients' clinical and laboratory data such as a histopathological classification of the NHL, performance status (according to The Eastern Cooperative Oncology Group - ECOG), Ann Arbor stage (the most often used staging system to present the extent of NHL), LDH level, treatment outcome, and the survival rate was collected from the medical records.

The control group consists of 152 healthy participants with no hematologic or other malignancies. Controls were randomly selected from the same geographical area, Transylvania region, and with a similar ethnic background as the cases.

All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was conducted with the approval of the Ethics Committee from the University of Medicine and Pharmacy Tîrgu Mureș, Romania (no. 116/14.12.2015).

2.2 GENOTYPING

Two milliliters of fresh peripheral blood were collected into EDTA vacutainers from both patients and control group and used for rapid purification of genomic DNA by using Quick-gDNA MiniPrep kit (Zymo Research, USA).

Genotyping of the *GSTT1* and *GSTM1* polymorphisms were conducted in the Department of Genetics of our institution by using the multiplex polymerase chain reaction (PCR) method as previously reported by Sharma A. et al. [15]. For the *GSTP1* polymorphism genotyping was carried out by the polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP) described by Hohaus S. et al. [13].

2.3 STATISTICAL ANALYSIS

The statistical analysis was performed with the GraphPad InStat software (GraphPad, San Diego, CA, USA). All statistical tests were two-sided and differences were considered significant when the *p*-value was less than 0.05. The strength of the association of the *GSTT1*, *GSTM1* and *GSTP1* genotype polymorphisms between patients with NHL and controls was examined with calculated odds ratios (OR) and their 95% confidence interval (95% CI).

3 RESULTS

In NHL patients, the frequencies of the *GSTT1* null and *GSTM1* null genotypes were 26.83% and 51.22%, respectively. We observed increased frequencies of the *GSTM1* null genotype in the patients (51.22%) with NHL and in controls (56.58%). An

association was found between *GSTT1* null genotype and risk of NHL (p = 0.4454; OR = 1.273, 95% CI = 0.6846-2.366) but was not statistically significant. Also, an association was found between *GSTT1* and *GSTM1* double null genotype and risk of NHL (p = 0.836; OR = 1.15, 95% CI = 0.508-2.61). There was a higher percentage of females than males.

Regarding the *GSTP1 Ile105Val* polymorphism, Ile/Ile genotype was more frequent in patients and controls (71.95% and 65.13%, respectively) and Ile/Val frequency in NHL patients was 25.61% and in controls 30.92% while Val/Val genotype was less frequent in both groups.

Table 1. shows the frequencies of the *GSTT1*, *GSTM1,* and *GSTP1* genotypes. The frequency distribution of the *GSTM1, GSTT1,* and *GSTP1* genotypes did not differ between NHL patients and controls.

There was a decreased risk of NHL for *GSTP1* Ile/Val + Val/Val genotypes between patients and controls (p = 0.2879, OR = 0.279, 95% CI = 0.4052-1.309) without statistical significance.

Table 1. Distribution of GSTT1, GSTM1 and GSTP1 genotypes in NHL cases and controls

	NHL no (%)	**Controls no (%)**	***p* value**	**OR (95% CI)**
GSTT1				
present	60 (73.17)	118 (77.63)	Ref.	Ref.
null	22 (26.83)	34 (22.37)	0.4454	1.273 (0.6846-2.366)
GSTM1				
present	40 (48.78)	66 (43.42)	Ref.	Ref.
null	42 (51.22)	86 (56.58)	0.432	0.8058 (0.4701-1.381)
GSTP1 Ile105Val				
Ile/Ile	59 (71.95)	99 (65.13)	Ref.	Ref.
Ile/Val	21 (25.61)	47 (30.92)	0.3517	0.7497 (0.4085-1.376)
Val/Val	2 (2.44)	6 (3.95)	0.7116	0.5593 (0.1093-2.863)
Ile/Val + Val/Val	23 (28.05)	53 (34.84)	0.2879	0.279 (0.4052-1.309)

Ref. – Reference, no – number

Moreover, we examined the association between the combined GSTs genotypes (null GSTT1, null GSTM1 and variant genotype of *GSTP1 Ile105Val)* and NHL and there was no increased risk of developing NHL (p > 0.05).

