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Comparative frequency distribution of glutathione S-transferase mu (*GSTM1*) and theta (*GSTT1*) allelic forms in Himachal Pradesh population

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Abstract

Background: Glutathione S-transferases (GSTs) are a class of important Phase II detoxification enzymes that catalyze the conjugation of glutathione and xenobiotic compounds (environmental carcinogens, pollutants and drugs) to protect against oxidative stress. *GSTT1* and *GSTM1* genetic polymorphisms have been extensively studied, and null genotypes or homozygous deletions have been reported in various populations. Previous studies have suggested that those who are homozygous null at the *GSTM1* or *GSTT1* loci are more susceptible and have a higher risk of cancers linked to environmental pollutants and drug-induced toxicity. Our study focused on *GSTM1* and *GSTT1* null allele frequency in the Doon population of Himachal Pradesh (India) with a comparison across other Inter and Intra-Indian ethnic groups to predict variation in the possible susceptible status.

Material and methods: Genomic DNA samples were extracted from 297 healthy unrelated individuals by a ReliaPrep™ Blood gDNA Miniprep kit (Promega, USA), and genotyped for allelic variation in *GSTM1* and *GSTT1* genotypes by multiplex polymerase chain reaction. Fisher's exact test was applied using SPSS.20 to analyze the genotypic distribution of *GSTM1* and *GSTT1* null alleles in male and female of Doon region (Solan) Himachal Pradesh.

Results: In our study, the frequency distribution of the homozygous null genotypes of *GSTM1*, *GSTT1* individually as well as combined was found as 33.3%, 32% and 9%, respectively. Upon gender-wise comparison, a non-significant distribution ($p > 0.05$) for null genotypes of *GSTM1* (32.8% and 35.4%, OR-0.77, 95% CI 0.42–1.41), *GSTT1* (33.2% and 27.7%, OR-1.12, 95% CI 0.63–2.0) individually and combined *GSTM1* and *GSTT1* (10.8% and 3.7%, OR-0.31, 95% CI 0.07–1.42) were observed in studied population.

Conclusions: In our studied population, the frequency of *GSTM1* null genotypes was found deviated from Inter- and Intra-Indian ethnic groups. However, the frequency of homozygous null type of *GSTT1* was not significantly different, when compared to previous Indian studies, comparison with global ethnic groups showed deviation. Thus, our study has highlighted possible susceptibility risk to various xenobiotics in the Doon population of Himachal Pradesh, India.

Keywords: *GSTM1*, *GSTT1*, Polymerase chain reaction, Polymorphism, Genotype, Allele

Introduction

The glutathione S-transferase (GSTs) are one of the important xenobiotics metabolizing gene family; it plays a vital role in the metabolic detoxification of oxidative stress stimulating, electrophilic compounds, carcinogens,

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and environmental toxins [13, 16, 37]. By their origin, GSTs are classified as cytoplasmic, mitochondrial, and membrane-associated proteins (MAPEG). Seven classes of cytoplasmic GSTs are categorized as Alpha (GSTA), Mu (GSTM), Omega (GSTO), Pi (GSTP), Sigma (GSTS), Theta (GSTT), and Zeta (GSTZ) [38].

GSTs have the ability to detoxify toxic metabolic products, like reactive nitrogen and oxygen species via glutathione peroxidase activity [9, 26]. Other than detoxification, GSTs perform a variety of biological functions including regulation of S-glutathionylation cycle, and kinase-mediated signal transduction [18, 25, 26, 41].

Previous studies have shown that deletion variations associated with *GSTM1* and *GSTT1* genes are located at chromosome 1 (1p13.3) and (22q11.23), respectively. Individuals having deletion variants (null/null) of *GSTM1* or *GSTT1* genes demonstrate a complete lack of enzymatic activity for corresponding protein [26, 28, 40]. A loss of function in the *GST*s classes (*M1* and *T1*) due to a structural deletion (Null mutation) impacts an individual's ability to detoxify genotoxic compounds [36, 37]. GSTM1 catalyzes and detoxifies polycyclic aromatic hydrocarbon diol epoxides, such as DNA hydroperoxides, alkyl halide (component of cigarette smoke), while GSTT1 catalyzes and detoxifies benzo (a) pyrene diol epoxide, and acrolein [17, 36]. *GSTM1* and *GSTT1* deficiencies, either alone or in combination, are thought to have reduced detoxifying characteristics; henceforth, contribute significantly toward increased susceptibility to various types of cancer [26, 42].

