Age- and gender-independent association of glutathione S-transferase null polymorphisms with chronic myeloid leukemia

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ABSTRACT

The glutathione S-transferase (GST) genes encode enzymes that mediate the detoxification of xenobiotics by catalyzing the conjugation of glutathione (GSH) to xenobiotic substrates. The aim of the current study is to investigate the association between *GSTT1* and *GSTM1* polymorphisms and chronic myeloid leukemia (CML) among Sudanese patients. Patients with CML (n = 115) were recruited to the study from the Radiation and Isotope Centre Khartoum (RICK) in Sudan. Healthy individuals (n = 104) were included as controls. Genotyping of *GSTT1* and *GSTM1* polymorphisms was performed using multiplex PCR. Null deletions in the *GSTT1* and *GSTM1* genes are common in the Sudanese population (control group), with frequencies of 33.9% and 38.2%, respectively. The frequencies of *GSTT1* (OR: 3.25, 95% CI: 1.87–5.65, $p < 0.001$) and *GSTM1* (OR: 2.14, 95% CI: 1.25–3.67, $p < 0.005$) null genotypes were significantly higher in CML patients vs. controls. The distribution of *GSTT1* and *GSTM1* null genotypes was not different between male and female ($p > 0.01$) and young and old CML patients ($p > 0.05$). Hematological parameters were not affected by the GST null polymorphisms in the patient group ($p > 0.05$). In addition, the frequency of *GSTM1* null genotype was lower in advanced-phase CML patients compared to chronic-phase patients ($p < 0.05$). The *GSTT1* and *GSTM1* null polymorphisms are associated with CML among Sudanese patients, independently of their age and gender.

KEY WORDS: GSTs; glutathione S-transferase; null polymorphism; *GSTT1*; *GSTM1*; CML; haplotype
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INTRODUCTION

Glutathione S-transferases (GSTs) are enzymes that mediate the detoxification of xenobiotics in the body. GSTs catalyze the conjugation of xenobiotic substrates to glutathione (GSH) to increase the solubility of such substrates in cells [1]. In addition, GSTs may directly bind xenobiotics to facilitate their intracellular transport [2]. Eight GST genes have been identified in the human genome [3], including *GSTM1* that encodes GST mu 1 and *GSTT1* which encodes GST theta 1 [4]. Both genes are of clinical interest, due to the occurrence of null genotypes that lack the whole gene [5]. For example, null *GSTM1* and *GSTT1* polymorphisms are associated with an increased risk of several types of malignancies, including lung, blood, breast, and head and neck cancer [6-9]. Low activity of GSTs and reduced detoxification might enhance the potency of therapeutic drugs and influence the patient response to chemotherapy [6,10,11]. GSTs may also modulate some of the drug effects, such as the generation of hydroperoxides or other reactive oxygen species in the case of adriamycin, mitomycin C, and cisplatin [12].

Chronic myeloid leukemia (CML) is a malignant disease of the blood-forming cells of the bone marrow [13]. The disease is characterized by the presence of the fusion gene *BCR-ABL1* in immature myeloid cells [14]. About 10% of all leukemias belong to this CML type [15]. Exposure to xenobiotics has been shown to increase the risk of cancer, including CML [16]. Since GSTs play a role in the detoxification of xenobiotics, polymorphisms in GSTs might modulate susceptibility to cancer and other diseases [17,18] and affect their onset [19]. In this study, we investigated the association between *GSTM1*

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and *GSTT1* null polymorphisms and CML among Sudanese patients. In addition, we compared the frequencies of these polymorphisms in the Sudanese population with those reported in other populations.

MATERIALS AND METHODS

Study design and patients

This case-control study was conducted on 115 patients with CML (50 females and 65 males, age range: 18–81 years) who attended the Radiation and Isotope Centre Khartoum (RICK) in Sudan for prognosis. Healthy individuals (n = 104, 49 females and 55 males, age range: 18–84 years) were included as a control group. The participants were recruited from May 2015 to June 2017.

