Frequency of glutathione-*S*-transferase null-M1 and null-T1 genotypes among the Turabah population in Saudi Arabia

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ABSTRACT. Glutathione-S-transferases (*GST*) are key phase II detoxifying enzymes that play critical roles in protection against products of oxidative stress and against electrophiles. Glutathione S-transferase mu (*GST-M1*) and theta (*GST-T1*) are isoforms of glutathione transferase enzymes that participate in the metabolism of a wide range of chemicals. Deletion variants that are associated with a lack of enzyme function exist at both these loci. The frequencies of homozygous *GSTM1* and *GSTT1* deletion carriers are very high in most of the populations studied to date. The aim of this study was to investigate the frequencies of *GSTM1* and *GSTT1* genotypes among the Turabah population in Saudi Arabia in comparison with the data published for some other Arabic populations. The subjects consisted of 164 unrelated healthy individuals from the Turabah population. GST genotyping was performed by multiplex polymerase chain reaction-based

methods. The *GSTM1* deletion homozygosity was 56.1% and *GSTT1* deletion homozygosity was 20.7%, while the *GSTM1 and GSTT1* double-deletion homozygosity was 11.0%. Comparison with published data from Bahraini, Lebanese, and Tunisian populations demonstrated no significant difference for *GSTM1* between these populations. The *GSTT1* null-allele frequency was significantly lower than those for the Lebanese and Tunisian populations (P = 0.001) but similar to that for the Bahraini population (P = 0.099). Characterization of GST genetic polymorphisms in the Saudi population may aid in genetic studies on the association of *GSTM1* and *GSTT1* polymorphisms with disease risks and the pharmacogenetics of chemotherapy.

Key words: Glutathione *S*-transferase; Genetic polymorphisms; Turabah; SA

INTRODUCTION

The human body is exposed to a wide range of xenobiotics, ranging from food components or environmental toxins to synthetic and natural xenoestrogens, in addition to exposure to its own steroidal estrogens. These synthetic chemicals include a number of chlorinated organic compounds, such as the insecticides kepone, dieldrin, and DDT and its metabolites and some polychlorinated biphenyl (PCB) congeners. More recently, nonchlorinated compounds used as antioxidants and plasticizers were found to be estrogenic and carcinogenic (Soto et al., 1997; Farmer et al., 2003).

The human body has developed complex enzymatic mechanisms to detoxify these substances. These mechanisms exhibit significant individual variability and are affected by environmental, lifestyle, and genetic factors (Liska, 1998). The detoxification process involves two phases: functionalization, which uses oxygen to form a reactive site, and conjugation, which results in addition of a water-soluble group to the reactive site to be excreted in urine. These two steps are termed as phase I and phase II detoxification, respectively (Estabrook, 1996). Several genes involved in phase I and phase II have recently been cloned and identified in humans. Many of them show polymorphisms that may cause alteration in expression, function, and activity and have been suggested to contribute to individual cancer susceptibility as genetic modifiers of cancer risk (Adam et al. 2003; Chacko et al., 2005; Habuchi, 2006).

Glutathione S-transferases (GSTs) are phase II xenobiotic metabolizing enzymes that are directly involved in catalyzing the conjugation of reactive intermediates of electrophilic xenobiotics with glutathione. GSTs are composed of four major groups: *GSTA* (α), *GSTT1* (θ), *GSTM1* (μ), and *GSTP1* (π) (Lai and Shields, 1999; Geisler and Olshan, 2001). The enzyme encoded by the *GSTT1* gene may also be active in endogenous mutagenic processes. *GST-M1* and *GST-T1* are isoforms of *GSTs* that participate in the metabolism of a wide range of chemicals, including possible carcinogens (Hayes and Pulford, 1995; Shukla et al., 2012; Matic et al., 2013; Acevedo et al., 2014). The known substrates for the GST-M1 enzyme include reactive peroxide intermediates generated from the activation of polycyclic aromatic hydrocarbons by cytochrome P450 enzymes. Deletion variants that are associated with a lack of enzyme function exist at both these loci. Individuals who are carriers of homozygous deletions in the *GSTM1* of *GSTT1* genes may have impaired ability to metabolically eliminate carcinogenic compounds and may therefore be at increased risk for

cancer. GST enzymes play with glutathione peroxidases (GPx) an important role in the catabolism of glutathione (*GSH*), which is a potent antioxidant (contains a thiol group); this prevents damage to important cellular components caused by reactive oxygen species such as free radicals and peroxides (Danyelle, 2003).

The frequencies of homozygous *GSTM1* and *GSTT1* deletion carriers is very high (i.e., 20-50%) in most populations studied to date.

