Erciyes Med J 2012; 34(4): 160-4 • DOI: 10.5152/etd.2012.44

Glutathione S-Transferase Z1 Gene Polymorphism in Turkish Population

ORIGINAL INVESTIGATION
ÖZGÜN ARAŞTIRMA

Türk Populasyonunda Glutatyon S-Transferaz Z1 Gen Polimorfizmi

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ABSTRACT
ÖZET

Objective: Glutathione S-Transferase zeta (GSTZ1) is a new member of glutathione S-transferase isoenzymes. There are several polymorphic regions in the GSTZ1 gene. The result of two base changes at nucleotide positions 94 and 124, GSTZ1 gene has four alleles, GSTZ1*A (A94A124), GSTZ1*B (A94G124), GSTZ1*C (G94G124) and GSTZ1*D (G94A124). The aim of the present study was to investigate the distribution of GSTZ1 gene polymorphism in the Turkish population.

Material and Methods: Eighty unrelated healthy subjects who were admitted to the hospital from the Mersin region were included in the study and DNA samples were extracted from the lymphocytes by using High Pure Template Preparation Kit. The polymorphism of GSTZ1 was performed by PCR-RFLP in Turkish population.

Results: The distributions of GSTZ1*A, GSTZ1*B, GSTZ1*C and GSTZ1*D allele frequencies are 1.2%, 20%, 76.9% and 1.9%, respectively.

Conclusion: This study presents the first results of GSTZ1 allele distributions in the Turkish population. In the present study the frequency of GSTZ1*A allele was lower than in the other populations.

Key words: Genetic polymorphism, metabolic detoxication, phase II, population

Amaç: Glutatyon S-Transferaz zeta (GSTZ1), GST izoenzimlerinin yeni bir üyesidir. GSTZ1 geninde bir çok polimorfik bölge vardır. 94 ve 124. pozisyonlardaki nükleotid değişimleri sonucu GSTZ1'in 4 alleli bulunmaktadır: GSTZ1*A (A94A124), GSTZ1*B (A94G124), GSTZ1*C (G94G124) ve GSTZ1*D (G94A124). Bu çalışmanın amacı Türk Populasyonundaki GSTZ1 gen polimorfizminin dağlımını belirlemektir.

Gereç ve Yöntemler: Mersin bölgesinden akraba olmayan 80 sağlıklı bireyin DNA'sı High Pure Template Preparation Kiti kullanılarak lenfositlerden izole edilmiştir. Türk Populasyonundaki GSTZ1 polimorfizmi PCR-RFLP yöntemi ile belirlenmiştir.

Bulgular: GSTZ1*A, GSTZ1*B, GSTZ1*C ve GSTZ1*D allel frekansları sırasasıyla %1,2; %20; %76,9 ve %1,9'dur.

Sonuç: Bu çalışmada Türk populasyonunda GSTZ1 allel dağılımını gösteren ilk sonuçlar verilmiştir. GSTZ1*A allel frekansının bu çalışmada diğer populasyonlara oranla daha düşük olduğu tespit edilmiştir.

Anahtar kelimeler: Genetik polimorfizm, metabolik detoksifikasyon, evre II, populasyon

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Submitted/Geliş Tarihi
14.08.2007

Accepted/Kabul Tarihi
12.09.2012

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Introduction

Living organisms are continuously exposed to non-nutritional foreign chemical species. These xenobiotics may interact deleteriously with an organism, causing toxic and sometimes carcinogenic effects (1). Enzymatic detoxification of these xenobiotics has been classified into two distinct phases which act in a tightly integrated manner. Phases I and II involve the conversion of a lipophilic, non-polar xenobiotic into a more water-soluble and therefore less toxic metabolite, which can in turn be eliminated more easily from the cell. Phase I is catalyzed mainly by the cytochrome P450 system. Phase II enzymes catalyze the conjugation of activated xenobiotics to an endogenous water-soluble substrate, such as reduced glutathione (GSH) (2).