A hematopathologist made the diagnosis of CML based on complete blood count (CBC), presence of a full spectrum of myeloid cells in peripheral blood film, reduced leukocyte alkaline phosphatase (LAP), and detection of t(9;22)(q34;q11) by routine cytogenetic analysis [20]. CML patients were classified into three groups (CML phases) according to the World Health Organization (WHO) criteria, including chronic (n = 93), accelerated (n = 20), and blast crisis phase (n = 2). The study was approved by the Institutional Review Boards of Alzaeim Alazhari University and Ministry of Health which utilizes the ethical principles of the Declaration of Helsinki to evaluate research proposals (approval ID: EC-AAU 25/2014). All participants signed written informed consent before inclusion in the study.

Collection of blood samples

A total of 2.5 ml venous blood samples were collected from each participant in vacutainer tubes containing the anticoagulant ethylenediaminetetraacetic acid (EDTA). Blood samples were stored at -20°C until used.

DNA extraction

DNA was extracted from EDTA-blood samples by a modified Chelex (100) protocol as described previously [21]. Briefly, a total of 500 µl of whole blood was added to an Eppendorf tube containing 1000 µl of red cell lysis buffer. The tube was mixed well and centrifuged at 12000 × g for two minutes. Then, the supernatant was discarded and the pellet was washed four times with 1000 µl of red cell lysis buffer. Next, the cleared pellet was washed with 1000 µl of phosphate-buffered saline, centrifuged at 12000 × g for two minutes, and the supernatant was removed. The pellet was then mixed with 200 µl of Chelex by vortexing and heated at 100°C for 20 minutes with vortexing every five minutes. After that, the samples were centrifuged at 14000 × g for two minutes and the supernatant was transferred into a clean Eppendorf tube. DNA samples were checked for purity using a spectrophotometer (Amersham Biosciences, Biochrom Ltd., Cambridge, UK) and stored at -20°C until used.

Genotyping of *GSTT1* and *GSTM1* polymorphisms

Multiplex polymerase chain reaction (multiplex PCR) was used for genotyping *GSTT1* and *GSTM1* null polymorphisms. The following primers were used: *GSTT1*, forward 5′-TTCCTTACTGGTCCTCACATCTC-3′ and reverse 5′-TCACCGGATCATGGCCAGCA-3′; *GSTM1*, forward 5′-GAACTCCCTGAAAAGCTAAAGC-3′ and reverse 5′-GTTGGGCTCAAATATACGGTGG-3′ [22,23]. PCR was carried out in a 25-µl reaction volume containing 100 ng of template DNA, 100 pmol of each primer, and ready-to-use master mix (12.5 µl Maxime PCR PreMix series, Intron Biotechnology, Korea). Amplification was performed in a BIO-RAD thermocycler (Mexico) using the following thermal cycle conditions: 94°C for five minutes, followed by 35 cycles of 94°C for 50 seconds, 61°C for 60 seconds, and 72°C for 60 seconds. The reaction was terminated by an extension time of seven minutes at 72°C. In a separate PCR reaction, a 436-bp long fragment of the *GSTP1* gene was amplified as a positive control. PCR products were stained with EtBr and visualized on a 2.5% agarose gel. The absence of the 480-bp PCR product for *GSTT1* and 219-bp PCR product for *GSTM1* indicated the presence of homozygous null genotypes in those samples (Figure 1). The absence of the *GSTP1* 436-bp PCR product on a gel indicated a failure of PCR reaction. We should mention here that this genotyping method does not discriminate between the homozygotes (+/+) for the wild type GST alleles and heterozygotes (+/–).

Statistical analysis

IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY) was used to analyze the data. The

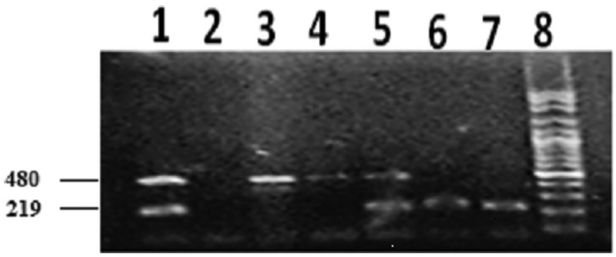

FIGURE 1. Genotyping of *GSTM1* and *GSTT1* null polymorphisms. PCR amplification of *GSTM1* and *GSTT1* gene fragments and their visualization using 2% agarose gel electrophoresis. PCR products of 219 bp and 480 bp indicate the presence of *GSTM1*(+) and *GSTT1*(+) genotypes, respectively. Lane 8: DNA ladder of 100–1500 bp fragments. Lanes 1 and 5: *GSTM1*+/*GSTT1*+. Lane 2: *GSTM1* null/*GSTT1* null. Lanes 3 and 4: *GSTM1* null/*GSTT1*+. Lane 6 and 7: *GSTM1*+/*GSTT1* null. GST: Glutathione S-transferase; *GSTT1*: GST theta 1; *GSTM1*: GST mu 1; PCR: Polymerase chain reaction.

frequencies of *GSTT1* and *GSTM1* genotypes were compared between patients and controls by Chi-square test. A p value of less than 0.05 was used as a threshold for significance.

