RESEARCH ARTICLE

Genetic Polymorphisms of *GSTM1* and *GSTT1* Genes in Delhi and Comparison with other Indian and Global Populations

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Abstract

The glutathione S-transferases (GSTs) are involved in the metabolism of many xenobiotics, including an array of environmental carcinogens, pollutants, and drugs. Genetic polymorphisms in these genes may lead to inter-individual variation in susceptibility to various diseases. In the present study, *GSTM1* and *GSTT1* polymorphisms were analysed using a multiplex polymerase chain reaction in 500 normal individuals from Delhi. The frequency of individuals with *GSTM1* and *GSTT1* null genotypes were 168 (33.6%) and 62 (12.4%) respectively, and 54(10.8%) were having homozygous null genotype for both the genes *GSTM1* and *GSTT1*simultaneously. The studied population was compared with reported frequencies from other neighbouring state populations, as well as with those from other ethnic groups; Europeans, Blacks, and Asians. The prevalence of homozygous null *GSTM1* genotype is significantly higher in Caucasians and Asians as compared to Indian population. The frequency of *GSTT1* homozygous null genotypes is also significantly higher in blacks and Asians. We believe that due to large number of individuals in this study, our results are reliable estimates of the frequencies of the *GSTM1*, *GSTT1* in Delhi. It would provide a basic database for future clinical and genetic studies pertaining to susceptibility and inconsistency in the response and/or toxicity to drugs known to be the substrates for GSTs.

Keywords: *GSTM1* - *GSTT1* - GSTP1 - polymorphism - North Indians.

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Introduction

All organisms are constantly and unavoidably exposed to a large number of foreign chemicals or xenobiotics. Most of these chemical carcinogens are not capable of inducing genetic damage themselves but require metabolic activation to electrophilic proximate carcinogens. Whether a compound contributes to cancer or other disease depends not only on the extent of an individual's exposure, but also on the effectiveness of the individual's ability to remove toxins from the body, involving phase-I (cytochrome P450) and phase-II (glutathione S- transferase) enzymes (Mannervik et al., 1992).

Glutathione S-transferases (GSTs), a multigene family of phase-II metabolic enzymes, are active in the detoxification of a wide variety of potentially toxic and carcinogenic electrophiles by conjugating them to glutathione (Pemble et al. 1994). In mammals the eight classes of GSTs, i.e. alpha (GSTA), mu (GSTM), theta (GSTT), Pi (GSTP), zeta (GSTZ), sigma (GSTS), kappa (GSTK), and omega (GSTO) have been identified (Mannervik et al., 1992), based on sequence homology and substrate specificity. Among them GSTM1andGSTT1 polymorphisms are extensively studied. GSTM1 is situated in the GSTμ cluster, which is localised to chromosome 1 in region 1p13.3 and is involved in the detoxification of polycyclic aromatic hydrocarbons and other mutagens. GSTT1 gene is located on chromosome 22q11.2 and is involved in the metabolism of small compounds found in tobacco smoke like mono halo methanes and ethylene oxide (Hayes and Pulford, 1995). The polymorphism in GSTM1 and GSTT1 gene loci is caused by a gene deletion which results in the absence of enzyme activity in individuals with the GSTT1 and GSTM1 null genotypes. These homozygous null polymorphisms of GSTM1 and GSTT1 may lead to wide inter-individual variations in the metabolic activation of chemical carcinogen (Board, 1981). The polymorphisms of GSTM1, GSTT1 have been associated with cancers of the lung, bladder, breast and colon (Autrup, 2000). Therefore, we evaluated the distribution of GSTM1, GSTT1 genotypes in Delhi population and compared it with GST polymorphism frequency in different states of India and with various populations worldwide.

Materials and Methods

Selection of controls

Peripheral blood from the controls was collected in vials containing ethlenediaminetetraacetic acid (EDTA) after receiving their informed consent. The controls selected for the study were either normal volunteers from

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the Institute, or normal healthy individuals visiting with the patients in various hospitals of Delhi, and were selected by social workers from our Institute who used to visit six major hospitals of Delhi for collection of samples from cervical cancer patients. Healthy individuals without any history of cancer were included in the study. Information on age, sex, smoking and alcohol habits was obtained. The ethical clearance was taken from our Institute.