The glutathione S-transferases (GSTs) are major phase II detoxification enzymes mainly found in the cytosol (3). The mammalian soluble GSTs are divided into five main classes, alpha (A), mu (M), pi (P), theta (T) and new form zeta (Z) and genetic polymorphisms have been reported for GSTM1, GSTP1, GSTT1 and GSTZ1, resulting in either decreased or altered enzyme activity and the frequency of these polymorphic genes varies among ethnic groups (4, 5).

GSTM1 and GSTT1 have null polymorphisms. The prevalence of the null genotype of *GSTM1* and *GSTT1* has been found to vary among ethnic groups (6). The *GSTM1* is absent in 35-60% of individuals (7-9), and *GSTT1* is absent in 10-65% of the human population (6, 9). The GSTP class is polymorphic and four alleles have been described at the GSTP1 locus located on chromosome 11q13: GSTP1*A, GSTP1*B, GSTP1*C and GSTP1*D (10). Two sites in the cDNA sequence are variable and are characterized by an A→G transition at nucleotide 313 (point mutation in exon 5) and a C→T transition at nucleotide 341 (point mutation in exon 6). The resulting codon variants result in amino acids Ile105 or Val105 and Ala114 or Val114. Studies on distribution of GSTP1 alleles have shown that

the I104 allele is the most frequent in human populations (11-14). For example, in a study involving Australian Aboriginals, Chinese, Australian European, and Indian subjects, Harris et al. (14) have reported that the frequency of the I104 allele varies between 0.66 and 0.89, whereas the frequency of the V104 allele ranges from 0.11 to 0.34 (11-13).

A polymorphic variant of the GSTZ1 gene was discovered by Blackburn et al. (15) in 2000 and this is characterized by base changes from A to G at nucleotides 94 and 124 of the coding region of the gene. Two base changes at nucleotide positions 94 and 124 result in amino acid alterations from lysine to glutamic acid (Lys-32Glu, rs.7975) and from arginine to glycine (Arg42Gly, rs.7972), respectively. Hence, *GSTZ1* has four alleles, *GSTZ1*A* (A94A124), *GSTZ1*B* (A94G124), *GSTZ1*C* (G94G124) and *GSTZ1*D* (G94A124). Some allelic variants are known to affect the activities of the resultant GSTZ1 enzyme for different substrates, particularly dichloroacetates (DCA) and fluroacetates, affecting the efficiency of removal for these substances. One GST Z1 variant (GST Z1A) has significantly higher activity with dichloroacetic acid as a substrate than other GST Z1 isoforms (16).

The frequencies of the GSTZ1 alleles in the Turkish population are yet to be determined. We analyzed the frequency of the GSTZ1 polymorphisms in the Southeast region of Turkey, since polymorphisms in these genes may predispose Turks to certain adverse drug reactions or disease occurrence.

Material and Methods

Study Subjects

The study population consisted of 80 unrelated healthy individuals. All of the subjects were Turks living in the Southeast region of Turkey. All participants were otherwise healthy according to medical histories and work-up.

GSTZ1 Genotyping

Genomic DNA was extracted from 200 µL of peripheral blood by High Pure DNA isolation Kit (Qiagen, Inc., Chatsworth, CA) following manufacturer instructions. A polymerase chain reaction (PCR)-based restriction fragment-length polymorphism (RFLP) method was used to genotype the GSTZ1 A94G and A124G variant, which creates an additional Alw 26I and Fok I restriction enzyme site, respectively. The PCR was performed in a 25 µL volume containing 10X PCR buffer, 3.0 mM $MgCl_2$, 0.25 mM dNTPs, 1.5 units of Taq polymerase (Promega, Madison, WI), and 0.3 µM of primers GSTZ1-5F (5′- TGA CCA CCC AGA AGT GTT AG -3′) and GSTZ1-5R (5′- AGT CCA CAA GAC ACA GGT TC -3′) for exon 3. The PCR thermal cycling conditions were an initial melting period at 94°C for 3 min; then 35 amplification cycles of 94°C for 30 s, 60°C for 30 s and 72°C for 30 s; and a 5-min extension step at 72°C. The PCR products were checked on a 1.5% agarose gel for the assay completion and then the PCR products of 308 base pair (bp) were digested with restriction enzyme Fok I by overnight incubation at 55°C and Alw 26I by overnight incubation at 37°C.

