Genetic polymorphism of drug metabolism enzymes (*GSTM1*, *GSTT1* and *GSTP1*) in the healthy Malian population

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Abstract

Glutathione S-transferase genes, known to be highly polymorphic, are implicated in the process of phase II metabolism of many substrates, including xenobiotics, anticancer and anti-infective drugs. The detoxification activity is linked to individual genetic makeup. Therefore, the identification of alleles and genotypes in these genes within a population may help to better design genetic susceptibility and pharmacogenetic studies. We performed the present study to establish the frequencies of the *GSTM1*, *GSTT1*, and *GSTP1* c. 313A > G (rs1695) polymorphisms in 206 individuals of the Malian healthy population. *GSTM1* and *GSTT1* were genotyped by using multiplex polymerase chain reaction, whereas genotypes of *GSTP1* were identified by polymerase chain reaction followed by restriction fragment length polymorphism. The frequencies of *GSTM1*-null and *GSTT1*-null genotypes were respectively 24.3 and 41.3%. The observed genotype frequencies for *GSTP1* were 25.73% homozygous wild-type AA, 49.03% heterozygous AG and 25.24% homozygous mutant GG. The frequency of *GSTP1*-A allele was 50.24% versus 49.76% for the *GSTP1*-G allele. The distribution of these three genes was homogeneous between men and women ($p > 0.05$). We found no statistical association between the presence of a particular profile of *GSTM1* or *GSTT1* with the genotypes of *GSTP1* ($p > 0.05$). Nevertheless, we noticed that the majority of the individuals harboring the *GSTM1*-present or the *GSTT1*-present harbor also the *GSTP1*-AG genotype. In addition, the triple genotype *GSTM1*-present/*GSTT1*-present/AG was the most frequent with 25.2%. Our findings will facilitate future studies regarding genetic associations of multifactorial diseases and pharmacogenetic, thus opening the way to personalized medicine in our population.

Keywords *GSTM1* · *GSTT1* · *GSTP1* c. 313A > G · Genotype · Mali

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Introduction

GSTM1, *GSTT1* and *GSTP1* belong to the super family of glutathione S-transferases (GSTs). These enzymes are known to play a key role in the metabolism of xenobiotic, anticancer and anti-infectious, through their participation in the second phase of xenobiotic metabolism [1, 2]. GSTs facilitate the excretion of electrophilic compounds from cells by conjugating them to hydrophilic compounds with reduced glutathione. In addition, GSTs appear to play a signaling role in the activation of cytoprotective genes by inhibiting the jun kinase pathway [3, 4]. This detoxification activity is intimately linked to the capacity of each individual, which is itself modulated by individual's genetic background [5, 6]. The superfamily of GST enzymes is divided in three main families including mitochondrial, microsomal and cytosolic families. Among these, the cytosolic family is composed of eight genes classes highly polymorphic: alpha (GSTA), mu (GSTM), theta (GSTT), pi (GSTP), zeta (GSTZ), sigma (GSTS), kappa (GSTK) and omega (GSTO) [7]. Of these, *GSTM1*, *GSTT1* and *GSTP1* are the most investigated in several situations, including genetic association studies exploring risk to disease and drug response. *GSTM1*, *GSTT1* and *GSTP1* are located on chromosome 1p13.3; 22q11.2 and 11q13.2 respectively [8, 9]. Deletions of *GSTM1* and *GSTT1* genes as well as the polymorphism c.313A > G (rs1695) in *GSTP1* have been associated not only with risk of developing certain multifactorial diseases such as cancer [10], diabetes [11], arterial hypertension [12], inflammatory bowel disease [13], hepatocellular carcinoma [14], but also therapeutic outcomes such as non-small cell lung cancer [15] and AIDS [16, 17]. Recently, the G allele of *GSTP1* was found to be associated with better performance in Russian athletes [18]. The Malian population is mainly composed of Bambara followed by Fulani, Soninke, Senufo, and Dogon [19]. It should be noted that the distribution of these genes varies significantly from one population to another [20]. However, to the best of our knowledge there is no data regarding the distribution of *GSTM1*, *GSTT1* and *GSTP1* genes in the Malian population. Therefore, we performed the present study to evaluate the genotypic and allelic distribution of these genes in the healthy Malian population. The results from the present study will facilitate future studies such as genetic susceptibility to disease and individual variability to drugs.