The distribution of the *GSTT1*, *GSTM1* and *GSTP1* gene polymorphisms in NHL patients stratified by gender, age, Ann Arbor stage, LDH level, ECOG performance status, treatment outcome and survival rate are shown in Table 2.

We did not detect significant differences between demographic characteristics of the patients and *GSTT1*, *GSTM1* and *GSTP1* genotypes (p > 0.05).

In the case of Ann Arbor stage according to the NHL group, it was not associated with variant *GSTT1, GSTM1* and *GSTP1* polymorphisms (p = 0.2476, p = 1.000, and p = 0.7816, respectively). Also, we investigated if there is an association between performance status (ECOG) and the risk group and we found a nearly significant difference (p = 0.0517) for *GSTT1* null genotype.

However, we observed that the frequencies of the NHL patients were similar according to the clinical stage and ECOG status, namely 14 and 13 for the *GSTT1* null genotype and 4 and 4 for the *GSTM1* null genotype. Similar results were found in the case of Ile/Val and Val/Val genotypes for *GSTP1 Ile105Val* gene polymorphism.

No differences were found regarding the LDH level (>190 UI/L) in NHL group and *GST* gene polymorphisms. Also, no association was observed regarding patients' treatment outcome (resistant, partial remission and complete remission to treatment) and *GSTT1, GSTM1* and *GSTP1* genotypes (p>0.05).

Furthermore, we analyzed how the *GSTT1*, *GSTM1,* and *GSTP1* genotypes influenced the outcome in patients group. Our data revealed that the lowest mean time survival was 41.935 months in the *GSTM1* null genotype comparing to the 60.336 months in the case of *GSTT1* null genotype and 17 months in Val/Val variant of the *GSTP1 Ile105Val* polymorphism. The *GSTT1* null and *GSTM1* null genotypes had no significant association according to 5-year survival (p = 0.0683; OR = 0.2688, 95% CI = 0.07287 – 0.9913 and p = 1.0000; OR = 1.217, 95% IC = 0.1162 – 12.759, respectively). In case of the *GSTP1* Ile/Val

genotype a positive association was found in 5-year survival (p = 0.2289; OR = 2.100, 95% IC = 0.6717-6.566) but no statistical significant.

In addition, we investigated the frequency of histological subtypes of NHL patients. Of the 82 cases, 35 had diffuse large B-cell lymphoma (DLBCL), 12 had follicular lymphoma (FL), 16 had marginal zone B-cell lymphoma (MZBL), 7 cases had T-cell lymphoma (T-cell), mucosa-associated lymphoid tissue lymphoma (MALT) was found in 2 cases, and 10 cases of primary lymphoma. Taking into account the increased frequency of the DLBCL, we tested whether there is any association between investigated gene polymorphisms and risk of developing DLBCL. Moreover, lack of associations was found between *GST* gene polymorphisms and DLBCL patients (p>0.05, for all genotypes).

Table 2. Patients' demographic and clinical characteristics of the GSTs genotypes

