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Frequencies of glutathione S-transferase A1 rs3957357 polymorphism in a Turkish population

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Abstract

Background/Aim: Glutathione-S-transferases (GSTs), a major group of phase II enzymes, play a significant role in the detoxification and metabolism of endogenous and exogenous compounds. The objective of the survey was to identify the distribution of genotype and allele frequencies of *GSTA1* -69C>T (rs3957357) polymorphism in a healthy Turkish population and compare the determined frequencies with those in various populations.

Methods: Polymerase chain reaction and restriction fragment length polymorphism methods were used to analyze *GSTA1* -69C>T polymorphism in DNA samples of 105 healthy Turkish individuals.

Results: The distribution of *GSTA1* CC, CT, and TT genotype frequencies were 32.4%, 48.6% and 19.0%, respectively while the allele frequencies were 56.7% for C allele and 43.3% for T allele. The findings obtained were compared with the results of various populations. The frequencies of *GSTA1* -69C>T polymorphism were similar to those of the African American population and the populations with White ancestry, but significantly different from those reported for the populations with Asian ancestry.

Conclusion: To the best of our knowledge, this is the first study to present the frequencies of the *GSTA1* -69C>T polymorphism among Turkish individuals. The findings of the current study may provide a perspective for further studies exploring the role of *GSTA1* -69C>T polymorphism on predisposition to diverse illnesses such as cancer and may be used as a control group for such studies. In addition, this study might contribute to epidemiological and toxicogenetic investigations.

Keywords: Glutathione S-transferases, *GSTA1*, rs3957357, Polymorphism, Turkish population

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Ethics Committee Approval
The study was approved by the Ethics Committee of Mersin University (date: 02/09/2020, protocol no: 2020/615).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Introduction

Biotransformation of xenobiotics and endogenous compounds occurs through phase I and/or phase II enzymes. One of the main groups of phase II enzymes is glutathione S-transferases (GSTs). GSTs play a significant role in the detoxification and metabolism of endogenous and exogenous substances that include a wide range of medications, products of oxidative stress, carcinogens, environmental toxins by catalyzing the conjugation between electrophilic substances and reduced glutathione [1, 2]. Different GST isoenzymes have been identified in humans. Alpha (GSTA), theta (GSTT), pi (GSTP) and mu (GSTM) are the most characterized GST classes [3]. The GSTA class is the most plentiful GST enzyme in the human liver among all hGSTs and accounts for approximately sixty-five to eighty percent of their total liver concentration [4]. Besides, the GSTAs are expressed in the small intestine, adrenal glands, testicles and kidneys [1]. The GSTA isoenzymes conjugate compounds like the nitrogen mustard group of some anticancer drugs, α, ß-unsaturated aldehydes and some heterocyclic amines, steroid and thyroid hormones, penicillin, bile acids and bilirubin [2]. GSTAs exhibit high glutathione peroxidase activity and play a significant part in the protection of cells against exogenous and endogenous electrophilic compounds [5].

Inter-individual variations in the activities of GST enzymes might be caused by environmental effects such as exposure to toxins in the environment, lifestyle (use of medication, etc.) and diet, but genetic variations may also play a role [4]**.** Nearly all the GST family members have genetic polymorphisms that result in reduction of enzyme activity or a complete lack [3].

Several single nucleotide polymorphisms (SNPs) have been detected in the promoter region of the *GSTA1* gene. One of SNPs are *GSTA1* -69C>T (rs3957357) [6]. There are four functional polymorphisms in *GSTA1*, which are full linkage disequilibrium, and called *GSTA1*A* for -52G, -69C, -567T, -631T and *GSTA1*B* for -52A, -69T, -567G, -631G [7]. The base change C-69T leads to an Ear1 restriction enzyme site into the *GSTA1*B* variant [8]. The homozygous mutant genotype of the *GSTA1* -69C>T gene polymorphism is reported to have a lower enzymatic activity than the wild-type genotype [9]. *GSTA1* -69C>T polymorphism is reportedly related with various disorders such as gestational hypertension, leukemia, bladder cancer [10].