GSTM1 and *GSTT1* genotypes were determined by multiplex PCR using three sets of primers to amplify fragments of 218, 460 and 350bp for *GSTM1*, *GSTT1* and Albumin gene (internal control) respectively (Arand et al., 1996) with slight modifications (Sharma et al., 2004). The primers used were *GSTM1*- forward 5'-GAA CTC CCT GAA AAG CTA AAG C-3'; *GSTM1* reverse -5'-GTT GGG CTC AAA TAT ACG GTG G-3'; *GSTT1* -forward 5'-TTC CTT ACT GGT CCT CAC ATC TC-3' and *GSTT1* - reverse 5'-TCA CCG GAT CAT GGC CAG CA-3'; Albumin forward - 5'-GCC CTC TGC TAA CAA GTC CTA C -3' Albumin reverse - 5'-GCC CTA AAA AGA AAA TCG CCA ATC-3'. Multiplex PCR was performed in 25μl reaction volume containing 50-100ng of genomic DNA, 50 mM KCl, 2.5mM MgCl2, 200 mM Tris-HCl (pH 8.4), 200 mM of dNTPs, *GSTM1*, *GSTT1* and Albumin primers at 0.2μM each and 1.5 units of DNA AmpliTaq polymerase (Applied Biosystems) in a Perkin-Elmer thermal cycler. After an initial denaturation at 95°C for 5 min, amplification was carried out for 35 cycles at 94°C for 1 min, 56°C for 1 min, and 72°C for 1 min, followed by final extension at 72°C for 7 min. The products of multiplex PCR were separated by electrophoresis with ethidium bromide stained 3% agarose gel. Presence of amplicons of 218 bp, 460bp and 350bp revealed the presence of *GSTM1*, *GSTT1* and Albumin (internal control) respectively (Figure 1).

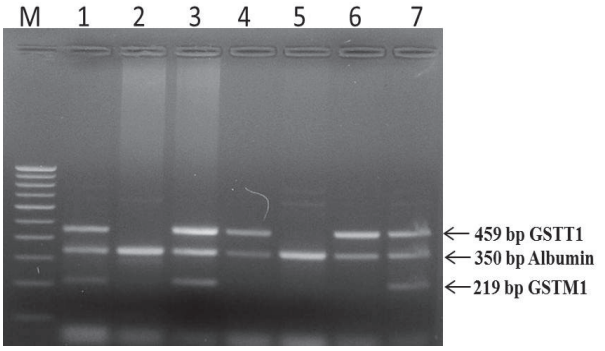

Figure 1. Multiplex PCR Analysis of *GSTM1*, and *GSTT1* Gene Resolved on 3% Agarose Gel Electrophoresis. M is a 100bp Ladder marker. A 350 bp product corresponding to Albumin gene product provide an internal positive control, seen in all lanes. A 219 bp product indicate the presence of at least one *GSTM1* non- null allele. Similarly 459 bp products indicate the presence of at least one *GSTT1* non- null allele. Absence of *GSTM1* or *GSTT1* product indicates homozygous null genotype of that gene.

Statistical analysis

The data were tabulated and analysed. The mean±SD were estimated for quantitative data. T test was used for the comparison of age. The chi-square test was used to compare demographic data between various variables of the present study. The studied population was compared with reported frequencies from other neighbouring state populations of India and global populations; Europeans, Blacks and Asians.

Results

A total of 500 healthy individuals participated in the study. The mean age was 32.9 years±6.8. The median age was 32 years and the range from 18-57 years. Of the 500 individuals, 274 were males and 226 females. The mean age of males and females was 33.1±6.7and 32.6±6.8 respectively and no significant differences in the mean age were observed between the two sexes. Number of individuals who were having homozygous null genotypes of *GSTM1* and *GSTT1* were 33.6% and 12.4% respectively and 10.8% individuals were homozygous null for both the genes simultaneously (Table 1). The frequency of *GSTM1*, *GSTT1* homozygous null alleles did not differ significantly among both the sexes (p>0.05). Total ninety seven (85 males and 12 females) individual were smokers. Number of female smokers was very less, so it was not possible to compare the results between both the genders. No significant differences were observed between smokers and non-smokers, alcoholic and non-alcoholic individuals, tobacco chewers and non-chewers, carrying homozygous *GSTM1*/*GSTT1*/*GSTM1*T1 null genotype (p>0.05) (Table

