African Journal of Pharmacy and Pharmacology Vol. 6(27), pp. 2068-2074, 22 July, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP12.339
ISSN 1996-0816 © 2012 Academic Journals

Full Length Research Paper

Drug/xenobiotic metabolizing enzyme polymorphisms in a Turkish population

Kunak S. C.[1], Ada A. O.[2]*, Karacaoglan V.[2], Soydas E.[2], Bilgen S.[2] and Iscan M.[2]

[1]Department of Pharmacology, Medical Faculty, Giresun University, Giresun, Turkey.
[2]Department of Toxicology, Faculty of Pharmacy, Ankara University, Ankara, Turkey.

Accepted 25 June, 2012

Genetic polymorphisms of drug/xenobiotic metabolizing enzymes can have great impact on the inter-individual variation in drug response or susceptibility to toxicities of xenobiotics. The frequencies of the polymorphic enzymes not also differ from ethnicity, but also differ from country to country in the same ethnic group. In this study, *CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and *GSTP1* exon 6 genetic polymorphisms were determined in 302 unrelated healthy individuals in a Turkish population and the results were compared with previous reports. The frequencies of *CYP2E1*5B* c1/c1, c1/c2 and c2/c2 genotypes were 94.7, 5.3 and 0%, respectively. The frequencies of the deleted *GSTM1* and *GSTT1* genotypes were 54.6 and 22.2%, respectively. The *GSTP1* exon 5 genotype frequencies were Ile/Ile: 56.0%, Ile/Val: 34.8% and Val/Val: 9.3%; *GSTP1* exon 6 genotype frequencies were Ala/Ala: 84.8%, Ala/Val: 14.2% and Val/Val: 1.0%. These results revealed that the frequencies of *CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and *GSTP1* exon 6 genetic polymorphisms in a Turkish population are similar to European Caucasian populations.

Key words: Drug metabolism, *CYP2E1* polymorphism, *GST* polymorphism, Turkish population.

INTRODUCTION

It is well known that cytochrome P-450 (CYP) enzymes are able to metabolize many xenobiotics, including drugs. The glutathione S-transferases (GSTs) are a family of cytosolic enzymes generally involved in the detoxification of activated xenobiotics and/or drug metabolites. Several CYPs and GSTs are known to be polymorphic (Mannervik et al., 1992; Nebert et al., 1996). Among several CYPs, CYP2E1 is a critical enzyme in the oxidation of drugs such as chlorzoxazone, acetaminophen, fluorinated anesthetics and ethanol (Griese et al., 2001). *CYP2E1* gene polymorphisms are thought to play a major role in interindividual variability in drug response, drug - drug, drug - xenobiotic interactions and toxicity (Lieber, 1997; Bolt et al., 2003). The best studied *CYP2E1* genetic polymorphisms are the *CYP2E1*5B* (*Pst*I/*Rsa*I) polymorphisms in the 5′ flanking region and the *CYP2E1*6* (*Dra*I) polymorphism in intron 6 of the *CYP2E1* gene (Wormhoudt et al., 1999). *CYP2E1*5B* polymorphism was found to be related with enhanced transcription and increased CYP2E1 activity *in vitro* (Liu et al., 2009; Hayashi et al., 1991) and *in vivo* (Ueshima et al., 1996; Ueno et al., 1996); whereas *CYP2E1*6* polymorphism does not give rise to any structural change in the CYP2E1 protein (Wormhoudt et al.,1999).

The 3 GST classes GSTM, GSTT and GSTP constitute an important part of the total GST family, and well-characterized polymorphisms are known for all 3 classes (Sorensen et al., 2004). *GSTM1* and *GSTT1* deletion polymorphisms result in loss of the corresponding enzyme activities (Smith et al., 1994; Pemble et al., 1994). Previous studies have suggested that genetic polymorphisms of *GSTP1* exon 5 (Ile105Val) and *GSTP1* exon 6 (Ala114Val) have a functional relevance on the *GST* gene product, resulting in reduced enzyme activity

*Corresponding author. E-mail: ada@pharmacy.ankara.edu.tr. Tel: +90 312 2033121. Fax: +90 312 2131081.

(Zimniak et al., 1994; Ali-Osman et al., 1997; Watson et al., 1998). Substrates of GSTs include a wide range of endogenous metabolites, xenobiotics and alkylating and free radical generating anti-cancer drugs (Lo and Ali-Osman, 2007). GST polymorphisms have been found to influence the pharmacokinetics of immunosuppressive drug azathioprine (Eklund et al., 2006; Stocco et al., 2007). GSTs also play an important role in chemo-resistance by decreasing the cytotoxic impact of various antineoplastic agents (Nakagawa et al., 1988; Townsend and Tew, 2003; Lo and Ali-Osman, 2007).