Materials and methods

Subjects

The study was approved by the Ethics Committee of the Faculty of Medicine and Odontostomatology (FMOS)/Faculty of Pharmacy (FAPH), University of Sciences, Techniques

and Technologies of Bamako (USTTB) under the number 2018/113/CE/FMPOS. All participants agreed and signed the informed consent. Then, five milliliters of peripheral venous blood were withdrawn in an EDTA tube at the Department of Infectious and Tropical Diseases, University Hospital Center of Point G. Samples were stored at -20°C at the laboratory of the International Center of Excellence in Research-Mali (ICER-Bamako, Mali) prior to DNA isolation. A total of 206 healthy and unrelated participants was recruited from August 2018 to January 2019.

Genotyping of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms

We used a multiplex polymerase chain reaction (PCR) with the *BCL2* gene as internal control was used to genotype *GSTM1* and *GSTT1* genes. The PCR reaction mixture consisted of 100 ng of genomic DNA, 1× of 10× Buffer (Invitrogen), 1.5 mM of MgCl_2 , 0.2 mM of each dNTP, 10 pM of each primer and 0.5 U of Taq polymerase (Invitrogen) completed to 25 μL with molecular grade water. The forwards and reverses primers used for *GSTT1*, *GSTM1* and *BCL2* as well as PCR amplification technical aspects were previously described in details by Kassogue et al. [21, 22]. DNA fragments were analyzed on a 2% agarose gel stained with 0.5 $\mu\text{g/mL}$ ethidium bromide. Expected product's sizes were 480 bp, 219 bp and 154 bp for *GSTT1*, *GSTM1* and *BCL2* respectively. *GSTT1* and *GSTM1* deletion were confirmed the presence of *BCL2* band. The *GSTT1*-null and *GSTM1*-null genotypes correspond to the deleted version of the genes, the *GSTT1*-present and *GSTM1*-present genotypes characterize the functional copies of the genes. The PCR amplification of c. 313A > G polymorphism in the *GSTP1* gene was performed as described by [23] with an initial denaturation at 94°C for 5 min, followed by 35 cycles of three steps: denaturation at 95°C for 45 s, annealing at 60°C for 60 s, extension at 72°C for 60 s and a final extension at 72°C for 5 min. PCR products were run on 2% agarose gel and showed 433 bp in length; the digestion was carried out with 10 units of restriction enzyme *BsmI* for 4 h. The digestion products were analyzed on a 3% agarose gel stained with 0.5 $\mu\text{g/mL}$ ethidium bromide. We used negative control in the PCR reactions by adding a DNA free-tube. Finally, 10% of the samples were retested to confirm the PCR results.

Statistical analysis

We used the statistical package SPSS version 16 (SPSS Inc., Chicago, IL, USA) to establish the genotypic and allelic frequencies in *GSTM1*, *GSTT1* and *GSTP1*. Hardy–Weinberg equilibrium was tested in the *GSTP1* gene by Chi square. The same test was used to determine the difference in genotype and allelic distribution with other populations. A *p* value less than 0.05 was considered as statistically significant.

Results

The present study included 206 healthy participants, composed of 54.9% women and 45.1% men; the mean age of participants was 30.65 years (range from 18 to 73 years).

Table 1 shows the distribution of GST polymorphisms identified in the Malian healthy population. The frequency of *GSTM1*-null genotype was 24.3%. This distribution of *GSTM1*-null between women and men showed no statistical difference 19.5% versus 30.1% ($X^2 = 3.14$; $p = 0.1$).