Table 1. Demographic Data and Association of Various Variables with GST Polymorphism in Normal Population of Delhi

Variables	Total (N=500)	*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 N	Non-null	
Gender										
Males	274(54.8)	91 (33.2)	183 (66.8)	p>0.05,	36 (13.1)	238 (86.9)	p>0.05,	30 (10.9)	244 (89.1)	p>0.05,
Females	226 (45.2)	77 (34.1)	149 (65.9)	0.96,(0.65-1.42)	26 (11.5)	200 (88.5)	1.2, (0.66-2.06)	24 (10.6)	202 (89.4)	1.0, (0.57-1.9)
Smoking status										
Smokers	97 (19.4)	35 (36.1)	62 (63.9)	p>0.05,	13 (13.4)	84 (86.6)	p>0.05,	11 (11.3)	86 (88.7)	p>0.05,
Non-smokers	403 (80.6)	133 (33.0)	270 (67.0)	1.2,(0.70-1.87)	41 (10.2)	362 (89.8)	1.4, (0.66-2.78)	43 (10.7)	360 (89.3)	1.1, (0.5-2.26)
Alcohol status										
Alcoholic	210 (42.0)	60 (28.6)	150 (71.4)	p>0.05,	32 (15.2)	178 (84.8)	p>0.05,	26 (12.4)	184 (87.6)	p>0.05,
Non-alcoholic	290 (58.0)	78 (26.9)	212 (73.1)	1.1, (0.72-1.65)	30 (10.3)	260 (89.7)	1.56, (0.88-2.75)	28 (9.7)	262 (90.3)	1.32, (0.72-2.41)
Tobacco chewing										
Chewers	140 (28.0)	51 (36.4)	89 (63.6)	p>0.05,	21 (15.0)	119 (85.0)	p> 0.05,	18 (12.8)	122 (87.2)	p>0.05,
Non-chewers	360 (72.0)	117 (32.5)	243 (67.5)	1.19, (0.77-1.83)	41 (11.4)	319 (88.6)	1.37, (0.75-2.5)	36 (10.0)	324 (90.0)	1.3, (0.7-2.52)

Table 2. Frequency of *GSTM1* and *GSTT1* Homozygous Null Genotypes in Indian Populations

Population	Number	*GSTM1* null %	*GSTT1* null %	*GSTM1*T1 null %	References
West Indians [b]	761	320(42.0)*	152(19.9)*	78(10.2)	Anantharaman, 2007; Buch et al., 2002; Nair et al., 1999
South Indians [c]	1744	485 (27.8)**	242 (13.9)	136 (7.8)	Naveen et al., 2004; Samson, 2007; Shehnaz et al., 2011; Sreelekha et al., 2001; Suneetha, 2011; Vettriselvi et al., 2006; Vijayalakshmi et al., 2005
East Indians [d]	67	18(27.0)	9 (13.0)		Sikdar et al., 2005
Central Indians [e]	282	99 (35.1)	37 (13.0)		Devi et al., 2008
North Indians [f]	1655	539 (32.6)	285 (17.2)**	74 (4.5)*	Bhat et al., 2012; Bid et al., 2010; Konwar et al., 2010; Mishra et al., 2004; Mittal et al., 2004; Singh et al., 2009; Srivastava et al., 2005
Present Study [a]	500	168 (33.6)	60 (12.0)	54 (10.8)	
Total	4509	1461 (32.4)	725 (16.1)	288 (6.9)	

*p<0.001; **p<0.01, when frequencies of present study were compared to that of other states ([a] vs [b/c/d/e/f])

Table 3. Comparative Frequency of *GSTM1* and *GSTT1* Homozygous Null Genotypes in Major Worldwide Populations