Meanwhile, a large inter-ethnic variation of polymorphic gene frequencies in control populations has been reported in various ethnic groups. Furthermore, intra-ethnic differences have been well established (Garte et al., 2001). For example, *GSTT1* deletion frequency was reported as 32.1% by Zirbs et al. (2012) and 19.5% by Garte et al. (2001) in two studies performed in German population. In addition, contradictory results have been reported for *GSTM1* gene deletions within Turkish population (Aktas et al., 2001; Pinarbasi et al., 2003; Altayli et al., 2009). On the other hand, previous reports on *CYP2E1*5B* and *GSTP1* exon 5 polymorphism in Turkish populations are rare and studies regarding the *GSTP1* exon 5 polymorphism are contradictory (Toruner et al., 2001; Ates et al., 2005; Altayli et al., 2009). For *GSTP1* exon 6 polymorphism, a rather limited data exist among Caucasian populations (Sorensen et al., 2004; Garcia-Closas et al., 2005; Ibarrolla-Villava et al., 2012). Previous studies performed in Turkish populations generally reported one or two polymorphic genes among same individuals (Omer et al., 2001; Ulusoy et al., 2007; Taspinar et al., 2012; Guven et al., 2007; Aktas et al., 2001; Aynacioglu et al., 2004; Oke et al., 1998).

To our knowledge there is no study in a Turkish population which investigates the polymorphism of more than three polymorphic genes in the same individuals with relatively large sample size exceeding 300 individuals. Therefore, we reported here the genotype frequencies of *CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and *GSTP1* exon 6 polymorphisms in a Turkish population.

MATERIALS AND METHODS

Subjects

In the present study, 302 unrelated individuals aged between 25 to 80 years (49.1 ± 12.0; mean ± SD), including 148 females (mean age 49.6 ± 12.9 years; range 25 - 80 years) and 154 males (mean age 48.6 ± 11.1 years; range 25 - 75 years) were used. All of the subjects were healthy volunteers without known history of cancer and other chronic diseases. On entry into the study, each individual had a personal interview based on a questionnaire in which they were asked to provide information that included socio-demographic variables such as age, gender, race, ethnicity and the geographical region they lived in. The study population consisted of native Turkish residents (Caucasians) without any other ethnicities (Africans or Asians) and represented Turkish population from all regions of the country. All subjects provided written informed consent, and the study was approved by a local Ethics Committee.

Genotyping

The genomic DNA used for polymorphic analysis was isolated from whole blood of patients by using DNA purification kit purchased from Promega Corporation (Madison, WI, USA), following the manufacturer's instructions. Isolated DNA was stored at -20°C until use. The genetic polymorphism analysis for the *CYP2E1*5B* (*Rsa*I/*Pst*I, rs3813867/rs2031920) was determined by using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method described by Hayashi et al. (1991). CYP2E1*5B polymorphism was also confirmed by real time PCR technique described by Choi et al. (2003). The genetic polymorphism analyses for the *GSTM1* and the *GSTT1* genes were determined simultaneously in a single assay using a multiplex PCR approach based on the method of Abdel-Rahman et al. (1996). *GSTP1* exon 5 (Ile105Val) (rs1695) and *GSTP1* exon 6 (Ala114Val) (rs1138272) genetic polymorphism analyses were determined by using the PCR-RFLP method described by Park et al. (1999). For quality control, laboratory personnel were blinded to the source of each DNA specimen and a random 10% of the samples were repeated with 100% concordance. Two authors reviewed independently 100% of the agarose gels and genotype data entry.

Statistical analysis

Chi-square test and Fisher's exact test were used to calculate statistical differences in the distribution of genotype frequencies between populations where necessary. If the cell values were less than five, the *P* values of Fisher's exact test were given. *P* values < 0.05 were considered as significant. SPSS 15.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

The genotype frequencies obtained from 302 individuals are shown in Table 1. The frequencies of *CYP2E1*5B* wild type **1A/*1A* (c1/c1) and heterozygous **1A/*5B* (c1/c2) genotypes were found to be 5.3 and 94.7%, respectively. Homozygous mutant **5B/*5B* (c2/c2) genotype was not observed in our study population. The *CYP2E1*5B* genotypes were in Hardy-Weinberg equilibrium (*P* = 0.636).