In the last few decades, *GSTM1* and *GSTT1* null genotypes have been investigated extensively in a variety of ethnic groups, and their widespread presence has been well established [8, 11, 32, 37]. For example, the prevalence of the *GSTM1* null genotype was observed 47–57% in Caucasians, 42–54% in Asians, and 16–36% in Africans, respectively, while the *GSTT1* null genotype was uncommon in Caucasians (13–26%), and shown higher prevalence among Asians (35–52%) [10, 37]. These variability of *GSTM1* and *GSTT1* null genotypes across the worldwide population might be linked to illness susceptibilities that are unique to each population. India's ethnic communities are diverse, both physiologically and culturally [22, 37], and northern India's ethnic groups are particularly diverse, because of various tribal groups of Indo-European ancestry that have lived here over several waves of migration. Therefore, we have been prompted to evaluate the *GSTM1*, *GSTT1* genotype distribution in the Northern state (Himachal Pradesh) population and to compare it with various Indian states and global populations. This is one of the first research of its type to be conducted among the people of Himachal Pradesh.

Materials and methods

Studied population and sample collection

The study was carried out among 297 healthy unrelated Himachal Pradesh residents (232 males and 65 females) with ages, ranging from 20 to 62 years. The study's goals were well explained to all the participants and were asked to fill out a questionnaire to collect personal details as well as information related to their socioeconomic status. The research was duly approved by Institutional Ethical Committee, Maharaja Agrasen University, Baddi (HP) India.

For DNA extraction, a blood sample (5 mL) was drawn from each of the participants and collected in a vacutainer tube containing K_2EDTA. All samples were transported to the laboratory in an insulated ice bucket for further processing.

Genotyping of *GSTM1* and *GSTT1*

Genomic DNA was extracted from 200 µL of whole blood using ReliaPrep™ Blood gDNA Miniprep kit (Promega, USA). The presence or absence of the *GSTM1* and *GSTT1* genes was determined by multiplex-PCR. As an internal control, a portion of exon 7 of the housekeeping gene such as *CYP1A1* was also co-amplified. The primer sequences [1, 20] and product size of the *GSTM1* and *GSTT1* genes are listed in Table 1. Both genes were genotyped using a 25-µL reaction mixture containing 1 µL of genomic DNA template (100 ng/µL), 1 µL of each primer (20 pmol/mL), 0.5 µL of dNTPs (200 µM), 2.5 µL of PCR buffer with 15 mM/L $MgCl_2$, and 0.5 µL of Taq polymerase (3 U/µL) and 19.5 µL sterile nuclease free water. In

Table 1 *GSTM1* and *GSTT1* gene's primer sequences

Name of gene	Sequence of primer	PCR product size (bp)
CYP1A1 (internal control)	Forward 5′-GAACTGCCACTTCAGCTGTCT-3′	312
	Reverse 5′-CAGCTGCATTTGGAAGTGCTC-3′	
GSTM1	Forward 5′-GAACTCCCTGAAAAGCTAAGC-3′	215
	Reverse 5′-GTTGGGGCTCAAATATACGGTGG-3′	
GSTT1	Forward 5′-TTCCTTACTGGTCCTCACATCTC-3′	480
	Reverse 5′-TCACCG GATCATGGCCAGCA-3′	

total, 30 thermal cycles were performed. PCR reaction cycle included, initial denaturation (at 94 °C for 10 min); denaturation (at 94 °C for 60 s); annealing (at 59 °C for 45 s); and extension (at 72 °C for 60 s). The final extension was carried out at 72 °C 10 min and the amplification results were examined on 2% agarose gel.

Statistical analysis

Allelic frequencies of *GSTM1* and *GSTM1* were determined by direct counting and by ensuring presence or absence of DNA bands on agarose gel. Fisher's exact test (SPSS 20; IBM, New York, USA) was applied for gender-wise distribution of both *GST*s genotypes in the studied population.

Results

The outcomes of *GSTM1* and *GSTT1* genotyping, as well as the general frequency distributions of *GST* polymorphisms in the studied population, are shown in Fig. 1 and Table 2. In our study, the frequency distribution of the homozygous null genotypes of *GSTM1*, *GSTT1* individually as well as combined was found as 33.3%, 32% and 9%, respectively. Upon gender-wise comparison, a non-significant distribution ($p > 0.05$) for null genotypes of *GSTM1* (32.8% and 35.4%, OR-0.77, 95% CI 0.42–1.41), *GSTT1* (33.2% and 27.7%, OR-1.12, 95% CI 0.63–2.0) individually and combined *GSTM1* and *GSTT1* (10.8% and 3.7%, OR-0.31, 95% CI 0.07–1.42) were observed in studied population (Table 2). Allelic distribution of *GSTM1* and *GSTT1* among various ethnic groups is shown in Table 3.