	***GSTT1* no. (%)**			***GSTM1* no. (%)**			***GSP1 Ile105Val* no. (%)**		
	present	**null**	***p***	**present**	**null**	***p***	**Ile/Ile**	**Ile/Val + Val/Val**	***p***
Gender									
female	19 (61.29)	19 (65.52)	Ref.	7 (77.78)	7 (53.85)	Ref.	20 (33.90)	10 (43.48)	Ref.
male	12 (38.71)	10 (34.48)	0.793	2 (22.22)	6 (46.15)	0.3802	39 (66.100)	13 (56.52)	0.4522
Age									
< 60 years	17 (54.84)	14 (48.28)	Ref.	5 (55.56)	4 (30.77)	Ref.	27 (45.76)	13 (56.52)	Ref.
> 60 years	14 (45.16)	15 (51.72)	0.8027	4 (44.44)	9 (69.23)	0.3842	32 (54.24)	10 (43.48)	0.4637
Ann Arbor stage									
I-II	14 (58.33)	9 (39.13)	Ref.	3 (50.00)	6 (60.00)	Ref.	22 (48.89)	10 (55.56)	Ref.
III-IV	10 (41.67)	14 (60.87)	0.2476	3 (50.00)	4 (40.00)	1	23 (51.11)	8 (44.44)	0.7816
LDH									
<190UI	4 (12.50)	7 (25.00)	Ref.	1 (11.11)	2 (15.38)	Ref.	9 (15.25)	5 (21.74)	Ref.
>190UI	28 (87.50)	21 (75.00)	0.3176	8 (88.89)	11 (84.62)	1	50 (84.75)	18 (78.26)	0.5215
ECOG performance status									
1,2	25 (80.65)	16 (55.17)	Ref.	7 (77.78)	9 (69.23)	Ref.	40 (67.80)	17 (73.91)	Ref.
3,4	6 (19.35)	13 (44.83)	0.0517	2 (22.22)	4 (30.77)	1	19 (32.20)	6 (26.09)	0.7901
Treatment outcome									
resistant	16 (55.17)	10 (45.46)	0.6892	6 (66.67)	1 (12.50)	0.0833	3 (5.36)	2 (8.70)	0.1515
partial remission	9 (31.04)	8 (36.36)	1	3 (33.33)	5 (62.50)	1	46 (82.14)	21 (91.30)	0.1808
complete remission	4 (13.79)	4 (18.18)	Ref.	0 (0.00)	2 (25.00)	Ref.	7 (12.50)	0 (0.00)	Ref.
Survival, 5-years									
>5-years	4 (14.81)	11 (61.11)	Ref.	1 (61.11)	2 (20.00)	Ref.	42 (80.77)	14 (66.67)	Ref.
<5-years	23 (85.19)	17 (38.89)	0.0683	7 (38.89)	8 (80.00)	1	10 (19.23)	7 (33.33)	0.2289

Ref. – Reference, no – number

4 DISCUSSIONS

The current case-control study is first to evaluate a possible association of the *GSTT1, GSTM1* and *GSTP1* gene polymorphisms with risk of NHL, conducted in a Romanian population from Transylvania region.

Considering that GSTs have a significant role in the regulation antioxidant defense mechanism and in the mediation of xenobiotics and several carcinogens, we hypothesized that genetic polymorphisms in genes encoding glutathione S-transferase T1, M1, and P1 previously reported for other studies may modulate the risk of developing several types of cancer [5], [6], [7], [8], [16] including malignant lymphomas.

The recent findings showed that the *GSTT1, GSTM1* and *GSTP1* gene polymorphisms have been involved in carcinogenesis, but the results remain inconsistent. For example, in a meta-analysis performed by Fang J. et al [6] in 2013 on 506 case-control studies, the *GSTT1* null and *GSTM1* null genotypes were associated with an increased risk of cancer in Caucasians and Asians (*GSTM1* had an OR = 1.17; 95%CI = 1.14-1.21 and *GSTT1* had an OR = 1.16; 95%CI = 1.11-1.21, respectively), but no association in Africans regarding *GSTM1* gene polymorphism. Some of the cancer types analyzed were

prostate cancer [16], colorectal cancer [17], breast cancer [6], bladder cancer [18], lung cancer [19], ALL [20] and gastric cancer [21]. Another study conducted by Lourenço G.J. et al. [22] showed that *GSTP1* polymorphism had an increased risk of HL.

In our study, we did not find an association between *GSTT1* null genotype and risk of NHL (p = 0.4454; OR = 0.1273, 95% CI = 0.6846-2.366). Similar findings were reported by Li Y. et al. [7] in a female study, but there was an association of the *GSTs*, *NATs* and cytochrome *P450s* polymorphisms in the relationship between alcohol consumption and risk of DLBCL. No association was observed between *GSTs* polymorphisms and tobacco smoking in a population of NHL (1,115 females) [23], but significant change was found for DLBCL.

Other studies that revealed no association of the *GSTT1* null and *GSTM1* null genotypes and risk of acute lymphoblastic leukemia (ALL) were described in Turkish children [4] and in an Argentinian population [20]. In a meta-analysis from 2015, Xu LY et al. [24] found a significant association between *GSTT1* null genotype and childhood ALL in Asians and no association in Caucasians and Africans.

