

Deletion Polymorphism of Glutathione S-transferases M1 and T1 genes in the Sudanese Population

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Abstract Glutathione S-transferases (GSTs) play a major role in the detoxification of various compounds. Polymorphic variants in GST genes were reported for different populations. The main objective of this study was to determine the frequencies of GSTM1 and GSTT1 null genotypes in the Sudanese population. GST genotyping was carried out using multiplex PCR. Study population included 114 unrelated healthy Sudanese subjects. The results showed that the prevalence of GSTM1 and GSTT1 deletion homozygosity among Sudanese were 54.7% and 42.1%, respectively. There are no significant differences in allelic distribution of GSTM1 gene between the Sudanese and other ethnic groups except for sub-Saharan Africans. As regards the allelic distribution of GSTT1 genes, the Sudanese population is similar to sub-Saharan Africans but significantly different from Europeans. Combined analysis of both genes revealed that 24.6% of Sudanese harbor the deleted genotype of both genes and it is the highest reported so far for an Arab and African population. This is the first study that addresses deletion polymorphism of GST genes in Sudanese. We provide a reference database of allelic frequencies of the GSTM1 and GSTT1 genotypes among Sudanese.

Keywords: *Glutathione S-transferase, deletion polymorphisms, Sudanese*

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1. Introduction

Pharmacogenetics is the study of the genetic basis for variation in drug response. An individual's response to a drug depends on both environmental factors and genetic factors. Individual variations in response to cancer therapy, and to toxic chemicals are related to the genetic differences in the drug metabolizing enzymes. The main causes of patient's heterogeneity are mainly due to genes polymorphisms which are involved in the metabolism of xenobiotics [1]. Assessment of polymorphisms of these genes in different populations may explain the variation in response to cancer therapy and to toxic chemicals.

Glutathione S-transferases (GSTs) are a family of Phase II detoxification enzymes that catalyze the conjugation of glutathione to a wide variety of xenobiotics. Glutathione S-transferases play a major role in cellular protection from environmental and oxidative stress, and in cellular resistance to drugs [2]. Glutathione S-transferases are present in many tissues, and contribute to the protection from broad range of compounds including carcinogens [1,3]. Human GSTs are divided into cytosolic, mitochondrial and membrane-bound microsomal families. The cytosolic family is further divided into seven classes: Alpha, Mu, Omega, Pi, Sigma, Theta and Zeta. GSTM1 gene (Mu

class) is located on chromosome 1p13 and GSTT1 gene (Theta class) is located on chromosome 22q11. These genes showed polymorphisms which result from gene deletion, and are associated with absent enzymatic activity in individuals carrying both deletions (i.e. null genotype) [4,5]. The GSTM1 and GSTT1 null genotype is associated with differential susceptibility to various forms of cancer [6], resistance to chemotherapy treatment, drug response [7], and cancer susceptibility [8,9].

Glutathione S-transferase M polymorphism is caused by a 50 kb deletion, and the frequency of GSTM1 null allele in different populations ranged from 0.3-0.5 [10]. In their study, Townsend and Kew [10,11] stated that livers from individuals who harbor homozygous deletions in GSTM1 gene have ~50% of the glutathione conjugating capacity of those with at least one copy of the GSTM1 gene. GSTM1 and GSTT1 null genotypes are associated with increased risk of hepatocellular carcinoma in Chinese population [12]. Children with acute myeloid leukemia who are homozygous for deletions in GSTT1 gene are three times as likely to die of toxicity as those patients who have at least one copy of GSTT1 gene following intensively timed antileukemic therapy [13].

Distribution of GSTM1 and GSTT1 null genotypes was varied in different populations [1]. About half of the European populations are homozygous deleted for

GSTM1 null allele, and hence fail to express the enzyme [1]. The frequencies of homozygous deletions of GSTM1 gene are higher in Caucasians and Asians than in African Americans [14], whereas homozygous deletions of GSTT1 gene are higher in Asians and Africans than in Caucasians [6]. So, gene polymorphism may predispose these populations to certain adverse drug reactions or disease occurrence, here we analyzed the frequency of GSTM1 and GSTT1 polymorphisms in the Sudanese population.

