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Role of glutathione S-transferase M1, T1 and P1 gene polymorphisms in childhood acute lymphoblastic leukemia susceptibility in a Turkish population

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ABSTRACT

The variations between different individuals in the xenobiotic metabolizing enzymes' activity were shown to modify susceptibility to childhood acute lymphoblastic leukemia (ALL). Polymorphisms associated with genes coding for the glutathione S-transferase (GST) enzyme were known to affect the metabolism of different carcinogens. The aim of this study was to evaluate the influence of the *GSTM1* and *GSTT1* deletion polymorphisms, and the *GSTP1* Ile105Val single nucleotide polymorphism (SNP) on the susceptibility to childhood ALL. The study was conducted in 95 children with ALL and 190 healthy control subjects from the Turkish population. The data revealed no difference in the prevalence of the *GSTM1* and *GSTT1* null genotypes between the childhood ALL patients and the controls. No association was found between *GSTP1* Ile105Val variants and the susceptibility to childhood ALL, separately or in combination. Our findings suggested that the status of heritable *GST* polymorphism might not influence the risk of developing childhood ALL. Studies with a larger sample size are needed to evaluate and confirm the validity of our results.

Introduction

Acute lymphoblastic leukemia (ALL) is one of the most prevalent types of childhood cancers, accounting for about 30% of all childhood cancer cases (Pui, 2000). Although significant improvements in both the diagnosis and treatment of ALL have been made over the past decades, the etiology of ALL has not been fully clarified (López-Terrada, 2006). Both genetic and environmental factors are suspected to contribute to the development of pediatric acute leukemia (Francis et al., 2014). DNA damage in the hematopoietic precursor cells is essential for the development of leukemia, and the body has developed a series of mechanisms to prevent and repair the DNA damage (Boehrer et al., 2009). One mechanism which can result in DNA damage is mediated by reactive oxygen species (ROS) generated by environmentally encountered carcinogens or endogenously as a result of oxidative mechanism (Udensi and Tchounwou, 2014). The carcinogenic effect of xenobiotics is influenced by a series of genes coding enzymes involved in the conjugation/detoxification of these compounds. The enzymes involved in the metabolism of these carcinogens have thus received a reasonable level of attention (Croom, 2012).

Genetic polymorphisms in the carcinogen-metabolizing genes are extremely common and may contribute to the risk of developing different cancers, including hematologic malignancies. These polymorphisms could explain the differences between the individuals' ability to metabolize different chemical agents (Krajinovic et al., 2002a). The glutathione-S-transferase (GST) genes are crucially involved in the detoxification of a variety of exogenous carcinogens. Furthermore, GSTs play a critical role by protecting against the ROS caused by the breakdown of the peroxidased lipids and they are capable of oxidizing DNA and generating damage (Singh and Michael, 2009). It is believed that the polymorphisms in the *GST* genes may play a role in the susceptibility to leukemogenesis (Rollinson et al., 2000). *GST* polymorphisms may also affect the treatment of leukemia as the GSTs play an important role in detoxifying the active metabolites of cytotoxic chemotherapeutic agents used to kill tumor cells (Takanashi et al., 2003).

GSTs are crucially involved in phase II metabolism, catalyzing the conjugation of soluble glutathione with reactive intermediates

Abbreviations: ALL, acute lymphoblastic leukemia; GST, glutathione S-transferase; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; ROS, reactive oxygen species; FAB, French–American–British; SD, mean and standard deviation; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg Equilibrium; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma.

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produced during the bioactivation of procarcinogens and detoxification of carcinogens (Board and Menon, 2013). The GST isoenzymes expressed in human tissues comprise the alpha, mu, pi, theta, kappa, sigma, zeta and omega gene families (Hayes et al., 2005). Of these classes of GSTs, five (*GSTM1*, *GSTM3*, *GSTT1*, *GSTP1* and *GSTZ1*) have been shown to be poly morphologically distributed (Board et al., 1990). Polymorphisms identified in *GSTM1* are *GSTM1*0*, *GSTM1*A* and *GSTM1*B*. When *GSTM1*0* is deleted, homozygotes (*GSTM1* null genotype) express no protein. *GSTM1*A* and *GSTM1*B* differ by a single base, and the catalytic effectiveness of the enzymes encoded by these alleles is similar. GSTT1 is represented by two alleles: a functional or wild allele (*GSTT1*1*), and a nonfunctional or null allele (*GSTT1*0*). Studies have shown that the *GSTT1*0* allele corresponds to total or partial deletion of the gene, causing a deficiency in its enzymatic activity (Pemble et al., 1994). The glutathione S-transferase pi gene (*GSTP1*) plays a central role in the inactivation of toxic and carcinogenic electrophiles. The 1578A > G substitution in *GSTP1* creates the *Ile105Val* polymorphism that leads to expression of an enzyme with reduced activity (Zimniak et al., 1994).