In contrast, several studies reported a significant association of the *GSTT1* null genotype and NHL risk. For instance, Bin Q. et al. [8] suggested that *GSTT1* deletion may significantly increase the risk of NHL (p = 0.02, OR = 2.75, 95% CI = 1.17-6.45) and the same effect remains in females, but no association in HL. According to Ruiz-Cosano J. et al. [9] *GSTT1* null genotype had a role in the development of lymphomas in relation to smoking and occupational exposures.

In the case of *GSTM1* null genotype, we observed a decreased risk of NHL in our cohort without statistical significance. In a meta-analysis conducted by Bin Q. et al. [8] and performed on 1626 patients and 2892 controls with malignant lymphomas, the *GSTM1* null, and *GSTP1* null genotypes were unrelated to lymphoma risk, but the double null *GSTT1* and *GSTM1* genotype was significant positive associated with risk of lymphoma. In another study described by Wu M. et al. [25] in 2004 the *GSTM1*, *GSTP1*, *IL-1beta* and *IL-1RN* genes did not differ between MALT lymphoma patients and controls in a Chinese population. In the study of Ruiz-Cosano J. et al. [9] no significant association of the *GSTM1* null genotype was found between patients and controls in malignant lymphomas.

An increased frequencies of the *GSTT1* null, *GSTM1* null, and double null genotypes in DLBCL (47.9, 52.1, and 23.9 % respectively) was reported by Abdel Rahman et al. in 2012 [26] in Egypt.

Moreover, we found a decreased risk of NHL in our cohort with regard to *GSTP1* Ile/Val and *GSTP1* Val/Val genotypes, but no significant (p = 0.3517 and p = 0.7116, respectively). Our results are in line with a study reported by Chiu et al. [27] who found a low risk of DLBCL for Val/Val variant genotype (OR = 0.2, 95% CI = 0.1-0.96) and no significant excessive risk for MZBL and other B-cell lymphomas. An association with a decreased risk of NHL of the *GSTP1* polymorphism was demonstrated in Korea by Kim H.N. et al. [28] in the large case-control study (713 cases and 1700 controls). In comparison to our findings, Li Y. et al. [7] showed a 2-fold increased risk of DLBCL in females regarding alcohol consumption with *GSTP1* Ile/Val and Val/Val genotypes. Similar results were observed in non-smokers with DLBCL by Kilfoy B.A. et al. [23].

We analyzed possible associations between combined *GST*s genotypes and patients' clinical characteristics, including histological subtype, stage of disease, performance status (ECOG), and LDH level. There were no differences between patients' clinical characteristics and combined *GTSs* genotypes (p>0.05, for all comparisons).

No particular association with treatment outcome was observed for the investigated *GSTs* genotypes. In contradiction, Cho H. et al. [29] reported that *GSTT1* deletion may significantly increase the risk of drug toxicity after combined chemotherapy in Korean patients with DLBCL. Similar findings were found by Yri O. et al. [10] in 2013, and in addition *GSTM1* gene polymorphism was associated with an inferior outcome in DLBCL patients with the low prognostic score (p=0.004).

The association between *GSTs* genotypes and overall survival was not significant (p>0.05), therefore, 5-year survival was not influenced by them. However, Hohaus S. et al. [30] and Han X. et al. [31] reported that *GSTT1* null and *GSTP1* genotypes were associated with worse FL survival. The same decreased event-free survival was also described by Cho H. et al. [29].

In addition, we determined the distribution histological subtypes of the NHL patients. We found that DLBCL, MZBL, and FL were most frequent in our patients and there were no differences regarding *GSTs* genotypes. Our findings, of no significant association between *GSTs* genotypes and histological subtypes of the NHL, are not consistent with previous reports [7, 11, 23, 25, 32-33]. [7] [11] [23] [25] [32] [33]

Also, we analyzed the association between the combined *GSTs* genotypes (null *GSTT1*, null *GSTM1* and variant genotype of *GSTP1 Ile105Val)* and NHL and there was no increased risk of developing NHL in our study (p > 0.05, for all comparisons). Similar results with no association between *GST* variant genotypes separately or in combination were described in Turkish

children with ALL [4]. There are no previously reported studies regarding any association between combined variants of the *GSTT1, GSTM1* and *GSTP1* gene polymorphisms and risk of NHL.