Epidemiological studies suggest that individuals who are homozygous null at the *GSTM1* and *GSTT1* loci (i.e., lack both copies of the *GSTM1* and/or *GSTT1* variants of the *GST* gene family) may have an increased risk of developing various types of neoplastic diseases, including cancers of the bladder, prostate, colon, skin, lung, and stomach (Strange and Fryer 1999; Altayli et al., 2009; Nock et al., 2009; Simic et al., 2009; Zhao et al., 2014). Therefore, knowledge regarding the inheritance of these susceptibility genes in different ethnic groups is very important for effective prevention of disease, especially cancer (Klusek and Gluszek, 2014).

This study focused on screening for double null mutations in *GSTs mu* and *theta* and determining their frequencies in the human population of Turabah in the western region of Saudi Arabia.

MATERIAL AND METHODS

Study subjects

Blood samples were collected from 164 unrelated individuals, who were born and were living in Turabah province, after obtaining their consent to participate in the study. The mean age of the study subjects was 44.87 ± 10.46 years; the minimum age was 30 years and the maximum was 60 years. From the study population, 98 (60%) were men and 66 (40%) were women. The study was approved by the Ministry of Health and Research Committee, Taif University.

Genomic DNA extraction

Genomic DNA was extracted from peripheral blood using standard procedures (Sambrook and Russel, 2001). Briefly, 5 mL blood was mixed with an equal volume of RBC lysis buffer (0.32 M sucrose, 5 mM $MgCl_2$, 10% Triton 100X, and 12 mM Tris-HCl, pH 8.0) and allowed to sit for 5 min. The cell lysate was then centrifuged at 3000 rpm and the upper layer was discarded. The pellet was resuspended in phosphate-buffered saline (PBS; pH 7.4) and 1% sodium dodecyl sulfate, and then digested with 0.2 mg/mL proteinase K at 55°C overnight. After digestion, the DNA was purified using phenol-chloroform extraction, followed by ethanol precipitation with 0.3 M potassium acetate, pH 5.2. The DNA was finally been stored in TE (10 mM Tris-HCl and 1 mM EDTA, pH 8.0) until use.

Genotyping of *GSTM1* and *GSTT1* polymorphisms

A multiplex polymerase chain reaction (PCR)-based method and three sets of primers were used for identification of the *GSTM1* and *T1* genotypes (Chen, 1996).

The sequences for the *GSTM1* forward and reverse primers were as follows:

5'-gaactccctgaaaagctaaagcc-3' and 5'-gttgggctcaaatatacggtgg-3', respectively (Bell et al., 1993). The sequences for the *GSTT1* forward and reverse primers were 5'-ttccttactggtcctcacatctc-3' and 5'-tcaccggatcatggccagca-3', respectively (Pemble et al., 1994). To ensure that a null genotype was due to the absence of *GSTM1* and *GSTT1* alleles rather than failure of PCR, we coamplified human *β-globin* as the internal control using the primers 5'-caacttcatccacgttcacc-3' and 5'-gaagagccaaggacaggtac-3'. The PCR was carried out in a Applied Biosystem 9700 Thermocycler in a 25-µL reaction mixture containing 50-100 ng genomic DNA; 1.6 mM dNTPs; 200 nM each GSTM1, GSTT1, and β-globin primer; 10 mM Tris/HCl, pH 9.2; 50 mM KCl; 2 mM MgCl$_2$; and 1.5 U Taq polymerase. Cycling conditions were as follows: an initial 4 min at 93°C for loading and denaturation, followed by 45 s at 61°C and 90 s at 72°C. This was followed by an additional 36 cycles of 93°C for 30 s, 63°C for 45 s, and 72°C for 90 s. Negative controls were includes for all amplifications; the reaction mixtures for these contained all the components except the DNA template. The PCR products were resolved on an ethidium bromide-stained 1.7% 1:1 NuSieve/MP agarose gel together with a DNA molecular weight marker. Amplification with *β-globin* primers produced a 268-bp band indicating that the PCR is reliable.

The presence of a 215-bp band indicated that this subject is primers for *GSTM1* homozygote or heterozygote, while its absence in the presence of the internal control band indicated the null *GSTM1*. The presence of a 480-bp band indicated that the subject was homozygote or heterozygote for *GSTT1*, while its absence in the presence of the internal control band indicated the null *GSTT1*.

Statistical analysis

The allele/genotype frequencies of the two polymorphisms were tested for Hardy-Weinberg equilibrium using the χ^2 test. The same test was used to compare the gene frequencies among the study population and published data from three Arabic populations, namely, Bahrainis, Jordanians, and Tunisians. The differences between the study population and each of these populations were considered significant if the P value did not exceed 0.05.