The digestion products were electrophoresed on 3.5% agarose gel and visualized by staining with ethidium bromide and evaluated using the gel documentation system (Vilber-Lourmat, Cedex, France).

Statistical Analysis

Glutathione S-Transferase zeta allele and genotype distributions were expressed as percentile scores to demonstrate the distribution of genotypes in population.

Results

The frequency distribution of GSTZ1 genotypes in 80 healthy subjects was determined by using PCR-RFLP methods. Figure 1 shows the PCR products before restriction enzyme digestions. After Alw 26I digestion Lys/Lys homozygotes were identified by the presence of 186 bp and a 125 bp fragments; Lys/Glu heterozygotes by the presence of 186 bp, 159 bp, 125 bp and 26 fragments; and Glu/Glu homozygotes by 159 bp, 125 bp and 26 fragments (Figure 2).

Fok I generates a 193 bp and a 115 bp fragment for the Gly allele, whereas the Arg allele remains uncut. The Arg/Arg homozygote was identified by the presence of an uncut 308 bp band, whereas the Arg/Gly heterozygote produces all three bands (308, 193, and 115 bp) following restriction digestion (Figure 3).

The distribution of each genotype for GSTZ1 polymorphisms is shown in Table 1 and Table 2. The frequencies of AA, AG and GG genotypes for GSTZ1 A94G polymorphism were 3.8%, 35.0% and 61.2% in healthy subjects. For GSTZ1 A124G polymorphism AA, AG, and GG genotypes frequencies were 1.3, 3.7, and 95.0%, respectively. GSTZ1*A, GSTZ1*B, GSTZ1*C and GSTZ1*D allel frequencies (Table 3) were 1.3, 20.0, 76.9 and 1.9, respectively.

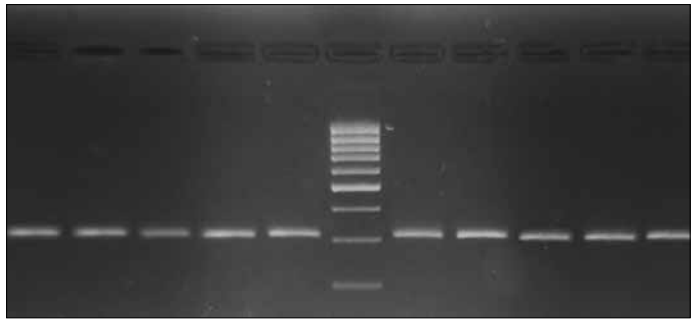

Figure 1. The 308 bp PCR product for GSTZ1 gene

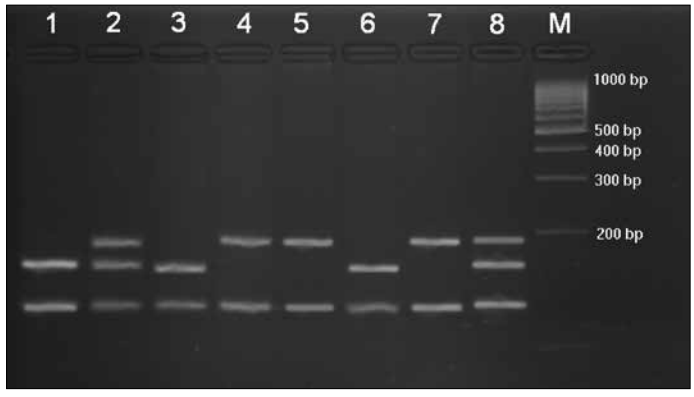

Figure 2. RFLP analysis of the 308 bp polymerase chain reaction product for GSTZ1 gene. Digestion with Alw 26I for nucleotide 94 determination. The 26 bp fragment is not visible at this intensity of staining. A/A, lane 4, 5 and 7, A/G lane 2, 8 and G/G lane 1, 3 and 6

Table 1. GSTZ1 A94G (Lys32Glu, rs.7975) polymorphism genotype and allele frequencies in different populations