According to the literature, there is only one study which investigates the association between ECOG performance status and *GSTT1*, *GSTM1* and *GSTP1* genotypes in NHL patients. Similar to our results, Sarmanová J. et al. [5] found no association between *GSTs* studied genotypes and clinical stage, performance status in a case-control study consisted of 219 patients with HL and NHL.

However, we presume that our relatively small group of patients could explain some of the discrepancies between our results and those of previous studies. The lack of environmental exposure data is an important limitation of our study, therefore we want to consider these risk factors for future studies.

5 CONCLUSIONS

In summary, the *GSTT1, GSTM1* and *GSTP1* gene polymorphisms were more frequent in DLBCL and our findings have not revealed associations between the *GSTs* genotypes and risk of NHL.

Therefore, our research suggests that *GSTT1, GSTM1* and *GSTP1* genotypes do not contribute to the risk of developing NHL.

Further investigations are required to explore the association between *GSTs* polymorphisms and risk of NHL and to a better understanding, the role of the detoxification enzymes in the xenobiotic metabolism.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

[1] J. Ferlay , I. Soerjomataram, M. Ervik , R. Dikshit, S. Eser, C. Mathers , M. Rebelo , D. M. Parkin , D. Forman and F. Bray, "GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]," Lyon, France: International Agency for Research on Cancer, 2013. [Online]. Available: http://globocan.iarc.fr (August 2, 2016)

[2] I. Kerridge, L. Lincz, F. Scorgie, D. Hickey , N. Granter and A. Spencer , "Association between xenobiotic gene polymorphisms and non-Hodgkin's lymphoma risk," *British Journal of Haematology,* vol. 118, no. 2, p. 477–481, 2002.

[3] A. Parkinson, "Biotransformation of Xenobiotics," 2013. [Online]. Available: http://farmasi.unud.ac.id/ind/wp-content/uploads/Bio-Transformation-of-Xenobiotics.pdf (August 2, 2016)

[4] M. Guven, S. Unal, D. Erhan, N. Ozdemir, S. Baris , T. Celkan , M. Bostancı and B. Batar , "Role of glutathione S-transferase M1, T1 and P1 gene polymorphisms in childhood acute lymphoblastic leukemia susceptibility in a Turkish population," *Meta Gene,* vol. 5, p. 115–119, 2015.

[5] J. Sarmanová, K. Benesová, I. Gut, V. Nedelcheva-Kristensen, L. Tynková and P. Soucek , "Genetic polymorphisms of biotransformation enzymes in patients with Hodgkin's and non-Hodgkin's lymphomas," *Human Molecular Genetics,* vol. 10, no. 12, pp. 1265-1273, 2001.

[6] J. Fang, S. Wang, S. Zhang, S. Su, Z. Song, Y. Deng, H. Cui , H. Wang , Y. Zhang , J. Qian , J. Gu , B. Liu, P. Li , R. Zhang , X. Liu and Z. Wang, "Association of the Glutathione S-Transferase M1, T1 Polymorphisms with Cancer: Evidence from a Meta-Analysis," *Public Library of Science one,* vol. 8, no. 11, p. e78707, 2013.

[7] Y. Li, T. Zheng, B. A. Kilfoy, Q. Lan, S. Zahm, T. Holford, P. Zhao, M. Dai, B. Leaderer, N. Rothman and Y. Zhang, "Genetic polymorphisms in cytochrome P450s, GSTs, NATs, alcohol consumption and risk of Non-Hodgkin lymphoma," *American Journal of Hematology,* vol. 85, no. 3, p. 213–215, 2010.

[8] Q. Bin and J. Luo , "Role of polymorphisms of GSTM1, GSTT1 and GSTP1 Ile105Val in Hodgkin and non-Hodgkin lymphoma risk: a Human Genome Epidemiology (HuGE) review," *Leukemia & lymphoma,* vol. 54, no. 1, pp. 14-20, 2013.

[9] J. Ruiz-Cosano , P. Conesa-Zamora , R. González-Conejero , E. Pérez-Ceballos, A. Martínez-Francés , V. Vicente and M. Pérez-Guillermo , "Role of GSTT1 and M1 null genotypes as risk factors for B-cell lymphoma: influence of geographical factors and occupational exposure.," *Molecular Carcinogenesis,* vol. 51, no. 6, pp. 508-513, 2012.