There have been many studies displaying that the distribution of GST polymorphisms differs among distinct regional, national and ethnic populations [11]. However, in the literature search, no studies were found on the *GSTA1* -69C>T polymorphism in Turkish population. Thus, the objective of the survey was to identify the distribution of the genotype and allele frequencies of the mentioned polymorphism in a healthy Turkish population, and compare the frequencies found with those of various populations.

Materials and methods

Samples

The DNA samples used for polymorphic analysis were obtained during the previous study approved by Mersin University Ethics Committee (22/10/2015, protocol no: 2015/317), and some of the DNA samples isolated were randomly contained to the present study. The present survey was also approved by the Ethics Committee of Mersin University (02/09/2020, protocol no: 2020/615). This study comprised the DNA samples of unrelated 105 Turkish healthy volunteers (age range: 18-65 years) and was conducted in accordance with the principles of the Good Clinical Practices and the Declaration of Helsinki.

Genotyping

Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods defined by Hezova et al. [9] with slight modifications were used for genotyping analysis of *GSTA1 -69C>T* polymorphism. *A* 400-bp fragment was amplified using the following primers: Forward: 5'-GCATCAGCTTGCCTTCA-3' and reverse: 5'-AAACGCTGTCACCGTCCTG-3'. The PCR reaction mixture contained 10x PCR buffer, 2.0 mM $MgCl_2$, 0.2 mM of each deoxynucleotide triphosphate, 20 pmol of each primer, 1.25 U of Taq DNA polymerase (Fermentas), approximately 300 ng DNA and last volume completed with distilled water to 30-µl. Amplification was for one cycle of 300 min at 94 ˚C, 30 cycles of 20 sec at 94 ˚C, 20 sec at 64 ˚C, 30 sec at 72 ˚C, and final 7 min extension at 72 ˚C. Negative control (NC), a DNA-free sample, was included in each PCR experiment and was used to determine whether the reagents used are contaminated with foreign DNA. PCR products (400-bp) were electrophoretically determined on a 2.0 % agarose gel containing ethidium bromide (EtBr, 500 µg/L) making the products visible. The PCR products were digested with FastDigest EarI (Eam1104I) (Thermo Fisher Scientific, USA) restriction enzyme and incubated at 37 °C for 15 min. The digested and undigested products were detected on 2.5% agarose gel visualized by EtBr. The wild-type genotype (CC) had no Eam1104I restriction enzyme site and was therefore 400 bp. On the other hand, the homozygous mutant genotype (TT) had Eam1104I restriction enzyme site and gave bands at 308 bp and 92 bp. The heterozygous genotype (CT) gave bands at 400 bp, 308 bp and 92 bp. Ten percent of the randomly selected samples were reanalyzed for confirmation. PCR-RFLP was conducted on a MiniAmp Plus Thermal Cycler (Thermo Fisher, USA).

Statistical analysis

Statistical data were analyzed using IBM SPSS 25.0 computer software for Windows. The frequencies of *GSTA1* -69C>T polymorphism were obtained by counting, and chi-square (X^2) test was used for assessment of Hardy–Weinberg equilibrium. The data obtained were compared with previously reported data of various populations. Distinctions in the allele and genotype frequencies between populations were tested by X^2 test. $P<0.05$ and $P<0.001$ were considered statistically significant.

Results

GSTA1 C-69T SNP was detected using PCR-RFLP technique in the DNA samples of unrelated 105 Turkish healthy individuals. Of the 105 individuals, 50 (48%) were male, and the remaining 55 (52%) were female. The distributions of the genotype frequencies obtained were consistent with Hardy-