2. Subjects and Methods

2.1. Subjects

Blood was collected in EDTA-containing tubes from 114 unrelated healthy Sudanese from the city of Khartoum, the capital of Sudan. The study sample was composed mostly of Sudanese Arabs. The study was done under institutionally approved internal review board (IRB) protocols. A written informed consent was obtained from all participants in this study.

2.2. GSTM1 and GSTT1 Genotyping

Genomic DNA was isolated from blood samples according to the manufacturer's instructions using DNA purification kit from Qiagen (QIAamp DNA Mini Kit, CAT # 51306). Genotyping of the GSTM1 and GSTT1 deletion polymorphisms was determined using multiplex PCR as described previously [15,16]. Multiple repeat samples were included in the PCR analysis to monitor quality control. PCR products were run on 1.5% agarose gel (Figure 1). Presence of the particular allele was designated as wild genotype (positive) and homozygous absence or deletion of the allele was designated as null genotype.

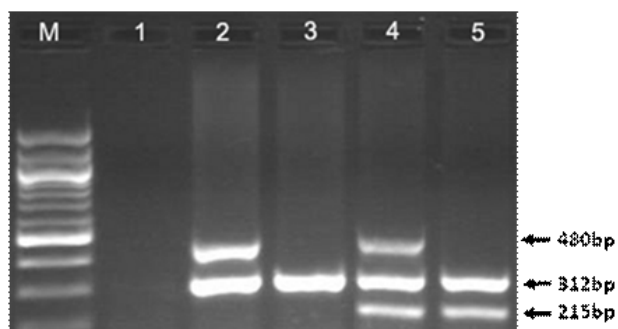


Figure 1. PCR products analyzed on 1.5% agarose gel. The presence of GSTT1 was detected by the presence of a band at 480 bp and the presence of GSTM1 was detected by the presence of a band at 215 bp. A band at 312 bp, corresponding to CYP1A1 gene, was used as an internal control. Lane 1 is a negative control. Lane 2 is an individual with GSTT1 present (480 bp) and GSTM1 null alleles. Lane 3 is individual with null alleles for both GSTT1 and GSTM1 genes showing only one band at 312 bp (internal control). Lane 4 is an individual with both GSTT1 and GSTM1 alleles present. Lane 5 is an individual with GSTT1 null and GSTM1 present (215 bp) alleles. M is a DNA molecular marker.

2.3. Statistical Analysis

Allele frequencies were calculated by direct counting, and were evaluated using the chi square goodness-of-fit test.

3. Results

In this study 114 Sudanese healthy volunteers were investigated with their age ranged between 20 and 79 years (mean age 51 years).

The study group included 46 men (aged between 20 and 79 years, mean age 55) and 68 women (aged between 22 and 72 years, mean age 48).

GSTM1 and GSTT1 genotypes were determined by multiplex PCR in 114 Sudanese individuals. This method does not differentiate between wild-type and heterozygous states, but it detects the percentages of the homozygous deletion of both GSTM1 and GSTT1 genes. GST genotypes were coded as positive (wild-type homozygotes and deletion heterozygotes), or as null (homozygous deletion). This made direct calculation of Hardy Weinberg Equilibrium impossible.

In the present study, the frequency of GSTM1 null genotype was 54.7% and that of GSTT1 null genotype was 42.1%. GSTM1 and GSTT1 null genotype frequencies and the combined GSTM1 null plus GSTT1 null genotype frequencies (double null genotype) was 24.6% (Table 1, Figure 2). The genotype frequency of combined presence (double wild genotypes) of GSTM1 plus GSTT1 alleles is 28.1%. The frequency of GSTM1 null genotype plus GSTT1 wild genotype is 29.8% and the frequency of GSTM1 wild genotype plus GSTT1 null genotype is 17.5% (Figure 2). No statistically significant gender difference was found. Table 2 shows null-genotype frequencies for the GSTM1 and GSTT1 reported in various populations.