Table 1 Distribution of Alleles, single and combined genotypes of *GSTs* genes in 206 healthy subjects

Genes	Genotypes/Alleles	All participants, N (%)	Male, N (%)	Female, N (%)	<i>P</i>
<i>GSTM1</i>	Null	50 (24.3)	28 (30.1)	22 (19.5)	0.1 ^a
	Present	156 (75.7)	65 (69.9)	91 (80.5)	
<i>GSTT1</i>	Null	85 (41.3)	37 (39.8)	48 (42.5)	0.7 ^b
	Present	121 (58.7)	56 (60.2)	65 (57.5)	
<i>GSTM1/GSTT1</i>	Null/Null	23 (11.2)	11 (11.8)	12 (10.6)	0.23 ^c
	Null/Present	27 (13.1)	17 (18.3)	10 (8.8)	
	Present/Null	62 (30.1)	26 (28)	36 (31.9)	
	Present/Present	94 (45.6)	39 (41.9)	55 (48.7)	
<i>GSTP1</i>	AA	53 (25.73)	27 (29)	26 (23)	0.43 ^d
	AG	101 (49.03)	46 (49.5)	55 (48.7)	
	GG	52 (25.24)	20 (21.5)	32 (28.3)	
	A	207 (50.24)	100 (53.76)	107 (47.35)	
	G	205 (49.76)	86 (46.23)	119 (52.65)	
<i>GSTM1/GSTP1</i>	Present/AG	82 (39.8)	35 (42.7)	47 (57.3)	0.45 ^e
	Present/GG	38 (18.4)	14 (36.8)	24 (63.2)	
	Present/AA	36 (17.5)	16 (44.4)	20 (55.6)	
	Null/AG	20 (9.7)	11 (55)	9 (45)	
	Null/AA	17 (8.3)	11 (64.7)	6 (35.3)	
<i>GSTT1/GSTP1</i>	Null/GG	13 (6.3)	6 (46.2)	7 (53.8)	0.6 ^f
	Present/AG	64 (31.1)	31 (48.4)	33 (51.6)	
	Present/GG	26 (12.6)	11 (42.3)	15 (57.7)	
	Present/AA	31 (15)	14 (45.2)	17 (54.8)	
	Null/AG	37 (18)	15 (40.5)	22 (59.5)	
<i>GSTM1/GSTT1/GSTP1</i>	Null/AA	22 (10.7)	13 (59.1)	9 (40.9)	0.45 ^g
	Null/GG	26 (12.6)	9 (34.6)	17 (65.4)	
	Present/Present/AG	52 (25.2)	24 (46.2)	28 (53.8)	
	Present/Null/AG	29 (14.1)	11 (37.9)	18 (62.1)	
	Present/Present/AA	22 (10.7)	24 (46.2)	28 (53.8)	
	Present/Present/GG	20 (9.7)	8 (40)	12 (60)	
	Present/Null/GG	19 (9.2)	6 (31.6)	13 (68.4)	
	Present/Null/AA	14 (6.8)	9 (64.3)	5 (35.7)	
	Null/Present/AG	12 (5.8)	7 (58.3)	5 (41.7)	
	Null/Present/AA	9 (4.4)	7 (77.8)	2 (22.2)	
	Null/Null/AA	8 (3.9)	4 (50)	4 (50)	
	Null/Null/AG	8 (3.9)	4 (50)	4 (50)	
	Null/Null/GG	7 (3.4)	3 (42.9)	4 (57.1)	
	Null/Present/GG	6 (2.9)	3 (50)	3 (50)	