[10] O. Yri , P. Ekstrøm , V. Hilden , G. Gaudernack, K. Liestøl , E. B. Smeland and H. Holte , "Influence of polymorphisms in genes encoding immunoregulatory proteins and metabolizing enzymes on susceptibility and outcome in patients with diffuse large B-cell lymphoma treated with rituximab.," *Leukemia & lymphoma.,* vol. 54, no. 10, pp. 2205-2214, 2013.

[11] F. Yang, J. Xiong, X. Jia, Z. Gu, J. Shi, Y. Zhao, J. Li, S. Chen and W. Zhao, "GSTT1 Deletion Is Related to Polycyclic Aromatic Hydrocarbons-Induced DNA Damage and Lymphoma Progression," *Public Library of Science One,* vol. 9, no. 2, p. e89302, 2014.

[12] M. A. Alshagga, N. Mohamed , A. Nazrun Suhid , I. Abdel Aziz Ibrahim and S. Zulkifli Syed Zakaria , "Frequencies of glutathione s-transferase (GSTM1, GSTM3 AND GSTT1) polymorphisms in a Malaysian population," *Archives of Medical Science,* vol. 4, pp. 572-578, 2011.

[13] S. Hohaus, A. Di Ruscio, A. Di Febo, G. Massini , F. D'Alo' , F. Guidi , G. Mansueto , M. Voso and G. Leone , "Glutathione S-transferase P1 Genotype and Prognosis in Hodgkin's Lymphoma," *Clinical Cancer Research,* vol. 11, no. 6, pp. 2175-2179, 2005.

[14] E. Jaffe, N. Harris, H. Stein and J. Vardiman , WHO/IARCS Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, 3 ed., vol. 3, Lyon: ARC Press, 2001.

[15] A. Sharma, A. Pandey, S. Sardana, A. Sehgal and J. Sharma , "Genetic Polymorphisms of GSTM1 and GSTT1 Genes in Delhi and Comparison with other Indian and Global Populations," *Asian Pacific Journal Of Cancer Prevention,* vol. 13, no. 11, pp. 5647-5652, 2012.

[16] N. A. Lavender, M. L. Benford, T. T. VanCleave, G. N. Brock , R. A. Kittles, J. H. Moore , D. W. Hein and . L. R. Kidd, "Examination of polymorphic glutathione S-transferase (GST) genes, tobacco smoking and prostate cancer risk among Men of African Descent: A case-control study," *BMC Cancer,* vol. 9, p. 397, 2009.

[17] J. Li, W. Xu, F. Liu, S. Huang and M. He , "GSTM1 polymorphism contribute to colorectal cancer in Asian populations: a prospective meta-analysis," *Scientific Reports,* vol. 5, 2015.

[18] K. Wu, X. Wang, Z. Xie, Z. Liu and Y. Lu , "Glutathione S-transferase P1 gene polymorphism and bladder cancer susceptibility: an updated analysis," *Molecular Biology Reports,* vol. 40, no. 1, pp. 687-695, 2013.

[19] Y. Wang, M. R. Spitz, M. B. Schabath, F. Ali-Osman, H. Mata and X. Wuc, "Association between glutathione S-transferase p1 polymorphisms and lung cancer risk in Caucasians: a case-control study," *Lung Cancer,* vol. 40, no. 1, pp. 25-32, 2003.

[20] N. Weich , M. Nuñez , G. Galimberti , G. Elena , S. Acevedo , I. Larripa and A. Fundia , "Polymorphic variants of GSTM1, GSTT1, and GSTP1 genes in childhood acute leukemias: A preliminary study in Argentina," *Hematology,* vol. 20, no. 9, pp. 511-516, 2015.

[21] Y. Zhao , X. Deng , G. Song and Z. Liu, "The GSTM1 Null Genotype Increased Risk of Gastric Cancer: A Meta-Analysis Based on 46 Studies," *Public Library of Science One,* vol. 8, no. 11, p. e81403, 2013.

[22] G. J. Lourenço, I. A. Néri, V. C. Sforni, R. Kameo, I. Lorand-Metze and C. S. Lima, "Polymorphisms of glutathione S-transferase Mu 1, glutathione S-transferase theta 1 and glutathione S-transferase Pi 1 genes in Hodgkin's lymphoma susceptibility and progression," *Leukemia & Lymphoma,* vol. 50, no. 6, pp. 1005-1009, 2009.