RESULTS

Frequencies of genotypes of the *GSTM1* and *GSTT1* polymorphisms among the study population

The frequencies of the genotypes of the *GSTM1* and *GSTT1* polymorphisms were screened using multiplex PCR in 167 individuals. This method only differentiated between homozygous deletion (null-genotype) of both polymorphisms and wild-type and heterozygous genotypes (positive genotype), as shown in Figure 1. The frequencies of *GSTM1* and *GSTT1* null-genotypes in the study population, as shown in Table 1, were 92 (56.1%) and 34 (20.7%), respectively. Genotyping showed that 74 (45.1%) individuals had the *GSTM1* null-genotype and were *GSTT1* positive while only 16 (9.7%) showed the *GSTM1* positive and *GSTT1* null-genotype. The double deletion was found in 18 individuals (11%). The *GSTM1* and *GSTT1* null-allele frequencies were 0.749 and 0.448, respectively.
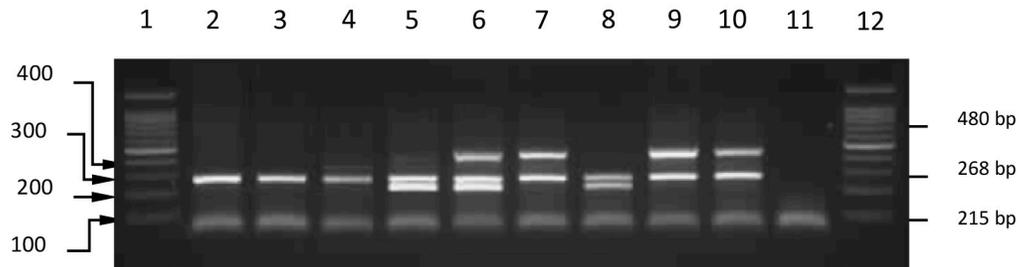

Figure 1. Genotyping of *GSTM1* and *GSTT1* polymorphisms by a multiplex PCR-based method. *Lanes 1* and *12*: 100-bp DNA marker. *Lane 11*: negative control. *Lanes 2*, *3* and *4*: individuals with null-*GSTM1*/null-*GSTT1* genotypes. *Lanes 5* and *8*: individuals with positive *GSTM1*/null-*GSTT1* genotypes. *Lane 6*: individual with positive *GSTM1*/positive *GSTT1* genotypes. *Lanes 7*, *9* and *10*: individuals with null-GSTM1/positive *GSTT1* genotypes.

Table 1. Frequencies of *GSTM1* and *GSTT1* polymorphisms in the study population.

GST		M1		Total (%)
		Null (%)	Positive (%)	
T1	Null (%)	18 (11)	16 (9.7)	34 (20.7)
	Positive (%)	74 (45.1)	56 (34.2)	130 (79.3)
		92 (56.1)	72 (43.9)	164 (100)

Frequencies of the *GSTM1* and *GSTT1* polymorphisms in the study population in comparison to those in the three Arabic populations

Figure 2 shows the frequencies of the null genotypes and null alleles of both polymorphisms among the study population in the present study and those of the Bahraini, Lebanese, and Tunisian populations that were published by Salem et al. (2011). Both *GSTT1* null- and double-deletion frequencies in the study population were lower than those in the other three populations. Comparison of the gene frequencies of the study population with those of the Bahraini, Lebanese, and Tunisian populations demonstrated that there was no significant difference in the gene frequencies between the study and Bahraini populations for *GSTM1* ($P = 0.059$) and *GSTT1* ($P = 0.146$; Table 2). Comparison of *GSTM1* and *GSTT1* gene frequencies in the study population with those in the Lebanese and Tunisian populations indicated that were significant differences in *GSTT1* genotypes between the study population and both these populations ($P = 0.0001$ and 0.0001, respectively) but not for the *GSTM1* genotypes ($P = 0.303$ and 0.327, respectively; Tables 3 and 4).
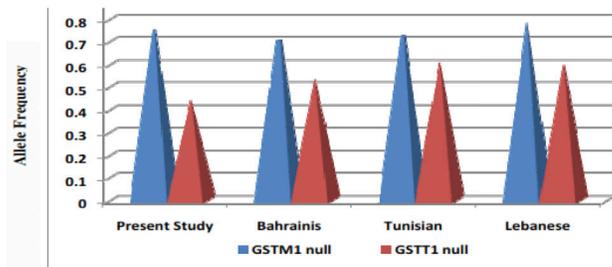

Figure 2. *GSTM1* and *GSTT1*-null allele frequencies in the study population.

Table 2. Comparison of *GSTM1* and *GSTT1* genotype frequencies between the study and Bahraini populations.