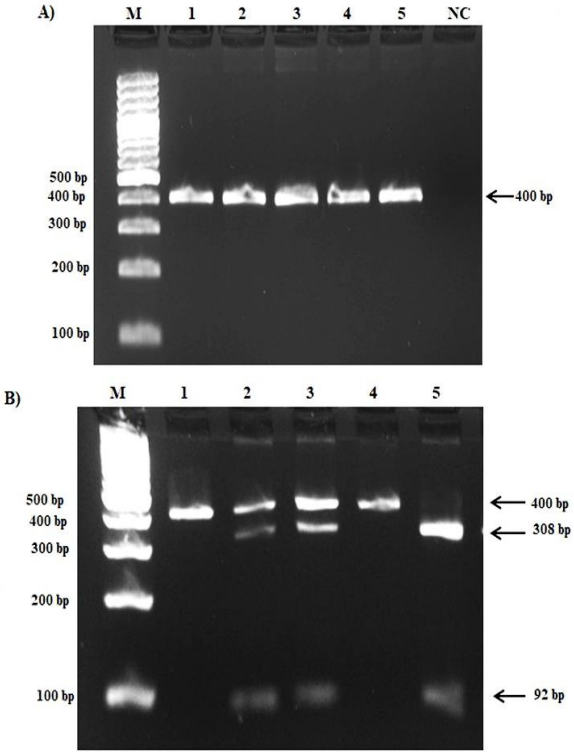
Weinberg equilibrium (X^2=0.013, P>0.05). The frequencies were 32.4% for the wild-type genotype (CC), 48.6% for the heterozygous genotype (CT) and 19.0% for the homozygous mutant genotype (TT). Thus, the frequencies of C and T alleles were 56.7% and 43.3%, respectively (Table 1).

Figure 1 shows agarose gel images of PCR and RFLP patterns of electrophoretically detected *GSTA1* -69C>T polymorphism.

Table 1: The frequencies of *GSTA1* -69C>T gene polymorphism in a healthy Turkish population

	Genotype				
	CC	CT	TT	TOTAL	
n (observed)	34	51	20	105	X^2: 0.013
Genotype frequencies, %	32.4	48.6	19.0	100	*df* =1; *P*>0.05
n (expected)	33.7	51.6	19.7	105	
	Allele				
Allele frequencies, %	C		T		
	56.7		43.3	100	

Figure 1: Electrophoresis examples of *GSTA1* -69C>T polymorphism identified using polymerase chain reaction (PCR) (A) and restriction fragment length polymorphism (RFLP) (B). For A (PCR) part; Lane M: 100 bp DNA ladder, Lane 1-5: PCR product (400 bp), NC: negative control. For B (RFLP) part; Lane M: 100 bp DNA Ladder, Lane 1,4: wild type genotype (400 bp), Lane 2,3: heterozygous genotype (400, 308, 92 bp), Lane 5: mutant genotype (308, 92 bp).



Discussion

The GSTs superfamily, one of the enzymatic families in phase II metabolism is highly polymorphic, and the polymorphic variations in the GSTs enzymes can influence their activities, therefore may lead to individual predisposition to a variety of diseases like cancer [2]. Due to genetic variants in GSTs, ethnic and inter-individual distinctions in the detoxification capacity of GSTs have been identified in diverse populations [12]. In this study, the frequencies of *GSTA1* -69C>T polymorphism were examined in a Turkish population. The distributions of frequencies of *GSTA1* CC, CT, and TT genotype were 32.4%, 48.6% and 19.0%, respectively, while the frequencies of C and T alleles were 56.7% and 43.3%, respectively.

The frequencies of genotype and allele of *GSTA1* -69C>T polymorphism have been reported in diverse populations. The findings obtained for the Turkish population were compared with the results reported for various populations [4, 6, 8, 9, 12-25] as depicted in Table 2. Accordingly, *GSTA1* -69T variant allele was more frequent in South Tunisians and Germans compared to other populations. In Asian ancestry, the frequencies of *GSTA1* -69T variant allele ranged from 10.5% to 16.0%. The allele and genotype frequencies of the Turkish population showed significant distinction when compared to those of Asian ancestry, including Chinese, Chinese Han, Asian (Northeast Thailand), Taiwanese, Japanese (*P<0.001*). In White ancestry, the frequencies of *GSTA1* -69T variant allele ranged from 35.1% to 48.4%. The frequency of *GSTA1* -69T variant allele in the Turkish population was very similar to those of White ancestry, including Serbian, Hispanic, Caucasian, Caucasian (USA), Danish, German, Italian, Polish, Caucasian (The Netherlands), Czech Central European, Eastern Slavs (Russia), Caucasian (Poland), South Tunisian (*P>0.05*). Moreover, no significant distinction was noted between the Turkish population and the American-African population with 35.7% allelic frequency (*P>0.05*).