Population	Number	*GSTM1* null %	*GSTT1* null %	*GSTM1*T1 null %	References
Indians[a]	4509	1460 (32.4)	730 (16.2)	266 (5.9)	Nair et al., 1999; Singh et al., 2009
Blacks[b]	3008	960 (31.9)	744 (24.9)*	298 (9.9)*	Adams et al., 2003; Benzamin et al., 2011; Coutinho et al., 2010; Dandara et al., 2002; Lavender et al., 2009; Masimirembwa et al., 1998; Millikan et al., 2000; Rossini et al., 2002
Caucasians[c]	2674	1064/2232 (47.7)*	448/2674 (16.7)	31 (9.3)	Amer et al., 2011; Baranova et al., 1997; Chen et al., 1996; D'Alo et al., 2004; Gsur et al., 2001; Kargas et al., 2003; Millikan et al., 2000; Mitrunen et al., 2001; Steinhoff et al., 2000; Welfare et al., 1999
Asians[d]	4735	2238/4126 (54.2)*	1944/4735 (41.0)*	199/951 (20.9)*	Ada et al., 2004; Amtha et al., 2009; Ansari et al., 2010; Cho et al., 2005; Chonlada et al., 2009; Hishida et al., 2005; Kim et al., 2000; Kiran et al., 2010; Kiyohara et al., 2003; Kunak et al., 2012; Lee et al., 1995; Rehan et al., 2010; Sata et al., 2003; Sayo et al., 2005; Setiawan et al., 2000; Settheetham-Ishida et al., 2009; Shen et al., 1998; Siraj et al., 2008; Yim et al., 2000

*p<0.001, Frequencies of [a] compared to [b/c/d]

1). The frequency distribution of *GSTM1* and *GSTT1* alleles were compared between different states of India and other populations all over the world (Table 2 and 3).

Discussion

Homozygous deletions of *GSTM1* or *GSTT1* genes have an impaired ability to metabolically eliminate carcinogenic compounds and may therefore put such individuals at increased risk for various diseases. In the present study we have examined the polymorphism of *GSTM1*, *GSTT1* genes in normal Delhi population.

There are substantial differences in the baseline frequencies of null genotypes for *GSTM1* and *GSTT1* in different ethnic groups. We have observed 33.6% individuals with *GSTM1* homozygous null genotype in Delhi population which is comparable with data reported from different regions of India (Table 2) except in Trivandrum (17.0%) and Chennai (15.0 %), where the frequency is very low (Nair et al., 1999; Vijayalakshmi et al., 2005) respectively. Higher frequency of *GSTM1* null genotypes was reported in two studies (49.2% and 59.9%) from Mumbai (Buch et al., 2002; Anantharaman, 2007). Otherwise, the frequency of *GSTM1* null genotype was almost similar throughout India. We observed 12.4% of North Indians were homozygous null for the *GSTT1* gene. The prevalence of *GSTT1* homozygous null genotype is less (8.0-22.0%) in Indian population as compared to *GSTM1* null (15.0-59.9%). The prevalence of *GSTM1* homozygous null genotype is significantly higher in Caucasians (range: 41.8-53.5) and Asians (range: 49.0- 65.2) as compared to Indian (range: 15.0-59.9) populations. The frequency of *GSTT1* homozygous null genotypes is also significantly higher in blacks (range: 14.0-57.0) and Asians (16.0-84.6) (Table 3). Very few results are available for the combined homozygous null genotypes of *GSTM1*and *GSTT1*. In the present study complete deletion of both *GSTM1* and *GSTT1* genotypes is observed in 10.8% individuals and the range in Indian population was between 4.5%-10.8%, whereas Nair et al. (1999) did not find any subject with homozygous null genotype for both *GSTM1* and *GSTT1* from Trivandrum. In Brazilian population, the range of both *GSTM1* and *GSTT1* homozygous null genotypes is between 4.5-17.0% and the frequency is higher in Asian population (19.6-37.0%) except Pakistanis and Indians from Singapore, where the frequency was low (5.0%) (Rehan et al., 2010). The high frequencies of *GSTM1* and *GSTT1* homozygous null genotypes observed in Chinese population are associated with the high incidence of oesophageal cancer. There were no significant differences between males and females in the frequency of *GSTM1* or *GSTT1* null genotypes in the present study. Similar results were reported in white and non-white individuals (Rossini et al., 2002).