In the current study, we investigated the distribution of the *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms in a sample of Turkish children with ALL and controls to explore the possible association between different *GST* variants and the incidence of childhood ALL.

Materials and methods

Subjects

Childhood ALL patients were diagnosed in the Department of Pediatric Hematology–Oncology of Cerrahpasa Medical Faculty of Istanbul University. The patients comprised 49 males and 46 females. The age at diagnosis ranged between 1 to 17 years (mean age, 6.08 ± 3.83 years). The diagnosis of ALL was made by using French–American–British (FAB) diagnostic criteria, which was performed after conventional cytochemical and surface-marker analysis. The people in the control group (n = 190) were randomly selected from healthy children during the same time period as the samples for the cases were collected. Control subjects with any hematologic or other malignancy were excluded. There were 91 male and 99 female children in the healthy control group. They were between the ages of 1 and 18 years (mean age, 7.24 ± 4.75 years). All participating subjects were of Turkish nationality. Informed consent was obtained from all the participating individuals and/or their parents. The study was conducted with the approval of the ethical committee from our institution and in keeping with the guidelines of the Declaration of Helsinki.

Blood samples and DNA isolation

We collected 3 ml of venous blood from ALL patients, who were in remission, and children in the control group. Immediately after collection, the whole blood samples were stored in aliquots at −20 °C until use. Genomic DNA was extracted from leukocytes using Roche DNA purification kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

Analysis of GSTM1 and GSTT1 polymorphisms

The *GSTM1* and *GSTT1* genetic polymorphisms were evaluated using the multiplex polymerase chain reaction (PCR) technique as described previously (Arand et al., 1996). Primers for GSTM1 were 5′-GAACTCCC TGAAAAGCTAAAGC-3′ and 5′-GTTGGGC TCAAATATACGGTGG-3′, and those for GSTT1 were 5′-TTCCTTACTGGTCCTCA CATCTC-3′ and 5′-TCACCGGATCATGGCCAGCA-3′. The β-globin locus was used as an internal control to avoid false negative readings. Primers for β-globin were 5′-CAACTTCATCCACGTTCACC-3′ and 5′-GAAGAGCCAAGGACAGGTAC-3′. PCR was carried out in a total volume of 25 μl containing 10 pmol/l of each primer, 2.5 mmol/l of $MgCl_2$, 0.2 mmol/l of each dNTP, 1 U of Taq polymerase and 100 ng of genomic DNA. Amplification was performed with initial denaturation at 94 °C for 5 min, followed by 30 cycles at 94 °C for 1 min, 64 °C for 1 min and 72 °C for 1 min, and a final extension at 72 °C for 7 min. The amplified products were identified by electrophoresis in a 2% agarose gel and stained with 0.5 mg/ml ethidium bromide. The product lengths were 215 bp, 480 bp, and 268 bp for *GSTM1*, *GSTT1* and *β-globin*, respectively. The absence of PCR product for *GSTM1* or *GSTT1* in the presence of the *β-globin* band was indicative of a null genotype for *GSTM1* or *GSTT1*. Individuals with one or two copies of the relevant gene were classified as the "present" genotype and those with homozygous deletions as the "null" genotype. Experiments were repeated at least twice using both of the standard genotyping protocols.

Analysis of GSTP1 polymorphism

The genotyping of polymorphisms of *GSTP1* was performed by using real-time PCR with a Light Cycler instrument (Roche Applied Science, Mannheim, Germany). All real-time PCR reactions were performed in a total volume of 20 μl, which contained 4 mM $MgCl_2$, 0.5 pmol of each hybridization probe, 10 pmol of each PCR primer, 2 μl of FastStart DNA Master HybProbe (Roche Diagnostics, GmbH), and 100 ng genomic DNA. Both the PCR primers (F:5′-ACCCCAGGGCTCTATGGGAA-3′ and R:5′-TGAGGGCACAAGAAGCC CCT-3′) and hybridization probes (5′-LCR640-TGTGAGCATCTGCACCAGGGTTGGGCG-3′ and 5′-TGCAAATACA TCTCCCTCATCTACACCAAC-FL-3′) were synthesized by TIB MOLBIOL (Berlin, Germany). The amplification programs for each allele were as follows: initial denaturation step at 95 °C for 3 min, followed by 45 cycles of denaturation (95 °C for 5 s), annealing (55 °C for 10 s), and extension (72 °C for 25 s). Melting curve analysis was one cycle denaturation at 95 °C for 2 min, followed by an increase in temperature from 50 to 80 °C at a slope of 0.4 °C/s. One cycle of a cooling-down step at 40 °C for 30 s followed.