^a $X^2 = 3.14$

^b $X^2 = 1.53$

^c $X^2 = 4.29$

^d $X^2 = 1.66$

^e $X^2 = 4.68$

^f $X^2 = 3.57$

^g $X^2 = 10.8$

The *GSTT1*-null genotype was observed in 41.3% of our participants. There was no statistical difference in the distribution of *GSTT1*-null genotype according to gender; the frequency in women was 42.5% versus 39.8% in men ($X^2 = 1.53$; $p = 0.7$) (Table 1). The distribution of *GSTP1* c. 313A > G (rs1695, p. 105 Ile > Val) did not deviate from the Hardy–Weinberg equilibrium for all participants, nor when gender was considered ($p > 0.05$). The observed genotype frequencies for *GSTP1* were 25.73% homozygous wild-type AA, 49.03% heterozygous AG and 25.24% homozygous mutant GG. We found that 50.24% of our participants harbor the wild type allele A versus 49.76% for the mutant allele G (Table 1). Furthermore, the analysis was extended to the combined double and triple genotypes. The combined *GSTM1*-null/*GSTT1*-null genotype was found in 11.2% of the participants while the combined *GSTM1*-present/*GSTT1*-present was observed in 45.6%. When considering participants' gender, we noticed that the frequencies of double null genotype in men and women were similar 11.8% versus 10.6% (Table 1). Overall, the combination of *GSTM1* and *GSTT1* regarding gender showed no statistical difference ($X^2 = 4.29$; $p = 0.23$). The combination of triple genotypes showed that, the most common genotypes in our population were 25.2% for *GSTM1*-present/*GSTT1*-present/AG; 14.1% for *GSTM1*-present/*GSTT1*-null/AG and 10.7% for *GSTM1*-present/*GSTT1*-present/AA (Table 1). We found no statistical association between the simultaneous presence of a particular profile of *GSTM1* or *GSTT1* with the different genotypes of *GSTP1* ($p > 0.05$). However, the majority of the individuals harboring the *GSTM1*-present or the *GSTT1*-present harbor also the heterozygous AG genotype (Table 1). Statistical analysis has not been extended to the interethnic distribution of GSTs genes due to mixing between different ethnic groups in the Malian population.

Discussion

Genetic association studies, including individual susceptibility to disease and individual variation in drug response have demonstrated that the *GSTM1*, *GSTT1* and *GSTP1* genes are involved in the metabolism of many substrates. As a result, GSTs play a crucial role in the daily detoxification of body cells against harmful compounds. To our knowledge, this is the first time that *GSTM1*, *GSTT1* and *GSTP1* profiles have been established in the Malian healthy population. In this study, we found that the distribution of *GSTM1*-null, *GSTT1*-null, and *GSTP1* in women and men were statistically comparable, $p > 0.05$ (Table 1). Santovito et al., reported similar results from north Ivory Coast regarding the distribution of *GSTM1*-null and