Further, we have compared the frequency of *GSTM1* and *GSTT1* homozygous null genotype in three main world populations namely Blacks, Caucasians, Asians and compared with Indians (Table 3). These results were

obtained by clubbing the individual data from the studies mentioned in Table 3 for all ethnic groups. *GSTM1* and *GSTT1* homozygous Null genotype was 31.9%; 24.9% in Blacks (N-3008), 32.4%; 16.2% in Indians (N=4509), 47.7%; 16.7% in Caucasians (N=2674) and 54.2%; 41.0% in Asians (N=4735) respectively. Considerable variations were observed in the frequencies of the homozygous null genotypes at the *GSTM1* and *GSTT1* loci among these four different ethnic groups. It shows that *GSTM1* homozygous null genotype is lowest in Blacks, followed by Indians, Caucasians and Asians. At a glance these figures indicate that null alleles are higher in Caucasians and Asians (including Japanese, Chinese and Koreans). Cancer incidence is also higher in these populations specially the cancer of Lung, Colorectal, stomach, oesophagus and the Ovary (Parkin et al., 2005). Though not supported statistically here, it gives an indication that these two homologous null genotypes can account for racial differences in incidence of some important cancers in world populations. This may be in part due to their differing evolutionary histories and in part to differential selection arising from differing exposures to toxic substances, such as diet and tobacco and alcohol consumption.

This type of study would provide us the basic data for epidemiological studies. Therefore, *GSTM1*, *GSTT1* polymorphism in combination with other detoxifying enzyme polymorphisms, could be used to identify high-risk individuals in clinical surveillance programmes. Individuals with different combinations of these alleles would also help in studying the effect of various carcinogens in different populations having various exposures. This data will be useful in designing various studies involving polymorphisms of *GSTM1*, *GSTT1* genes and to compare results from various geographical regions of India.

References

Ada AO, Suzen SH. Iscan M (2004). Polymorphisms of cytochrome P450 1A1, glutathione S-transferases M1 and T1 in a Turkish population. *Toxicol Lett*, **151**, 311-5.

Adams CH, Werely CJ, Victor TC, et al (2003) Allele frequencies for glutathione S-transferase and N-acetyltransferase 2 differ in African population groups and may be associated with oesophageal cancer or tuberculosis incidence. *Clin Chem Lab Med*, **41**, 600-5.

Amer MA, Ghattas MH, Abo-Elmatty DM, SH, A-E-E. (2011) Influence of glutathione S-transferase polymorphisms on type-2 diabetes mellitus risk. *Genet Mol Res*, **10**, 3722-30.

Amtha R, Ching CS, Zain R, et al (2009) *GSTM1*, *GSTT1* and CYP1A1 polymorphisms and risk of oral cancer: a case-control study in Jakarta, Indonesia. *Asian Pac J Cancer Prev*, **10**, 21-6.

Anantharaman D, Chaubal PM, Kannan S, Bhisey RA, Mahimkar MB (2007). Susceptibility to oral cancer by genetic polymorphisms at CYP1A1, *GSTM1* and *GSTT1* loci among Indians: tobaco exposure as a risk modulator. *Carcinogenesis*, **28**, 1455-62.

Ansari SB, Vasudevan R, Bakhshi A, et al (2010). Analysis of glutathione S-transferase (M1, T1, and P1) gene polymorphisms in Iranian prostate cancer subjects. *African J Biotechnology*, **9**, 7230-5.

Arand M, Muhlbauer R, Hengstler J, et al (1996). A multiplex polymerase chain reaction protocol for the simultaneous analysis of the glutathione S-transferase *GSTM1* and *GSTT1* polymorphisms. *Anal Biochem*, **236**, 184-6.

Autrup H (2000). Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxic response. *Mutat Res*, **464**, 65-76.

Baranova H, Perriot J, Albuisson E, et al (1997). Peculiarities of the *GSTM1* 0/0 genotype in French heavy smokers with various types of chronic bronchitis. Hum Genet, **99**, 822-6.

Benzamin UE, Oluseye OB A, MM C (2011). Glutathione-S-transferase (M1 and T1) polymorphisms in Nigerian populations. *J Medical Genetics and Genomics*, **3**, 56-60.