RESULTS

Table 1 shows demographic characteristics of participants. The CML and control groups were not statistically different with respect to age, gender, and ethnicity ($p > 0.05$). The frequencies of *GSTT1* and *GSTM1* null genotypes in CML group were 66.1% and 62%, respectively, while in control group they were 33.9% and 38%, respectively (Table 2). The frequencies of *GSTT1* (OR: 3.25, 95% CI: 1.87–5.65, $p < 0.001$) and *GSTM1* (OR: 2.14, 95% CI: 1.25–3.67, $p < 0.005$) null genotypes were significantly higher in CML patients vs. controls. Similarly, when the combination of *GSTT1* and *GSTM1* null genotypes was considered, a significant difference was observed between CML patients and controls (OR: 2.57, 95% CI: 1.44–4.56, $p < 0.01$; Table 2).

We further analyzed the frequencies of *GSTT1* and *GSTM1* null genotypes among CML patients in relation to their gender, age, and CML phases (Table 3). The distribution of *GSTT1* and *GSTM1* null genotypes was not different between male and female ($p > 0.01$) and young and old CML patients ($p > 0.05$). However, the frequency of *GSTM1* null genotype was lower in advanced-phase CML patients compared to chronic-phase patients ($p < 0.05$).

Table 4 shows hematological parameters of CML patients. Hematological parameters, including hemoglobin (Hb), platelet count, and white blood cell (WBC) count were not affected by GST null polymorphisms in CML patients ($p > 0.05$).

TABLE 1. Demographic characteristics of participants

Characteristic	Controls	CML patients
Age (mean±SD)	37.6±13.8	43.5±16.6
Gender (male: female)	1.3 : 1	1.12 : 1
Ethnicity	Sudanese	Sudanese
City	AL Khartoum district	AL Khartoum district
Duration of disease (years)	-	4.19±3.12

CML: Chronic myeloid leukemia

DISCUSSION

The current study showed a strong association between *GSTT1* and *GSTM1* null polymorphisms and CML in Sudanese patients.

Exposure to xenobiotics can lead to genetic alterations that increase the risk of cancer development [24,25]. GSTs are a group of enzymes which play an important role in the detoxification and elimination of xenobiotics from the body [19]. Therefore, genetic variations that affect the expression of GST genes are expected to modulate the risk of cancer, including CML [26]. Examples of such variations are *GSTT1* and *GSTM1* null polymorphisms that result in the complete deletion of these genes [27]. The results of our study showed a strong association between *GSTT1* and *GSTM1* null polymorphisms and the risk of CML among Sudanese patients. This finding is consistent with the majority of previous studies involving other populations (Table 5). For example, a strong association between *GSTT1* and *GSTM1* null polymorphisms and CML was reported in Egyptian [23], Syrian [28], German [29], and some other populations [30]. A positive association between *GSTT1* null polymorphism and CML was reported in Turkish [31], Indian [32], and Kashmiri [22] population. On the other hand, several other studies reported a lack of association between CML and *GSTT1* and *GSTM1* null polymorphisms [33], which may be due to the differences in ethnicity and/or sample size.

The present study showed that the association between CML and *GSTT1* and *GSTM1* null polymorphisms was not affected by the gender and age of patients, which is consistent with previous reports [34,35]. However, our results indicated a significantly lower frequency of the *GSTM1* null genotype in advanced-phase CML patients compared to chronic-phase patients. Still, this finding needs to be confirmed in studies with larger sample sizes, as the number of CML patients in advanced phase was very small in our study. We showed no significant differences in Hb, platelet count, and WBC count between CML patients with and without the GST null polymorphisms and this is consistent with previous studies involving Egyptian and Indian populations [34,35].