GSTT1-null [24]. This finding may support the hypothesis that women and men probably have similar detoxification capabilities when exposed to xenobiotics. The frequency of *GSTM1*-null genotype observed in the Malian was statistically comparable to those reported across West Africa particularly in Gambia, Nigeria, and Ghana except Ivory Coast where we noted a significant statistical difference ($p = 0.02$) in the distribution of *GSTM1*-null (Table 2). The frequency of *GSTT1*-null in our population was higher than that reported in the Ghanaian population ($p = 0.003$). On the other hand, the distribution of *GSTT1*-null in other West Africa countries listed in Table 2 was comparable to the frequency observed in the Malian population. Considering the North Africa, we noticed that, the frequency of *GSTM1*-null in our population was comparable to the frequencies observed in Egypt and Algeria. However, the frequencies observed in Tunisia, Morocco and Sudan were statistically higher than the frequency of our population $p = 0.000$ for both Morocco and Tunisia and 0.003 for Sudan (Table 2). The *GSTT1*-null frequencies observed in Tunisia, Morocco and Algeria were statistically lower than those observed in the Malian population ($p = 0.009$ for both Algeria and Tunisia and 0.000 for Morocco). However, the distribution of *GSTT1*-null in Egypt, Sudan and Mali showed similar trends. We found no difference in the distribution of *GSTM1*-null and *GSTT1*-null between Cameroon representing Central Africa and Mali. The *GSTM1*-null distribution map in East Africa showed that Ethiopia and Somalia had higher frequencies of the null genotype compared to that observed in Mali. However, the frequency of *GSTM1*-null reported in Tanzania was not statistically different from that of the Malian population (Table 2). Meanwhile, the *GSTT1*-null distribution map was opposed to that of the *GSTM1*-null. Indeed, the frequencies of *GSTT1*-null reported in Ethiopia and Somalia were similar to that seen in Mali. In the contrary, the *GSTT1*-null observed in Mali was statistically higher than that observed in Tanzania ($p = 0.01$). In Southern Africa, the frequency of *GSTM1*-null seen in Mali was in line to those reported in Zimbabwe and South Africa, but higher than that observed in Namibia ($p = 0.003$). We have noted that, the frequency of *GSTT1*-null in Namibia was statistically comparable to that reported in Mali. However, the distribution of *GSTT1*-null in Zimbabwe and South Africa were statistically lower when compared to that of the Malian population (Table 2). Overall, the mean frequency of *GSTM1*-null in Africa increases from South to the East (19.5–38.93%) in a clockwise direction. However, the mean frequency of *GSTT1*-null is similar between West and East (35.32–35.33%) on the one hand and between South and North (27.16–29.11) on the other hand (Table 2). It noteworthy to mention that the frequency of *GSTM1*-null observed in our population

Table 2 Distribution of *GSTM1* and *GSTT1* polymorphisms in different African population

Populations	N	<i>GSTM1</i> null %	P	<i>GSTT1</i> null %	P	References
West Africa						
Malian (this study)	206	24.3	–	41.3	–	
Gambia	294	25.6	0.7	44.9	0.4	[35]
Ivory Coast	133	36.1	0.02	33.1	0.13	[24]
Nigeria	300	30	0.15	37.3	0.37	[36]
Ghana	60	18.3	0.34	20	0.003	[26]
Mean %		26.86		35.32		
North Africa						
Egypt	80	31.25	0.23	41.25	1	[37]
Morocco	129	48.1	0.000	19.4	0.000	[27]
Algeria	41	14.6	0.18	19.5	0.009	[30]
Tunisia	154	53.9	0.000	27.9	0.009	[28]
Sudan	104	40.4	0.003	37.5	0.5	[29]
Mean %		37.65		29.11		
Central Africa						
Cameroon	126	27.8	0.5	46.8	0.3	[20]
East Africa						
Tanzania	115 ⁿ¹ /81 ⁿ²	33	0.09	24.7	0.01	[38]
Ethiopia	153	43.8	0.000	37.3	0.44	[20]
Somalia	100	40	0.005	44	0.64	[39]
Mean %		38.93		35.33		
South Africa						
South Africa	96 ⁿ¹ /71 ⁿ²	23	0.8	19.7	0.001	[38]
Namibia	134	11.2	0.003	35.8	0.31	[31]
Zimbabwe	148 ⁿ¹ /132 ⁿ²	24.3	0.99	26	0.005	[38]
Mean %		19.5		27.16		

ⁿ¹Number of samples tested for *GSTM1*ⁿ²Number of samples tested for *GSTT1*

is lower than those reported in the European population (38–67%), the Asian population (33 à 63%) but consistent with those observed in Africans and African-Americans (22 à 35%) [25]. It was reported that the *GSTM1*-null and *GSTT1*-null were associated with the risk of hepatotoxicity in HIV positive patients [17]. In addition, significant association of *GSTM1*-null with the development of Stevens-Johnson syndrome and toxic epidermal necrolysis has been reported in HIV patients in Mozambique [16]. Therefore, identification of these genes in our antiretroviral-prescribed patients could facilitate the determination of higher-risk groups. The frequency of the double deletion found in our population 11.2% was lower than those reported in Ivory Coast 14.3% [24], Ghana 16.66% [26], Morocco 15.5% [27], Egypt 16.25% [28], Tunisia 18% [28] and Sudan 32.9% [29], but higher than that seen in Algeria 7.31% [30] and Namibia 3% [31]. The distribution of the mutant allele G in *GSTP1* gene observed in our population 49.76% was statistically comparable to that reported in the Gambian population 53.6%, ($p = 0.2$). On the other