Bhat G, Bhat A, Wani A, et al (2012). Polymorphic variation in Glutathione-S-transferase genes and risk of Chronic Myeloid Leukemia in the Kashmiri population. *Asian Pac J Cancer Prev*, **13**, 69-73.

Bid HK, Konwar R, Saxena M, et al (2010). Assocition of glutathione S-transferase (*GSTM1*, T1, P1) gene polymorphisms with type 2 diabetes mellitus in north Indian population. *J Postgrad Med*, **56**, 176-81.

Board PG (1981). Biochemical genetics of glutathione-S-transferase in man. *Am J Hum Genet*, 33, 36-43.

Buch SC, Notani PN, Bhisey RA (2002). Polymorphism at *GSTM1*, GSTM3 and *GSTT1* gene loci and susceptibility to oral cancer in an Indian population. *Carcinogenesis*, **23**, 803-7.

Chen CL, Liu Q, Relling MV (1996). Simultaneous characterization of glutathione S-transferase M1 and T1 polymorphisms by polymerase chain reaction in American whites and blacks. *Pharmacogenetics*, **6**, 187-91.

Cho HJ, Lee SY, Ki CS, Kim JW (2005). *GSTM1*, *GSTT1* and GSTP1 polymorphisms in the Korean population. *J Korean Med Sci*, **20**, 1089-92.

Chonlada V, Pornpen P, Chanin L, et al (2009) Glutathione S-transferase P1 variant plays a major contribution to decreased susceptibility to liver cancer in Thais. *Asian Pac J Cancer Prev*, **10**, 783-8.

Coutinho P, Sandim V, Oliveira, J, et al (2010). Lack of association between glutathione-S-transferase polymorphiosm and primary glioma in a case-control study in Rio de Janeiro. *Genet Mol Res*, **9**, 539-44.

D'Alo F, Voso MT, Guidi F, et al (2004). Polymorphisms of CYP1A1 and glutathione S-transferase and susceptibility to adult acute myeloid leukemia. *Haematologica*, **89**, 664-70.

Dandara C, Sayi J, Masimirembwa CM, et al (2002). Genetic polymorphism of cytochrome P450 1A1 (Cyp1A1) and glutathione transferases (M1, T1 and P1) among Africans. *Clin Chem Lab Med*, **40**, 952-7.

Devi SS, Vinayagamoorthy N, Agrawal, M, et al (2008). Distribution of detoxifying genes polymorphism in Maharastrian population of central India. *Chemosphere*, **70**, 1835-1839.

Gsur A, Haidinger G, Hollaus P, et al (2001). Genetic polymorphisms of CYP1A1 and *GSTM1* and lung cancer risk. *Anticancer Res,* **21**, 2237-42.

Hayes, JD, Pulford DJ (1995). The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol*, **30**, 445-600.

Hishida A, Terakura S, Emi N, et al (2005). *GSTT1* and *GSTM1* deletions, NQO1 C609T polymorphism and risk of chronic myelogenous leukemia in Japanese. *Asian Pac J Cancer Prev*, **6**, 251-5.

Kargas C, Krupa R, Walter Z (2003) Combined genotype analysis of *GSTM1* and *GSTT1* polymorphisms in a Polish