GSTZ1 A94G (Lys32Glu, rs.7975) Polymorphism							
Population		**Genotypes**			**Alleles**		**Reference**
		Lys/Lys %	**Glu/Glu %**	**Glu/Glu %**	**Lys %**	**Glu %**	
Spain	Control	9.4	41.3	49.3	30.0	70.0	25
	Bladder Cancer	10.4	41.9	47.8	31.3	68.7	
Iran	Control	10.5	36.5	53.0	28.7	71.3	26
	Preeclampsia	7.9	29.8	62.3	22.8	77.2	
Iran	Chemotherapy Non-Responders	26.1	26.1	47.8	39.1	60.9	27
	Chemotherapy Responders	27.6	23.0	49.4	39.1	60.9	
Iran	Control	5.3	35.4	59.3	23.0	77.0	28
	Schizophrenia	6.9	33.3	59.8	23.5	76.5	
Australia	PD (Ever-smokers)	11.0	44.2	44.8	33.1	66.9	29
	PD (Never-smokers)	11.3	42.1	46.6	32.4	67.6	
Germany	Control	10.9	44.6	44.5	33.1	66.9	30
	Breast Cancer	9.2	43.4	47.4	30.9	69.1	
USA	Healthy Men	9.0	36.0	55.0	26.8	73.2	31
Our Study	Healthy Subjects	3.8	35.0	61.2	21.3	78.7	

PD: Parkinson's Disease

Table 2. GSTZ1 GSTZ1 A124G (Arg42Gly, rs.7972) genotype and allele frequencies in different populations

GSTZ1 A94G (Lys32Glu, rs.7975) Polymorphism							
Population		**Genotypes**			**Alleles**		**Reference**
		Arg/Arg	**Arg/Gly**	**Gly/Gly**	**Arg**	**Gly**	
Spain	Kontrol	0.9	13.6	85.5	7.7	92.3	25
	Bladder Cancer	0.6	15.2	84.2	8.2	91.8	
Iran	Control	0.0	10.0	90.0	5.0	95.0	26
	Preeclampsia	0.0	2.6	97.4	1.3	98.7	
Iran	Chemotherapy Non-Responders	0.0	0.08	91.2	4.4	95.6	27
	Chemotherapy Responders	0.0	6.0	94.0	3.0	97.0	
Iran	Control	0.0	5.3	94.7	2.6	97.4	28
	Schizophrenia	0.0	6.5	93.5	3.3	96.7	
Australia	PD (Ever-smokers)	1.2	15.6	83.2	9.0	91.0	29
	PD (Never-smokers)	0.5	16.5	83.0	8.7	91.3	
USA	Healthy Men	0.6	9.9	89.5	5.6	94.4	31
Our Study	Healthy Subjects	1.3	3.7	95.0	3.1	96.9	

PD: Parkinson's Disease

Discussion

The zeta class of cytosolic GST proteins has only recently been identified (17). GSTZ1 has been demonstrated to have activity towards both xenobiotic and endogen substrates. Previous studies have shown that zeta class GSTs catalyze the metabolism of a range of alpha-haloacids, including dichloroactate (DCA) and fluoroacetate DCA is a common contaminant in chlorinated drinking water, is hepatocarcinogenic in rodents and dogs and is used clinically in the management of lactic acidosis (18-22).

Table 3. Frequency of GSTZ1 alleles in the Turkish population (n=80)

	GSTZ1 Allele Frequencies			
	GSTZ1*A	GSTZ1*B	GSTZ1*C	GSTZ1*D
n	2	32	123	3
(%)	1.2	20.0	76.9	1.9

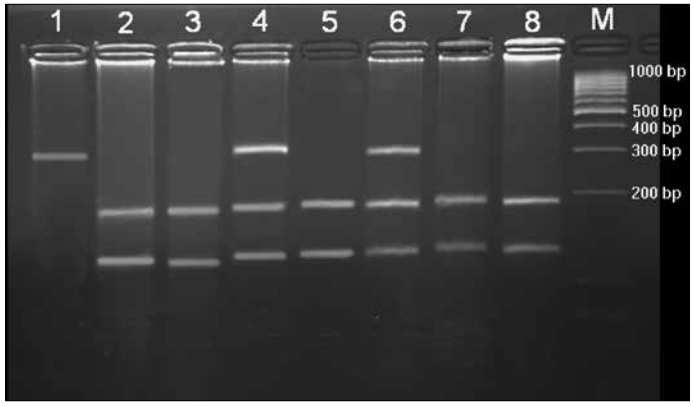

Figure 3. RFLP analysis of the 308 bp polymerase chain reaction product for GSTZ1 gene. Digestion with Fok I for nucleotide 124 determination. A/A, lane 1, A/G lane 4, 6 and G/G lane 2, 3, 5, 7 and 8