[23] B. A. Kilfoy, T. Zheng, Q. Lan, X. Han, Q. Qin, N. Rothman, T. Holford and Y. Zhang, "Genetic polymorphisms in glutathione S-transferases and cytochrome P450s, tobacco smoking, and risk of non-Hodgkin lymphoma," *American Journal of Hematology,* vol. 84, no. 5, p. 279–282, 2009.

[24] L. Xu and L. Cao, "GSTT1 genetic polymorphism and susceptibility to childhood acute lymphoblastic leukemia: a meta-analysis," *Tumour Biology,* vol. 35, no. 2, pp. 1433-1437, 2015.

[25] M. Wu , C. Shun , S. Huang , A. Cheng , L. Chen and J. Lin, "Effect of interleukin-1beta and glutathione S-transferase genotypes on the development of gastric mucosa-associated lymphoid tissue lymphoma.," *Haematologica.,* vol. 89, no. 8, pp. 1015-1017, 2004.

[26] H. Abdel Rahman , M. Khorshied , H. Elazzamy and O. Khorshid , "The link between genetic polymorphism of glutathione-S-transferases, GSTM1, and GSTT1 and diffuse large B-cell lymphoma in Egypt.," *Journal of cancer research and clinical oncology,* vol. 138, no. 8, pp. 1363-1368, 2012.

[27] B. C.-H. Chiu, C. Kolar, S. M. Gapstur, T. Lawson, J. R. Anderson and D. D. Weisenburger , "Association of NAT and GST polymorphisms with non-Hodgkin's lymphoma: a population-based case–control study," *British Journal of Haematology,* vol. 128, p. 610–615, 2005.

[28] H. N. Kim, N. Y. Kim, L. Yu, Y. Kim, I. Lee, D. Yang, J. Lee, M. Shin, K. Park, J. Choi and H. Kim, "Polymorphisms of drug-metabolizing genes and risk of non-Hodgkin lymphoma," *American Journal of Hematology,* vol. 84, p. 821–825, 2009.

[29] H. Cho , H. Eom , H. Kim , I. Kim, G. W. Lee and S. Kong, "Glutathione-S-transferase genotypes influence the risk of chemotherapy-related toxicities and prognosis in Korean patients with diffuse large B-cell lymphoma.," *Cancer genetics and cytogenetics.,* vol. 198, no. 1, pp. 40-46, 2010.

[30] S. Hohaus , G. Mansueto , G. Massini, F. D'Alo, M. Giachelia , M. Martini, L. Larocca , M. Voso and G. Leone, "Glutathione-S-transferase genotypes influence prognosis in follicular non-Hodgkin's Lymphoma.," *Leukemia & lymphoma.,* vol. 48, no. 3, pp. 564-569, 2007.

[31] X. Han, T. Zheng, F. M. Foss, Q. Lan, T. R. Holford , N. Rothman , S. Ma and Y. Zhang , "Genetic polymorphisms in the metabolic pathway and non-Hodgkin lymphoma survival," *American Journal of Hematology,* vol. 85, no. 1, p. 51–56, 2010.

[32] F. Al-Dayel, M. Al-Rasheed , M. Ibrahim, R. Bu , P. Bavi , J. Abubaker , N. Al-Jomah , G. Mohamed, A. Moorji , S. Uddin , A. Siraj and K. Al-Kuraya, "Polymorphisms of drug-metabolizing enzymes CYP1A1, GSTT and GSTP contribute to the development of diffuse large B-cell lymphoma risk in the Saudi Arabian population.," *Leukemia & lymphoma.,* vol. 49, no. 1, pp. 122-129, 2008.

[33] S. Rollinson, A. P. Levene, F. K. Mensah, P. L. Roddam, J. M. Allan, T. C. Diss, E. Roman, A. Jack, k. MacLennan, M. F. Dixon and G. J. Morgan, "Gastric marginal zone lymphoma is associated with polymorphisms in genes involved in inflammatory response and antioxidative capacity," *Blood,* vol. 102, pp. 1007-1011, 2003.