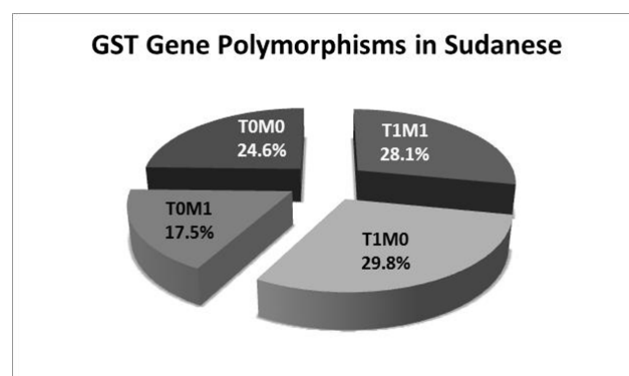


Figure 2. GST gene polymorphism in Sudanese samples. TOM0 (double null for both GSTT1 and GSTM1 genes), T1M1 (both GSTT1 and GSTM1 alleles present), TOM1 (GSTT1 null and GSTM1 present), T1M0 (GSTT1 present and GSTM1 null alleles)

Table 1. Frequency of GSTs null genotypes in Sudanese population

		Genotype Frequency (%)				
Population	n	GSTM1		GSTT1		Double null
		positive	null	positive	null	
Sudanese	114	52 (45.6%)	62 (54.4%)	66 (57.9%)	48 (42.1%)	28 (24.6%)

Table 2. Frequency of GSTs null genotypes in various ethnic groups.

Population	n	% GSTM1 null	% GSTT1 null	% double null	Reference
Arabs					
Sudanese	114	54.4	42.1	24.6	Present study
Bahrainis	167	49.7	28.7	14.4	[16]
Lebanese	141	52.5	37.6	16.3	[16]
Tunisians	186	63.4	37.1	21	[16]
Egyptians	200	55.5	29.5	NA	[17]
Saudi	513	54.6	25	17.2	[18]
Asians					
Turkish	133	51.9	17.3	NA	[19]
Indians	198	20.7	18.2	NA	[20]
Chinese	735	56.5	56.5	31.4	[21]
Japanese	143	44.1	43.4	15.4	[22]
Koreans	1051	53.8	54.3	29.1	[23]
Europeans					
British	373	54	18	NA	[24]
French	1184	53.4	16.8	NA	[25]
German	734	51.6	19.5	NA	[26]
Africans					
Cameroonians	126	27.8	46.8	NA	[27]
Gambians	337	20.2	37.1	NA	[28]
Ivory Coast	133	36.1	33.1	14.3	[29]

4. Discussion

The frequencies of GSTM1 and GSTT1 null genotypes have been reported in diverse ethnic groups [30,31]. Here we investigated the polymorphism at GST loci in Sudanese population. To our knowledge, this is the first study done on Sudanese population regarding the frequencies of GST deletion polymorphisms. The homozygosity for the GSTM1 deletion in Sudanese (54.4%) was generally comparable to those reported for Arabs from Bahrain (49.7%) [16]; Saudi Arabia (54.6%) [18,32]; Egypt (55.5%) [17]; Lebanon (52.5%) [16] and Tunisia (63.4%) [16] whereas no statistically significant differences were found (Table 2).

An ethnic and geographic basis for variations in the distribution of GSTM1 null genotype among diverse population was suggested [31,33]. The prevalence of individuals not expressing the GSTM1 enzyme due to a homozygous gene deletion is reportedly higher in Europeans and Asians, as compared to Africans [1]. The frequencies of GSTM1 null genotypes vary from 38-67% in Europeans, 33-63% in Asians, and 16-36% in sub-Saharan Africans [31,34]. The prevalence of GSTM1 homozygous deletion seen among Sudanese (54.4%) was comparable for Europeans from Great Britain [24,31], France [25], and Germany [26]. In addition, they were comparable to Asians, such as Turkish [19], Chinese [21], Koreans [23] and Japanese [22] (Table 2). Significant differences in GSTM1 null genotype distribution were seen with respect to Asians from India ($p < 0.001$) [20], and sub-Saharan Africans, including Gambians ($p < 0.0001$) [28], Cameroonians ($p < 0.001$) [27], and from Ivory Coast ($p < 0.004$) [29] (Table 2). The frequency of GSTM1 null genotype among Sudanese was comparable

to those reported for Arabs, European and Asian population (apart from Indians) but was significantly higher than those from sub-Saharan Africans.