population. *Hum Biol*, **75**, 301-307.
Kim JW, Lee CG, Park YG et al (2000). Combined analysis of germline polymorphisms of p53, *GSTM1*, *GSTT1*, CYP1A1, and CYP2E1: relation to the incidence rate of cervical carcinoma. *Cancer,* **88**, 2082-91.
Kiran B, Karkucak M, Ozan H, et al (2010). GST (*GSTM1*, *GSTT1*, and GSTP1) polymorphisms in the genetic susceptibility of Turkish patients to cervical cancer. *J Gynecol Oncol*, **21**, 169-73.
Kiyohara C, Wakai K, Mikami H, et al (2003). Risk modification by CYP1A1 and *GSTM1* polymorphisms in the association of environmental tobacco smoke and lung cancer: a case-control study in Japanese nonsmoking women. *Int J Cancer*, **107**, 139-44.
Konwar R, Manchanda PK, Chaudhary P, et al (2010). Glutathione S-transferase (GST) gene variants and risk of benign prostatic hyperplasia: A report in a North Indian population. *Asian Pac J Cancer Prev*, **11**, 1067-72.
Kunak SC, Ada AO, Karacaoglan V, et al (2012). Drug / Xenobiotic metabolizing enzyme polymorphisms in a Turkish population. *African J Pharmacy and Pharmacology*, **6**, 2068-74.
Lavender NA, Benford ML, VanCleave TT, et al (2009). Examination of polymorphic glutathione S-transferase (GST)genes, tobacco smoking and prostate cancer risk among men of African descent: a case -control study. *BMC Cancer*, **16**, 397.
Lee EJ, Wong JY, Yeoh PN, Gong NH (1995). Glutathione S-transferase-theta (*GSTT1*) genetic polymorphism among Chinese, Malays and Indians in Singapore. *Pharmacogenetics*, **5**, 332-4.
Mannervik B, Awasthi YC, Board PG, et al (1992). Nomenclature for human glutathione transferases. *Biochem J*, **282,** 305-6.
Masimirembwa CM, Dandara C, Sommers DK, Snyman JR, Hasler JA. (1998). Genetic polymorphism of cytochrome P4501A1, microsomal epoxide hydrolase, and glutathione S-transferases M1 and T1 in Zimbabweans and Venda of southern Africa. *Pharmacogenetics*, **8**, 83-85.
Millikan R, Pittman G, Tse CK, et al (2000). Glutathione S-transferases M1, T1, and P1 and breast cancer. *Cancer Epidemiol Biomarkers Prev*, **9**, 567-73.
Mishra DK, Kumar A, Srivastava DS, Mittal RD (2004). Allelic variation of *GSTT1*, *GSTM1* and GSTP1 genes in North Indian population. *Asian Pac J Cancer Prev*, **5**, 362-5.
Mitrunen K, Jourenkova N, Kataja V, et al (2001). Glutathione S-transferase M1, M3, P1, and T1 genetic polymorphisms and susceptibility to breast cancer. *Cancer Epidemiol Biomarkers Prev*, **10**, 229-36.
Mittal RD, Srivastava DS, Mandhani A, Kumar A, Mittal B (2004). Polymorphism of *GSTM1* and *GSTT1* genes in prostate cancer: a study from North India. *Indian J Cancer*, **41**, 115-9.
Nair UJ, Nair J, Mathew B, Bartsch H (1999). Glutathione S-transferase M1 and T1 null genotypes as risk factors for oral leukoplakia in ethnic Indian betel quid/tobacco chewers. *Carcinogenesis*, **20**, 743-8.
Naveen AT, Adithan C, Padmaja N, et al (2004). Glutathione S-transferase M1 and T1 null genotype distribution in South Indians. *Eur J Clin Pharmacol*, **60**, 403-6.
Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
Pemble S, Schroeder KR, Spencer SR, et al (1994). Human glutathione S-transferase theta (*GSTT1*): cDNA cloning and the characterization of a genetic polymorphism. *Biochem J*, **300**, 271-6.
Rehan SS, Amir M, Ahmed IM, et al (2010). Frequency distribution of *GSTM1* and *GSTT1* null allele in pakistani population and risk of disease incidence. *Envir Toxi Pharm*, **30**, 76-9.
Rossini A, Rapozo DC, Amorim LM, et al (2002). Frequencies of *GSTM1*, *GSTT1*, and GSTP1 polymorphisms in a Brazilian population. *Genet Mol Res*, **1**, 233-40.