Statistical analysis

Mean and standard deviations (SDs) were presented in the case of continuous variables. Differences between the means of the two continuous variables were evaluated by the Student's *t*-test. Chi-square (χ^2, two-sided) statistics were used to; compare the gender distribution, test the association between the genotypes and alleles in relation to the cases and controls, and test for the deviation of genotype distribution from Hardy–Weinberg equilibrium (HWE). p values of <0.05 were considered as statistically significant. The odds ratio (OR) and their 95% confidence interval (CI) were calculated to estimate the strength of the association in the polymorphism genotype alleles between patients and controls. The post hoc power analysis was performed by using PS Power.

Table 1
Characteristics and clinical prognostic factors of ALL cases.

Parameters	
WBC count ($\times 10^3$ mm^{-3})	9.0 (1.2–280)
Bone marrow blast cell count (%)[a]	93.0 (60–100)
Peripheral blast cell count (%)[a]	38.0 (0–100)
FAB classification, *n* (%)	
L1	75 (79)
L2	20 (21)
Immunophenotype, *n* (%)	
Common-ALL	78 (82)
Pre-B-ALL	6 (6)
T-ALL	11 (12)

WBC: white blood cell.
FAB: French–American–British.
[a] Median (range).

Table 2
Demographic data of ALL cases and controls.

	ALL cases	Controls	*p*-Value
Number	95	190	
Gender, n (%)			0.65
Male	49 (52)	91 (48)	
Female	46 (48)	99 (52)	
Age, years			
Mean ± SD	6.08 ± 3.83	7.24 ± 4.75	0.07
Range	1–17	1–18	

Results

Characteristics and clinical prognostic factors for 95 childhood ALL cases at the time of diagnosis were given in Table 1. The demographic data of ALL cases and controls were presented in Table 2. There was no statistically significant difference ($p > 0.05$) in gender and age between groups.

Table 3 showed the genotype and the allele distributions of the polymorphisms in *GST* genes for both cases and controls. No statistically significant difference was found for the genotypic distributions of the polymorphisms in the *GSTM1*, *GSTT1*, and *GSTP1* genes between ALL cases and controls. As shown in Table 3, no statistical difference in the allele frequency was detected between ALL cases and controls for *GSTP1* polymorphism (Table 3). The distribution of *GSTP1* genotypes within cases and controls was not significantly different from that under HWE ($p = 0.94$ and 0.40, respectively). As shown in Table 4, gender stratification did not result in any significant change in the risk, among males and females with respect to *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms.

Table 5 showed the frequency of combined genotypes. There was no significant statistical difference for the genotypic distribution of the polymorphisms in the *GST* genes between ALL cases and controls.

Discussion

Genetic polymorphism had been described in the enzymes involved in the metabolism of carcinogens and cancer risk. The GSTs are involved in the metabolism of many environmental carcinogens, drugs and other xenobiotics. The polymorphisms result in a lack of enzymatic activity leading to a reduced detoxification role for GSTs. Thus the polymorphisms in the G*ST* genes may be the factors contributing to the differences in leukemia and susceptibility to other cancer types (Rollinson et al., 200; Cong et al., 2014).

In this case–control study, we determined the effects of genetic polymorphisms of *GSTM1*, *GSTT1*, and *GSTP1* on the risk of childhood ALL in the Turkish population. Our data showed no significant differences in genotype frequencies between the patients with ALL and the controls for the *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms. There was no difference in the frequencies of the combined *GSTM1*, *GSTT1*, and *GSTP1* genotypes in the patients and the controls.