Discussion

GSTM1 and *GSTT1* are the most important phase II xenobiotic metabolizing or detoxifying enzymes that catalyze glutathione conjugation, play a key role in metabolism of different types of reactive species. *GST* enzymes protect nucleic acids such as DNA from endogenous oxidants and save the cells by detoxifying the carcinogens and environmental contaminants. GSTs family members are major candidates for cancer disease risk, because they have the potential to regulate a person's ability to metabolize a carcinogen. It has been reported that carries with homozygous deletions lack GST-m and GST-θ enzyme activity. The presence of deletion variations (null type) in *GSTM1* and *GSTT1* genes, could damage DNA and result in different types of cancer. The results of our investigation suggest that the frequencies of *GSTM1* and *GSTT1* null genotypes in the Doon population of Himachal Pradesh (North Indian region of Asian continent) are comparatively higher.

The allelic distribution of *GSTM1* and *GSTT1* among various ethnic groups has been studied (Table 3). The highest percentage of null alleles of *GSTM1* (66.3%) and *GSTT1* (42.5%) was observed in Asian and American populations, respectively [4, 6], while the lowest percentage of *GSTM1* (11.2%) and *GSTT1* (10.4%) null alleles were found in African and Asian populations, respectively [8, 27].

In our study, 33.3% of the Doon population of Himachal Pradesh had *GSTM1* homozygous null or deletion genotype (Tables 2 and 3). Our results were in agreement with those of Asian, who had *GSTM1* null frequencies ranging

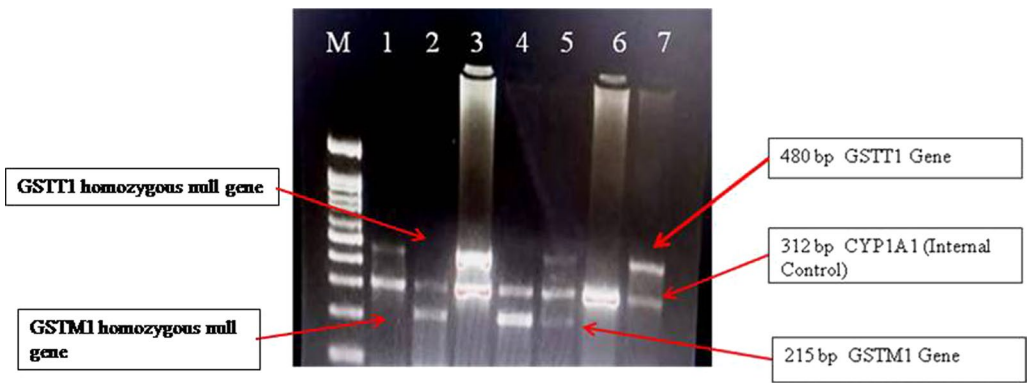

Fig. 1 2% agarose gel is showing M lane is 100 pb marker, in lane 1, 3 and 7 are showing GSTT1 non-null and GSTM1 homozygous null genotyping. Lane 2 and 4 are showing GSTM1 non-null and GSTT1 homozygous null genotyping. Lane 5 is showing both GSTM1 and GSTT1 non-null genotyping and Lane 6 is showing both GSTM1 non-null and GSTT1 homozygous null genotyping

Table 2 Overall distributions of *GSTT1* and *GSTM1* genotypes according to gender in the Himachal Population

Gender	No (%)	*GSTM1 N* (%)		*P* value OR (CI 95%)	*GSTT1 N* (%)		*P* value OR (CI 95%)	*GSTM1* + *T1 N* (%)		*P* value OR (CI 95%)
		Null	Non-null		Null	Non-null		Null	Non-null	
Males	232 (78)	76 (32.8)	156 (67.2)	$p > 0.05$	77(33.2)	155(68.8)	$p > 0.05$	25(10.8)	107(46.2)	$p > 0.05$
				1.12			0.77			0.31
Females	65 (22)	23 (35.4)	42 (64.6)	(0.63–2.00)	18(27.7)	47(72.3)	(0.42–1.41)	2 (3.07)	27(41.5)	(0.07–1.42)
Total	297 (100)	99 (33.3)	198 (66.7)		95 (32)	202 (68)		27 (9%)	134 (45.1)	

Fisher's exact test was used for comparison of gene frequency between male and female participants. No significant differences were observed ($p > 0.05$).CI- Class Interval, OD- Odd ratio, Null genotype is representing homozygous deletion (absence of both alleles)

Table 3 *GSTM1* and *GSTT1* null genotype frequency distribution among the different ethnic groups