GSTT1 and *GSTM1* null polymorphisms have been shown to increase the risk of different cancers such as oral [9], head

TABLE 2. Association of GST null polymorphisms with CML

Gene	CML patients (%)	Controls (%)	Odds ratio	95% confidence interval	p
Genotype					
GSTT1 null	76 (66.1)	39 (33.9)	3.25	1.87–5.65	0.001
GSTM1 null	68 (61.8)	42 (38.2)	2.14	1.25–3.67	0.004
Combination					
T1 M1 (null) haplotype	53 (67.1)	26 (32.9)	2.57	1.44–4.56	0.001

GST: Glutathione S-transferase; CML: Chronic myeloid leukemia; *GSTT1:* GST theta 1; *GSTM1*: GST mu 1

TABLE 3. Distribution of *GSTT1* and *GSTM1* null polymorphisms among CML patients according to gender, mean age, and CML phase

Genotype	Males n (%)	Females n (%)	*p*
GSTT1+	20 (30.8)	19 (38)	0.41
GSTT1 null	45 (69.2)	31 (62)	
GSTM1+	27 (41.5)	20 (40)	0.890
GSTM1 null	38 (58.5)	30 (60)	
	Below mean age n (%)	Above mean age n (%)	*p*
GSTT1+	21 (32.3)	18 (36)	0.79
GSTT1 null	39 (67.8)	37 (64)	
GSTM1+	26 (40)	21 (42)	0.95
GSTM1 null	38 (60)	29 (58)	
	Chronic phase n (%)	Accelerated and blast crisis n (%)	*p*
GSTT1+	31 (33.3)	8 (36)	0.78
GSTT1 null	62 (66.7)	14 (64)	
GSTM1+	34 (36.6)	13 (59.1)	0.05
GSTM1 null	59 (63.4)	9 (40.9)	

GST: Glutathione S-transferase; CML: Chronic myeloid leukemia; *GSTT1*: GST theta 1; *GSTM1*: GST mu 1

TABLE 4. Effect of *GSTM1* and *GSTM1* null polymorphisms on hematological parameters of CML patients

Parameter	*GSTT1* null	*GSTT1*+	*p*
Hemoglobin (%)	77.6±1.5	77.9±2.1	0.891
Platelet count ($\times 10^9$/L)	334.6±49.2	360.7±63.5	0.754
WBC count ($\times 10^9$/L)	16780±3752	25500±8115	0.254
Parameter	*GSTM1* null	*GSTM1*+	*p*
Hemoglobin (%)	78.44±1.7	76.74±1.5	0.485
Platelet count ($\times 10^9$/L)	347.6±42.8	327.6±93.5	0.835
WBC count ($\times 10^9$/L)	18670±5143	20650±5313	0.797

GST: Glutathione S-transferase; CML: Chronic myeloid leukemia; *GSTT1*: GST theta 1; *GSTM1*: GST mu 1; WBC: White blood cell

TABLE 5. Frequency of *GSTM1* and *GSTT1* null polymorphisms in other populations

Population	*GSTT1* null %	*GSTM1* null %	Association with CML	Study
Sudan	34	38	T1: +ve , M1: +ve	Current study
Germany	16	51	T1: +ve	[29]
India	9	25	T1: +ve , M1: -ve	[32]
Turkey	18	43	T1: +ve , M1: -ve	[31]
Syria	17	23	T1: +ve , M1: +ve	[28]
Brazil	23.8	64.5	T1: -ve , M1: +ve	[37]
Kashmiri	35	21	T1: +ve , M1: -ve	[22]
Egypt	8	14	T1: +ve , M1: +ve	[23]
Romania	24	68	T1: -ve , M1: -ve	[33]

GST: Glutathione S-transferase; CML: Chronic myeloid leukemia; *GSTT1*: GST theta 1; *GSTM1*: GST mu 1; +ve: Positive association; -ve: Negative association

and neck [8], prostate [7], and cervical cancer [36]. Moreover, these polymorphisms were associated with treatment outcomes in breast [10], non-small cell lung [6], and bladder cancer [11]. One of the possible mechanisms explaining the effect of GST null polymorphisms on treatment outcomes in cancer is the involvement of GST enzymes in the detoxification of environmental and food xenobiotics and the subsequent elimination of their mutagenic potential in cells [10].

Overall, our study suggests that *GSTT1* and *GSTM1* null polymorphisms are associated with CML among Sudanese patients independently of their age and gender.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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