Several previous studies focused on the possible association between the polymorphisms of *GSTM1* and *GSTT1* genes and the risk of childhood ALL development but the results are variable. In the most recent meta-analysis, it was showed that the *GSTM1* genotype, but neither the *GSTT1* nor the *GSTP1* genotype, was associated with risk of childhood ALL (Moulik et al., 2014). Krajinovic et al. (1999) reported a statistically significant association between the presence of the null *GSTM1* genotype (64.9% in the ALL group and 51.3% in the control group) and an increased risk of childhood ALL. For the *GSTT1* gene (the null genotype, 15.9% in the ALL group and 17.2% in the control group) the authors had not detected any apparent role in the etiology of ALL (Krajinovic et al., 1999). In accordance with this study, Alves et al. (2002) found that the null *GSTM1* genotype (68.1% in the ALL group and 49% in the controls) was correlated with an increased risk of developing ALL. No statistically significant difference between the ALL patients and the healthy controls due to frequency of the *GSTT1* genotype (for the null genotype, 19.2% ALL and 25.5% in the controls) was observed (Alves et al.,2002). Similar results were obtained by Suneetha et al. for the null *GSTM1* genotype (39% ALL and 24.6% controls) and the risk of developing childhood ALL (Suneetha et al., 2008). A study from India found an association with the *GSTM1* gene deletion (40.7% ALL and 24.6% controls) and the risk of developing ALL. For the *GSTT1* gene, the null genotype (14.4% ALL and 8.5% controls) did not show statistical significance (Joseph et al., 2004). However, in contrast to these studies, Davies et al. (2002) did not find any association between the null *GSTM1* and the null *GSTT1* genotype frequencies and childhood ALL [24]. Sala et al. (2003) had shown that there was no association between genotypes of the *GSTM1* and the *GSTT1* genes with the outcome in childhood ALL. Another study from Brazil found that the null *GSTM1* and the null *GSTT1* genotype frequencies were not associated with the risk of developing childhood ALL (Canalle et al., 2004). A study on the Turkish population, performed by Aydin-Sayitoglu et al. (2006) could not find an association between the frequency of the null *GSTM1* and the null *GSTT1* genotypes (65.5% in the ALL group and 55% in the controls; 24.4% in the ALL group and 20.7% in the controls, respectively) and the risk of developing childhood ALL.

There are several studies about the role of the *GSTP1* Ala105Val polymorphism in susceptibility to risk of developing childhood ALL. In accordance with our results, Suneetha et al. (2008) found that no significant risk was associated with the *GSTP1* gene for the development of ALL. Similar results were obtained by Zheng and Honglin (2005) in childhood ALL patients. On the other hand, in contrast to these results, Krajinovic et al. (2002b) reported that there was an association between the *GSTP1* variants and increased risk of developing childhood ALL. Canalle et al. (2004) found that there was an increased risk of developing ALL associated with the carriers of the rare *GSTP1* 105Val allele.

Many studies have determined the effects of genetic polymorphisms of *GSTs* on the risk of a variety of common cancers including other hematologic malignancies such as Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), and non-Hodgkin lymphoma (NHL). There have been few studies that linked the *GST* genetic variations to the development AML. Rollinson et al. (2000) reported that there was an association between the null *GSTT1* and the null *GSTM1* genotypes and the risk of developing AML. In a meta-analysis, it was suggested that the presence of the dual null genotype *GSTM1-GSTT1* increased the risk of developing AML in both the Caucasians and the East Asians (He et al., 2014). Lemos et al. (1999) showed that there was no statistically significant relationship between the *GSTM1* gene status and the development of CLL. However, Yuille et al. (2002) reported a relationship between *GSTM1* null genotype and risk of CLL. Multiple studies reported higher risk of developing NHL associated with the null *GSTM1* genotype (Dieckvoss et al., 2002; Gra et al., 2008). Another study

Table 3
Distribution of genotype frequencies of *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms in ALL cases and controls.

Genotype	ALL Cases n (%)	Controls n (%)	*p*-Value	OR (95% CI)
GSTM1				
Present	50 (53)	91 (48)	Ref.	
Null	45 (47)	99 (52)	0.45	0.83 (0.51–1.36)
GSTT1				
Present	71 (75)	138 (73)	Ref.	
Null	24 (25)	52 (27)	0.71	0.90 (0.51–1.57)
GSTP1				
Ile/Ile	48 (51)	81 (43)	Ref.	
Ile/Val	40 (42)	95 (50)	0.19	0.71 (0.43–1.19)
Val/Val	7 (7)	14 (7)	0.73	0.84 (0.32–2.24)
Ile allele frequency	0.72	0.68	Ref.	
Val allele frequency	0.28	0.32	0.54	0.83 (0.45–1.52)

Ile: isoleucine, Val: valine.