References	Studied population	No. of individual	GSTM1 Null genotype (%)	GSTT1 Null genotype (%)
Pinheiro et al. [29]	American	147	43.5	12.2
Millikan et al. [24]	American	268	26.9	36.6
Possuelo et al. [30]	American	49	41.2	38.3
de Souza et al. [6]	American	134	44.8	42.5
Fujihara et al. [8]	African	341	11.2	35.8
Kassogue et al. [15]	African	60	45.0	22.0
Medjani et al. [23]	African	101	49.5	22.7
Alshagga et al. [4]	Asian	137	66.0	18.0
Wu et al. [39]	Asian	895	36.4	40.1
Dadbinpour et al. [7]	Asian	57	55.5	22.7
Al-Achkar et al. [2]	Asian	172	23.0	17.0
Shukla et al. [34]	Asian	238	37.8	24.4
Kumar et al. [20]	Asian	308	40.6	32.8
Ritambhara Tiwari et al. [31]	Asian	100	46.0	33.0
Present Study	**Asian (India)**	**297**	**33.3**	**32.0**
Peddireddy et al. [27]	Asian	250	24.0	10.4
Suthar et al. [37]	Asian	700	42.4	25.3
AL-Eitan et al. [3]	Asian	219	53.4	26.9
Sikdar et al. [35]	Asian	67	27.0	13.0
Ihsan et al. [14]	Asian	154	42.9	27.3
Klusek et al. [19]	European	104	45.2	20.2
Bu et al. [5]	European	203	51.0	18.0
Lopez-Cima et al. [21]	European	789	53.5	21.3
Schneider et al. [33]	European	622	52.5	16.5
Gra et al. [12]	European	352	50.0	19.0

The bold statement indicates the results of our study, where, we have compared the prevalence of GST genotypes in the global population on the basis of ethnicity

from 36.4 to 37.8% [34, 39]. Furthermore, we observed 32% of Doon population of were homozygous null or deletion for *GSTT1* gene. The prevalence of homozygous null genotype of GSTT1 in in Doon population (Table 2) shows similar trend to other northern Indian populations (Table 3), [20, 31]. When compared to other Asian populations, the frequency of *GSTT1* null genotype varies 10.4–27.3% which was less than and contradicting our findings [14, 27] in Asian populations. However, few studies also have shown higher percentage (35.8–40.1) of *GSTT1* null genotype among different ethnic groups [8, 39]. *GSTM1* and *GSTT1* null frequency among Europeans varied from 45.2 to 53.5% and 16.5 to 21.3%, respectively (Table 3). *GSTM1* null variants in African people varied from 11.2 to 49.5%, while *GSTT1* null frequencies ranged from 22 to 35.8% (Table 3). Genotyping studies of both *GSTM1* null and *GSTT1* null in Asian population varied from 23.0 to 66% and 10.4 to 40.1%, respectively (Table 3). In the American, the genotype percentage of *GSTM1* and *GSTT1* alleles varied from 26.9 to 44.8 and 12.2 to 42.5% (Table 3). In our study, we also found non-significant differences ($p > 0.05$) in homozygous null genotypes of *GSTM1*, *GSTT1* gene, individually as well as in combination among males and females in the studied population (Table 2). Upon gender-wise comparison, the non-significant differences of *GST*s null genotypes might be due to the unequal number of male and female participants in the study. However, our results were in agreement with findings of a few Asians studies [10]. The difference in the gene frequency of *GSTM1* and *GSTT1* among the various ethnic populations is largely due to their different evolutionary histories and method selection. Our research would be useful to the Doon population of Himachal Pradesh, and globally, it will allow us to find out risk factors for disease like cancer within the susceptible individuals.

Conclusions

GSTs are involved in the detoxification of various xenobiotic compounds; therefore, knowing the prevalence of various GST alleles in a population might help in determining a risk due to susceptibility. The current study reveals

the allelic distribution of *GSTM1* and *GSTT1* genes in the Himachal Pradesh population of the Northern region of India. Our findings have further strengthened the heterogeneity of *GSTT1* and *GSTM1* gene polymorphisms in the global population and also highlighted its role as a biomarker of susceptibility. From future perspectives, our findings might lay down a pathway for future bio-monitoring studies involving the risk of xenobiotic exposure in Himachal Pradesh. Moreover, our findings might add to a better understanding of the relationship between ethnicity and illness prevalence. It also might be helpful in explaining the significance of gene behavior in epidemiological and clinical research.

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Author contributions
Hemlata has done entire analysis of the research work. SKG has supervised this work. JS assists with the genotyping of genes. AB, AK and GS helped in the manuscript editing. KP has given valuable suggestions. All authors read and approved the manuscript.

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Availability of data and materials
The data that support the finding are available on request from corresponding author. The data are not publicly available due to privacy or ethical restriction.

Declarations

Ethics approval and consent to participate
Participants were requested to sign a permission form (consent form), and each was questioned in person using a predetermined set of questions (standard questionnaire) which included information about their socioeconomic situation. Institutional ethical committee (IEC), Maharaja Agrasen University, Baddi (HP) India approved the study's research methodology.

Consent for publication
All the authors have permitted the submission of the research paper in your journal.

Competing interests
The authors declare no conflict of interest.

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