Table 2: Comparison of the frequencies of *GSTA1 -69C >T* polymorphism in various populations

Ethnicity &Population	Healthy, control & patients etc.	Sample size	Genotype frequencies n (%)			Allele frequencies n (%)		Ref#
		n	CC	CT	TT	C	T	
WHITE								
Turkish	Healthy	105	34 (32.4)	51 (48.6)	20 (19.0)	119 (56.7)	91 (43.3)	Present study
Serbian	Healthy Control	66	23 (34.8)	36 (54.5)	7 (10.7)	82 (62.1)	50 (37.9)	[3]
Serbian	Control	122	49 (40.0)	57 (47.0)	16 (13.0)	155 (63.5)	89 (36.5)	[13]
Caucasian	Control	278	106 (38.0)	133 (48.0)	39 (14.0)	345 (62.0)	211 (38.0)	[8]
Caucasian (USA)	Control	81	24 (29.6)	44 (54.3)	13 (16.1)	92 (56.8)	70 (43.2)	[14]
Danish women	Control	396	123 (31.0)	210 (53.0)	63 (16.0)	456 (57.6)	336 (42.4)	[15]
German	Control	826	256 (31.0)	395 (47.8)	175 (21.2)	907 (54.9)	745 (45.1)	[16]
Caucasian (The Netherlands)	Healthy Control	411	168 (40.9)	184 (44.8)	59 (14.3)	520 (63.3)	302 (36.7)	[17]
Hispanic women	Control	53	19 (36.0)	27 (51.0)	7 (13.0)	65 (61.3)	41 (38.7)	[8]
Italian women	Control	137	46 (33.6)	65 (47.4)	26 (19.0)	157 (57.3)	117 (42.7)	[18]
Eastern Slavonic origin women (Russia)	Ovarian cancer	104	43 (41.3)	49 (47.1)	12 (11.6)	135 (64.9)	73 (35.1)	[19]
Polish	Healthy	160	54 (33.7)	74 (46.3)	32 (20.0)	182 (56.9)	138 (43.1)	[1]
Caucasian (Poland)	Control	365	137 (37.5)	165 (45.2)	63 (17.3)	439 (60.1)	291(39.9)	[6]
Czech Central European	Control	218	76 (34.9)	108 (49.5)	34 (15.6)	260 (59.6)	176 (40.4)	[9]
South Tunisian	Healthy	154	38 (24.7)	83 (53.9)	33 (21.4)	159 (51.6)	149 (48.4)	[12]
ASIAN								
Chinese*	Healthy	140	105 (75.0)	34 (24.3)	1 (0.7)	244 (87.1)	36 (12.9)	[4]
Chinese Han women*	Healthy Control	112	86 (76.8)	24 (21.4)	2 (1.8)	196 (87.5)	28 (12.5)	[20]
Asian (Northeast Thailand)*	Healthy Control	198	141 (71.2)	53 (26.8)	4 (2.0)	335 (84.6)	61 (15.4)	[21]
Taiwanese*	Non-diabetes mellitus	198	157 (79.3)	38 (19.2)	3 (1.5)	352 (88.9)	44 (11.1)	[22]
Taiwanese*	Control	274	214 (78.1)	56 (20.4)	4 (1.5)	484 (88.3)	64 (11.7)	[23]
Japanese *	Healthy	147	104 (70.8)	39 (26.5)	4 (2.7)	247 (84.0)	47 (16.0)	[24]
Japanese*	Healthy Control	294	238 (81.0)	50 (17.0)	6 (2.0)	526 (89.5)	62 (10.5)	[25]
BLACK								
African-American	Control	63	25 (39.7)	31 (49.2)	7 (11.1)	81 (64.3)	45 (35.7)	[14]

n: total number of subjects. Distinctions between the frequencies were studied using X^2, * P<0.001 at significance when compared to the results of the present study.