Samson M SR, Rama R, Sridevi V, Nancy KN, Rajkumar T (2007). Role of *GSTM1* (Null/Present), GSTP1 (Ile105Val) and P53 (Arg72Pro) genetic polymorphisms and the risk of breast cancer: a case control study from South India. *Asian Pac J Cancer Prev*, **8**, 253-7.
Sata F, Yamada H, Kondo T, Gong Y, et al (2003). Glutathione S-transferase M1 and T1 polymorphisms and the risk of recurrent pregnancy loss. *Mol Hum Reprod*, **9**, 165-9.
Sayo K, Kazuko N, Sakurako N, et al (2005). Multiplex PCR with confronting two- pair primers for CYP1A1 Ile462Val, GSTM1, GSTT1, and NQO1 C609T. *Asian Pac J Cancer Prev*, **6**, 346-52.
Setiawan VW, Zhang ZF, Yu GP, et al (2000). *GSTT1* and *GSTM1* null genotypes and the risk of gastric cancer: a case-control study in a Chinese population. *Cancer Epidemiol Biomarkers Prev*, **9**, 73-80.
Settheetham-Ishida W, Youenyao P, Kularbkaew C, settheetham D (2009). Glutathione S-transferase (*GSTM1* and *GSTT1*) polymorphisms in cervical cancer in Northeastern Thailand. *Asian Pac J Cancer Prev*, **10**, 365-8.
Sharma A, Sharma JK, Murthy NS, Mitra AB (2004). Polymorphisms at *GSTM1* and *GSTT1* gene loci and susceptibility to cervical cancer in Indian population. *Neoplasma*, **51**, 12-6.
Shehnaz S, Venkata K, Vidyullatha P, et al (2011). Glutathione S-transferase M1 and T1 gene polymorphism in South Indian stroke patients. *J Medical Genetics and Genomics*, **3**, 68-73.
Shen J, Lin G, Yuan W, et al (1998). Glutathione transferase T1 and M1 genotype polymorphism in the normal population of Shanghai. *Arch Toxicol*, **72**, 456-8.
Sikdar N, Sila D, Paul RR, Panda CK, Roy B (2005). Homozygous null genotype at Glutathione S- transferase M1 locus as a risk factor for oral squamous cell carcinoma in Indian tobacco users. *Int J Hum Genet*, **5**, 37-44.
Singh S, Kumar V, Thakur S, et al (2009). Genetic polymorphism of glutathione S-transferase M1 and T1 in Delhi population of Northern India. *Environmental Toxicology and Pharmacology*, **28**, 25-9.
Siraj AK, Ibrahim M, AI-Rasheed MJ, et al (2008). Polymorphisms of selected xenobiotic genes contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. *BMC Med Genet*, **9**, 61.
Sreelekha TT, Ramadas K, Pandey M, et al (2001). Genetic polymorphism of CYP1A1, *GSTM1* and *GSTT1* genes in Indian oral cancer. *Oral Oncol*, **37**, 593-8.
Srivastava DS, Mishra DK, Mandhani A, et al (2005). Association of genetic polymorphism of glutathione S-transferase M1, T1, P1 and susceptibility to bladder cancer. *Eur Urol*, **48**, 339-44.
Steinhoff C, Franke KH, Golka K, et al (2000). Glutathione transferase isozyme genotypes in patients with prostate and bladder carcinoma. *Arch Toxicol*, **74**, 521-6.
Suneetha KJ, K Nirmala Nancy, KR Rajalekshmy et al (2011). Role of glutathione-S- transferase and CYP1A1*2A polymorphism in the therapy outcome of south Indian acute lymphoblastic leukemia patients. *Indian J Med Paediatr Oncol*, **32**, 25-29.
Vettriselvi V VK, Solomon Fd P, Venkatachalam P (2006) Genetic variation of *GSTM1*, *GSTT1* and GSTP1 genes in a South Indian population. *Asian Pac J Cancer Prev*, **7**, 325-8.
Vijayalakshmi K, Vettriselvi V, Krishnan M, et al (2005) Polymorphisms at *GSTM1* and GSTP1 gene loci and risk

of prostate cancer in a south Indian population. *Asian Pac J Cancer Prev*, **6**, 309-14.

Welfare M, Monesola AA, Bassendine MF, Daly AK (1999). Polymorphisms in GSTP1, *GSTM1*, and *GSTT1* and susceptibility to colorectal cancer. *Cancer Epidemiol Biomarkers Prev*, **8**, 289-92.

Yim JJ, Park GY, Lee CT, et al (2000). Genetic susceptibility to chronic obstructive pulmonary disease in Koreans: combined analysis of polymorphic genotypes for microsomal epoxide hydrolase and glutathione S-transferase M1 and T1. *Thorax*, **55**, 121-5.