Table 4
Distribution of genotype frequencies of *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms in ALL cases and controls stratified for sex.

Genotype	Male				Female			
	ALL	Controls	*p*	OR (95% CI)	ALL	Controls	*p*	OR (95% CI)
GSTM1								
Present	22	38	Ref.		28	53	Ref.	
Null	27	53	0.85	1.13 (0.53–2.42)	18	46	0.52	1.35 (0.62–2.92)
GSTT1								
Present	40	65	Ref.		34	73	Ref.	
Null	9	26	0.26	1.77 (0.70–4.57)	12	26	0.85	1.00 (0.42–2.41)
GSTP1								
Ile/Ile	22	30	Ref.		26	51	Ref.	
Ile/Val	21	54	0.13	1.88 (0.83–4.26)	19	41	0.93	1.10 (0.50–2.40)
Val/Val	6	7	0.95	0.85 (0.21–3.40)	1	7	0.40	0.40 (1.20–71.70)
Ile allele frequency	0.66	0.63	Ref.		0.77	0.71	Ref.	
Val allele frequency	0.34	0.37	0.76	1.15 (0.61–2.12)	0.23	0.29	0.42	1.36 (0.69–2.71)

showed that the null *GSTT*1 genotype was associated with increased risk of developing NHL (Kerridge et al., 2002).

The differences between these results on the risk of developing leukemia and the gene polymorphisms could be the result of two situations. The first is that the influences of the GSTM1, the GSTT1, and the GSTP1 genotypes on genetic susceptibility of developing leukemia vary between populations. The second is that there are different patterns of carcinogen exposure involved in leukemogenesis due to specific gene–gene and gene–environment interactions. The differences in the number of subjects studied in genetic studies also could have led to different outcomes. The null genotype with no enzymatic activity in the *GSTM1* gene was reported in 38–62% of the Caucasians and the null *GSTT1* genotype was present at a frequency of 27–73% in the Caucasian population (Magno et al., 2009). The prevalence of the *GSTP1* Val105 in Caucasians ranges from 24% to 37% (Sharma et al., 2014). We observed that the null *GSTM1* and the null *GSTT1* genotype frequencies were 52% and 27% respectively, while the *GSTP1* allelic frequency was 0.68 for the Ile allele and 0.32 for the Val allele in our control group. The results in our control population were similar to those that are found in Caucasians and the Turkish population that were found in other studies. In a recent study that was performed in the Turkish population, by Karaca et al. (2015), it was reported that the frequencies of the null genotype of the *GSTM1* and the *GSTT1 genes* were 52% and 23%, respectively, and the frequency of the Val105 allele of the *GSTP1* was 29%.

In conclusion, the results of this study indicate that the individual *GSM1*, *GSTT1*, and *GSTP1* genetic polymorphisms and a combination of polymorphisms in these genes may not play a role in the development of childhood ALL. The statistical power was 35% to detect an OR of 1.4. The main limitation of our study was the small sample size, which would reduce the statistical power to find the difference between the groups, especially when separated by gender. Therefore, further studies with larger sample size are greatly needed to confirm the association between the *GST* gene polymorphisms and the risk of developing ALL.

Table 5
Distribution of combined *GSTM1*, *GSTT1*, and *GSTP1* genotypes in ALL cases and controls.

Genotype combinations			Patients n (%)	Controls n (%)	*p*-Value	OR (95% CI)
GSTM1	GSTT1	GSTP1				
Present	Present	Ile/Ile	17 (18)	26 (14)	0.62	0.77 (0.27–2.18)
Present	Null	Ile/Ile	8 (8)	16 (8)	0.67	0.83 (0.36–1.93)
Null	Present	Ile/Ile	18 (19)	33 (18)	0.72	1.28 (0.34–4.84)
Null	Null	Ile/Ile	5 (5)	6 (3)	0.67	0.83 (0.36–1.93)
Present	Present	Ile/Val and Val/Val	18 (19)	33 (18)	0.46	0.67 (0.23–1.97)
Present	Null	Ile/Val and Val/Val	7 (8)	16 (8)	0.22	0.60 (0.26–1.36)
Null	Present	Ile/Val and Val/Val	18 (19)	46 (24)	0.19	0.44 (0.12–1.55)
Null	Null	Ile/Val and Val/Val	4 (4)	14 (7)	0.62	0.77 (0.27–2.18)

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