Genetic variations in the genes encoding enzymes that metabolize xenobiotics may alter the expression level of the protein product, thereby affecting an individual's susceptibility to various diseases and carcinogens and influencing the efficacy and toxicity of certain drugs [1]. As mentioned above, the frequencies of *GSTA1* C-69T polymorphism can be variable among distinct populations, which may lead to intra- and inter-population distinctions in xenobiotic-induced toxic effects.

In the study conducted by Sweeney et al. [26] on a total of 245 breast cancer patients, 198 of which were Caucasian and 47 of which were African American, *GSTA1* -69C>T polymorphism was related with survival after treatment with combination chemotherapy containing cyclophosphamide, and that a significantly decreased risk of dying was noted for subjects with *GSTA1* –69TT genotype. Khrunin et al. [19] declared that in 104 ovarian cancer patients of East Slavic origin, the allelic state of the *GSTA1* C-69T polymorphism was associated with overall survival and that the subjects carrying *GSTA1* -69TT genotype indicated better survival compared to the *GSTA1* -69CC carriers. Rossi et al. [27] reported that the *GSTA1* rs3957357 C>T polymorphism might be related with event-free survival (EFS) in patients with diffuse large B-cell lymphoma (DLBCL) and reported that patients with DLBCL carrying the CT/TT genotypes showed better EFS than patients with the CC genotype. Iorio et al. [18] explored the role of the *GSTA1* -69C>T SNP in genetic susceptibility to gestational hypertension (GH) in 195 case-control populations of Italian origin. It was notified that GH subjects had an importantly lower allele frequency of *GSTA1* -69T compared to control groups and that the subjects carrying at least one *GSTA1* -69T allele had a forty-five percent decrease in GH risk compared to those with *GSTA1* -69CC genotype (odds ratio [OR]=0.54, 95% confidence Interval [CI]=0.29–0.99; $P<0.05$). The *GSTA1* -69C>T polymorphism was significantly related with GH risk.

Contrary to the above, Akhdar et al. [28] examined the associations between the risk of hepatocellular carcinoma (HCC) development and the rs3957357C>T SNP in *GSTA1* among European individuals and reported that TT genotype was related with a 2 times increased risk of HCC occurrence (OR=2.1, $P=0.02$). In a meta-analysis study performed by Deng et al. [29], the variant genotype and allele of the *GSTA1* rs3957357 polymorphism was related with an incremental risk of cancer, particularly colorectal cancer, in Caucasian populations.

Liu et al. [10] investigated the potential relationships between schizophrenia (SCZ) and *GPX3* rs736775 and *GSTA1* rs3957357 polymorphisms in a case-control study of 648 healthy control and 617 schizophrenia patients from northern Han Chinese populations, and *GSTA1* rs3957357 polymorphism and the interplay between *GPX3* and *GSTA1* was reported to have impacts on SCZ risk.

Genetic polymorphisms may alter the activities of enzymes playing significant roles in the metabolism and detoxification of various xenobiotics that include carcinogens and drugs, and thus may lead to intra- and inter-population distinctions in predisposition to diverse diseases, xenobiotics toxicities, drug safety and efficacy [30].

Conclusion

To our knowledge, this is the first investigation to present the frequencies of the *GSTA1* -69C>T polymorphism among Turkish individuals. In the current study, the -69C>T polymorphism in the *GSTA1* gene is observed to be common among Turkish individuals. The frequencies of *GSTA1* -69C>T polymorphism were similar to those in the African American population and the populations with White ancestry, but significantly different from those reported for the populations with Asian ancestry. The findings of the current study may ensure a perspective for further studies exploring the role of *GSTA1* -69C>T polymorphism on predisposition to diverse illnesses such as cancer and may be used as a control group for such investigation. In addition, this study might contribute to epidemiological and toxicogenetic investigations as well.

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