hand, the frequencies of *GSTP1*-G mutant allele reported in other Africa regions, including North, East and South Africa were significantly lower than that observed in the Malian population, $p = 0.000$ (Table 3). In a meta-analysis, Ma et al showed that *GSTP1* polymorphism can be considered as a factor of toxicities prediction in breast cancer patients receiving chemotherapy [32]. Therefore, identification of this polymorphism in our breast cancer patients may help to determine the group at risk of toxicities. The majority of people harboring the *GSTM1*-present or the *GSTT1*-present also harbor the heterozygous AG genotype. The combination of three genotypes showed that the most common combined genotypes in our population were 25.2% for *GSTM1*-present/*GSTT1*-present/AG. A Similar frequency was reported in the Argentinean population 24.7% [33]. We found no statistical association between *GSTM1* and *GSTT1* genotypes with *GSTP1* genotypes. This suggests the absence of a protective mechanism to compensate for a reduced activity of one of these genes. On the contrary, Weich et al. have noted

Table 3 Distribution of *GSTP1* c.313 A>G polymorphism in different African population

Populations	N	AA N (%)	AG N (%)	GG N (%)	G Allele N (%)	P	References
West Africa							
Malian (this study)	206	53 (25.73)	101 (49.03)	52 (25.24)	205 (49.76)	–	
Gambia	338	45 (13)	224 (66)	69 (21)	362 (53.6)	0.2	[40]
North Africa							
Egypt	80	53 (66.25)	25 (31.25)	2 (2.5)	29 (18.1)	0.000	[37]
Tunisia	128	79 (30.61)	41 (52.42)	8 (14.96)	57 (22.3)	0.000	[41]
Sudan	104	60 (57.69)	42 (40.39)	2 (1.92)	46 (22.1)	0.000	[42]
East Africa							
Tanzania	102	79 (77)	14 (14)	9 (9)	32 (15.7)	0.000	[38]
Ethiopia	100	64 (64)	29 (29)	7 (7)	43 (21.5)	0.000	[43]
Somalia	100	53 (53)	39 (39)	8 (8)	55 (27.5)	0.000	[39]
South Africa							
South Africa	87	67 (77)	19 (22)	1 (1)	21 (12.1)	0.000	[38]
Zimbabwe	97	56 (58)	35 (36)	6 (6)	47 (24.2)	0.000	[38]

a statistical association between the combined genotypes *GSTM1*-present and *GSTP1*-AG or *GSTP1*-GG genotypes [33]. Zhou et al. have reported that breast cancers patients carrying either AG or GG genotypes of *GSTP1* and receiving thiotepa-containing chemotherapy regimens were at increased risk for metastatic lesions in the liver [34]. The results from this study could facilitate evidence-based management of our breast cancers patients undergoing chemotherapeutic treatment.

Our results showed that the frequencies of the null genotypes of *GSTM1* and *GSTT1* observed in the Malian population are comparable to those reported in the West African population, except Ivory Coast for *GSTM1* and Ghana for *GSTT1*. The frequency of the GG mutant genotype of *GSTP1* in our population was higher than those reported in the African population except in the Gambia. This study confirms the diversity of the ethnic and geographical distribution of these genes in different populations worldwide.

Conclusion

We have established the allelic and genotypic frequencies of the *GSTM1*, *GSTT1* and *GSTP1* c.313A>G genes in the healthy Malian population. The results from this study will facilitate not only future studies of genetic associations on multifactorial diseases, but also pharmacogenetic studies, thus opening the way to personalized medicine in our population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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