Population	N	Genotype frequency (%)			
		GSTM1		*GSTT1*	
		Positive	Null	Positive	Null
Present Study	164	72 (43.9)	92 (56.1)	130 (79.3)	34 (20.7)
Bahrainis	167	84 (50.3)	83 (49.7)	119 (71.3)	48 (28.7)
P value		0.146		0.059	

Table 3. Comparison of *GSTM1* and *GSTT1* genotype frequencies between the study and Lebanese populations.

Population	N	Genotype frequency (%)			
		GSTM1		*GSTT1*	
		Positive	Null	Positive	Null
Present Study	164	72 (43.9)	92 (56.1)	130 (79.3)	34 (20.7)
Lebanese	141	67 (47.5)	74 (52.5)	88 (62.4)	53 (37.6)
P value		0.303		0.001	

Table 4. Comparison of *GSTM1* and *GSTT1* genotype frequencies between the study and Tunisian populations.

Population	N	Genotype frequency (%)			
		GSTM1		*GSTT1*	
		Positive	Null	Positive	Null
Present Study	164	72 (43.9)	92 (56.1)	130 (79.3)	34 (20.7)
Tunisians	186	68 (36.6)	118 (52.5)	117 (62.9)	69 (37.1)
P value		0.327		0.001	

DISCUSSION

The human body is exposed to a wide range of xenobiotics, ranging from food components or environmental toxins to synthetic and natural xenoestrogens. The GST gene family consists of several genes that are located on different chromosomes. The expression of the GST genes has been reported to vary in different ethnic populations due to GST gene deletion polymorphisms. *GSTM1* and *GSTT1* deletion polymorphisms were found to be associated with relatively higher susceptibility to different malignancies and diseases in people sharing the same environment (Naveen et al., 2004; Garte et al., 2007).

In the present study, the frequency of the *GSTM1* null genotype in the Saudi population was 56.1%, which was similar to those reported in many other Arabic populations, that is, Bahrainis, Tunisian, Lebanese (Salem et al., 2011), and Egyptian (Hamdy et al., 2003) populations. The frequency of the *GSTM1* null genotype in the present study was significantly higher than those in Asian populations, that is, Indian and Japanese (Kihara and Noda, 1999; Sharma et al., 2012) populations, and African populations, that is, Zimbabwean and Cameroonian populations (Piacentini et al., 2011). Likewise, the frequency of the *GSTT1* null-genotype in the Saudi population is 20.1%. Comparison of the frequencies with those reported in other Arabic populations, that is, Bahraini, Tunisian, and Lebanese populations (Salem

et al., 2011), demonstrated that the frequency was similar to that reported in Bahrainis but was significantly lower than those for the Tunisians and Lebanese (P = 0.0001 and 0.0001, respectively). Although both Tunisian and Lebanese populations are of Arabic ethnicity, these differences in *GSTT1* null frequencies could be attributed to many factors. One reason could be the different environments inhabited by each population and the natural selection process that may affect the frequencies of genes that interact with environmental factors and common diseases in different population. Second, the Saudi population still preserved several Arabic social habits and behaviors. Almost all the Saudi subpopulations and tribes are living as small isolated and closed populations with firm restrictions on random genetic mating with high levels of consanguinity and inbreeding. Thus, mating between individuals in such subpopulations that are closely related (based on shared genes) is nearly the same as that between brothers and sisters, resulting in equal fertility for all genotype groups without selection and gene flow (or migration of individuals) in or out. This may result in increased homozygosity in these populations and may explain the high *GSTM1* frequency observed, positive assortative mating and lower *GSTT1* null genotypes and alleles, and negative assortative mating noted in the study population. The Saudi population may be similar to the Bahraini population but clearly differed from the Tunisian and Lebanese populations, which explains the significant differences between the study population and Tunisian and Lebanese populations. The positive assortative mating for the *GSTM1* null genotype in this population may have a protective effect against common diseases in the study population or recently selected with changes in living standards, nutritional habits, and behavioral style during the last few decades, especially after the discovery and mining of petroleum in this area (Abu-Amero et al., 2006; Siraj et al., 2008; Saeed et al., 2013).

In conclusion, the observed frequencies of *GSTM1* and *GSTT1* null polymorphisms in the Saudi population in Turabah Province, Western region of Saudi Arabia, differed from those found in some other populations. Moreover, changes in living standards and behavioral style and habits are associated with increase in the frequencies of malignancies and metabolic diseases, and the susceptibility to disease incidences due to environmental pollutants will vary. Therefore, further and more detailed studies are highly recommended in this region and other regions in Saudi Arabia in order to identify the genetic as well as environmental factors related to predisposition to malignant and metabolic diseases. Thus, accumulation of such data will provide a basic database for future clinical and preventive measures against these diseases.

Conflicts of interest

The authors declare no conflict of interest.

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