The prevalence of GSTT1 null homozygotes in Sudanese (42.1%) was comparable to those reported for Arabs from Lebanon (37.6%) and Tunisia (37.1%) and was significantly higher than those reported for Bahrainis (28.7%, $p < 0.020$), Saudi Arabians (25%, $p < 0.001$) [18, 32], and Egyptians (29.5%, $p < 0.023$) [17]. The GSTT1 frequencies reported for Caucasians, Africans and Asians are 20%, 40% and 60%, respectively [6]. The frequencies of GSTT1 deletion in Sudanese population was significantly higher than that described for Europeans, including British ($p < 0.001$) [24], French ($p < 0.001$) [25], and German ($p < 0.001$) [26], as well as Turkish population ($p < 0.001$) [19], but was comparable to those reported for South-East Asians, such as Chinese [21], Koreans [23] and Japanese [22]. The frequencies of GSTT1 null genotype in Sudanese samples was similar to that of the sub-Saharan Africans as Gambians [28], Cameroonians [27], and from Ivory Coast [29] (Table 2).

The difference of frequency of GSTM1 and GSTT1 null alleles between Sudanese individuals and those of others is likely to be attributed to admixture of Sudanese population, and also to selection arising from varied exposures to toxic substances [35]. The distribution of GSTM1 null deletion in Sudanese was higher, but that of the GSTT1 null genotype was comparable to that of sub-Saharan Africans. This can be explained by the ethnic mixture of the Sudanese, with influence from sub-Saharan Africans and Arabs. Our data showed that Sudanese are similar to Arabs, Europeans and Asians (apart from Indians) with regards to the frequency of GSTM1 null genotype, and to Asians (Chinese, Japanese and Koreans) and sub-Saharan Africans regarding the distribution of the GSTT1 null genotype.

The significance of the high frequencies of homozygous null deletions at GSTM1 and GSTT1 loci remains to be seen. Data on the prevalence of various diseases, particularly those related to toxicity of anticancer drugs among Sudanese are scarce. Therefore, it is difficult to define the causes of variation in the frequencies of GST null deletions, and the effects of this variation on epidemiology of diseases. The frequency of double null genotype reported for Sudanese is the highest frequency described for Arab and African populations, with Asians having the highest frequencies of double null genotype (20-33%), with Africans and Europeans shows low prevalence rates ranging from 10 - 17% [1]. The frequency of the double null genotypes in Sudanese was higher than that found in Arabs from Saudi Arabia, Bahrain, Lebanon, and Tunisia and to Africans from Ivory Coast but was less than those reported for Asians from China and Korea.

As regards the frequency of GSTT1 null genotype in Sudanese, it was comparable to Lebanese and Tunisian Arabs, to those reported for Asians from China, Japan and Korea and to sub-Saharan Africans. It was significantly different from those reported for Egyptians, Bahraini and Saudi Arabians, and to those reported for Europeans and Turkish population.

Cancer is an increasing problem among Arabs and it ranks as the fourth leading cause of death in Arab countries [36]. The age standardized incidence (ASR) of all cancers among Arabs is 3 to 4 times lower than in the developed countries and it is expected to double in the next 15 years. Among Sudanese, ASR per 100,000 populations was higher in women (206.3) than in men (160.0). The prostate and breast is the most commonly diagnosed cancer in men and women in Khartoum, Sudan [35]. Associations of GSTM1 and/or GSTT1 null genotypes with several types of cancer have been reported [6,14,18,21,34,37]. GSTM1 and GSTT1 null genotypes are associated with increased risk of prostate cancer in Asians and they are considered as risk factors for the development of prostate cancer [38]. GSTM1 and GSTT1 null genotypes may predispose the cell of patients with non-small cell lung cancer to increased oxidative damage [39,40,41]. The presence of high frequencies of GSTM1 and GSTT1 null alleles among Sudanese is impotent clinically as GSTs genes can modulate response to cancer treatment. More studies are required to test the potential risk of the GST null alleles in Sudanese.

In conclusion, this is the first report on the polymorphic distribution of the GSTM1 and GSTT1 genotypes in Sudanese population. Sudan is located in northeastern part of Africa and Sudanese population show considerable ethnic and linguistic diversity. In this study, we provide a reference database of allelic distribution of the GSTM1 and GSTT1 genotypes in Sudanese population. Further detailed studies of GST variants could be helpful in understanding the roles of these variants as genetic susceptibility markers and its association drugs pharmacogenomics among Sudanese population.

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Conflict of Interest

None to declare.

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