The study of Fernandez-Cannon and Penalva (23) reported that maleylacetoacetate isomerase (MAAI) has an identical sequence to that of GSTZ1 revealed that this enzyme also plays a significant role in the pathway responsible for the catabolism of phenylalanine and tyrosine.

It is revealed that there are several polymorphic alleles of the GSTZ1 locus during the characterization of the human GSTZ1 gene (15). The investigation of the activities of the recombinant proteins encoded by these alleles indicates that GSTZ1*A/A has different catalytic properties from GSTZ1* B/B and GSTZ1* C/C (16). However, the frequency GST alleles are different among various ethnic populations but it is not clear yet what those polymorphic variants frequencies of GSTZ1 gene are in different ethnic populations. Blackburn et al. (15) reported the incidences of the alleles of GSTZ1 as 9% for GSTZ1*A, 28% for GSTZ1*B and 63% for GSTZ1*C; however, they found no incidence of GSTZ1*D and reported that it was non-existent, most probably due to its rarity.

Smith et al. (24), who investigated the relationship between GSTZ1 gene polymorphism and breast cancer, found that the frequency of the GSTZ1*A allele, GSTZ1*B allele, GSTZ1*C allele and GSTZ1*D allele were 13.59%, 26.21%, 55.34% and 4.85%, respectively, on healthy controls, in the Australian population. Also, they did not find any association between GSTZ1 genotypes and breast cancer. In our study, in the Turkish population the frequency of GSTZ1*C allele was higher and GSTZ1*A allele was lower than these two populations.

Also Taylor et al. (25) studied association between the GSTZ1 polymorphisms (A94G, A124G, and C245T) and Parkinson's disease in the Australian population. Similar to our study, they found that GSTZ1*C allele is the most common variant in white control populations. However, they found no overall association between the *GSTZ1* polymorphisms and Parkinson's disease.

Glutathione S-Transferase zeta polymorphisms were studied in various diseases in different populations (25-31). Allele and genotype frequencies of GSTZ1 A94G and A124G polymorphisms for patients and controls are shown in Table 1 and Table 2 according to the studied population. There was no data about GSTZ1*A, GSTZ1*B, GSTZ1*C and GSTZ1*D allele frequencies in these studies. It gave only the genotype and allele frequency of GSTZ1 A94G and A124G polymorphisms.

As shown in Table 1, in our population Lys/lys genotype frequency is lower than populations in Spain, Australia, Germany and USA (25, 29-31). However, it is in accordance with the study of Nafissi et al. (28) who investigated the relationship between GSTZ1 gene polymorphism and schizophrenia in the Iranian population. Also the lys/lys genotype frequency is highest in a study by Saadat et al. (27) in the Iranian population. In this study the association between GSTZ1 polymorphisms and clinical response to chemotherapy in breast cancer was investigated, so all participants were cancer patients. The increase in the lys/lys genotype may be due to the fact that GSTZ1 gene polymorphism is associated with breast cancer in this population.

For GSTZ1 A124G polymorphism, Arg/Arg genotype was not observed in the Iranian populations (26-28), is relatively rare in our population as in Spain, Germany and USA populations (Table 2; 25, 30, 31).

Conclusion

This study presents the first results of GSTZ1 allele distributions in the Turkish population and provides a reliable estimate of the frequencies of GSTZ1 alleles (GSTZ1*A, GSTZ1*B, GSTZ1*C and GSTZ1*D) in the Turkish population.

Conflict of interest

No conflicts of interest were declared by the authors.

Authors' contributions: DNA extraction was conducted by SKÇ and LT, PCR-RFLP was conducted by SKÇ and NAA, manuscript was written by SKÇ, NAA and LT.

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