GSTM1 and *GSTT1* genotype frequencies are shown in Table 1. The frequencies of *GSTM1* positive and null genotypes were 45.4 and 54.6%; *GSTT1* positive and null genotypes were 77.8 and 22.2%, respectively. Moreover, *GSTP1* exon 5 genotype frequencies were 56.0% for wild type (Ile/Ile), 34.8% for heterozygous (Ile/Val) and 9.3% for homozygous mutant (Val/Val). The genotype frequencies of *GSTP1* exon 6 polymorphism were 84.4% for wild type (Ala/Ala), 14.2% for heterozygous (Ala/Val) and 1.0% for homozygous mutant (Val/Val). The GSTP1 exon 5 and GSTP1 exon 6 *GSTP1* exon 6 genotype frequencies obtained in this

Table 1. Frequencies of CYP2E1, GSTM1, GSTT1 and GSTP1 genotypes.

Genotype	Number (n)	Percentage (%)
Total	302	
*CYP2E1*5B*		
c1/c1	286	94.7
c1/c2	16	5.3
c2/c2	0	0
GSTM1		
positive	137	45.4
null	165	54.6
GSTT1		
positive	235	77.8
null	67	22.2
GSTP1 exon 5		
Ala/Ala	169	56.0
Ala/Val	105	34.8
Val/Val	28	9.3
GSTP1 exon 6		
Ile/Ile	256	84.4
Ile/Val	43	14.2
Val/Val	3	1.0

*CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and genotypes were in Hardy-Weinberg equilibrium (P = 0.054 and 0.434, respectively). study were compared with previously published data in European Caucasian populations (Tables 2, 3, 4 and 5). Significant difference was not observed between genotype frequencies in terms of age and gender when compared with chi-square test (data not shown).

DISCUSSION

In this study, the genotype frequencies of *CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and *GSTP1* exon 6 polymorphisms were studied in the same individuals of a Turkish population and the results were compared with previous findings in European Caucasian populations and Turkish population. This study provides additional data on the frequencies of *CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and *GSTP1* exon 6 polymorphisms in a Turkish population. In our study *CYP2E1*5B* genotypes were in line with previous reports in Turkish and European Caucasian populations (Table 5). There was no difference between three study populations in Turkey for *CYP2E1*5B* polymorphism. Considering these results, it seems to be a consistent finding.

The *GSTM1* null frequency in our study was found consistent with European Caucasian populations (Table 3). In the current study, the frequency of the *GSTM1* null genotype was found parallel with three previous reports in Turkish population (Toruner et al., 2001; Altayli et al., 2009; Taspinar et al., 2012). However, Aktas et al. (2001) and Pinarbasi et al. (2003) have found very low *GSTM1* null frequencies when compared with our study as well as other studies in Turkish population. *GSTM1* null genotype frequencies were reported between 42 and 60% in Caucasians (Garte et al., 2001). This result, when taken into account with previous reports from Turkey, shows that the GSTM1 null frequency in Turkish population is close to the frequency range in Caucasians reported by Garte et al., (2001). The prevalence of the *GSTT1* null genotype is ranges from 12.9 to 25.5% in Caucasians (Garte et al., 2001). In our study, *GSTT1* null frequency was found to fall in this range (Table 3). The result obtained with regard to *GSTT1* null frequency in this study is in agreement with previous reports in Turkish populations except one study (Altayli et al., 2009) (Table 3). When the results of this study and previous studies in Turkish populations were taken into consideration, the *GSTT1* null genotype frequency ranged between 16 and 26% in Turkish population (Table 3).

The genotype distribution of *GSTP1* exon 5 polymorphism in our study is similar to the reports in other European Caucasian populations except Denmark (Table 4). Our results are consistent with the results of Aynacioglu et al. (2004) and Altayli et al. (2009), but significantly different from two previous reports in Turkey(Toruner et al., 2001; Ates et al., 2005). *GSTP1* exon 6 genotype distributions in different populations are shown in Table 5. The genotype distribution of *GSTP1* exon 6 polymorphism in our study was similar to Denmark, but significantly different from Spain. There are a few data about *GSTP1* exon 6 polymorphism among European Caucasian populations. The reasons of distinct observations within Turkish population are not clear. However, it could be due to several reasons such as variability of ethnic backgrounds, the differences in the assays used for genotyping and/or sample size of the studies. Moreover, we did not find any significant difference in genotype distribution of the studied polymorphisms with age or gender. No differences have also been reported for the genetic polymorphisms of *CYP2E1*, *GSTM1*, *GSTT1* and *GSTP1* as a function of either gender or age in Caucasians (Garte et al., 2001; Wang et al., 2003; Sorensen et al., 2004). In line with the results obtained herein, recently, the frequencies of some other polymorphic genes such as *mEH* (Pinarbasi et al., 2010) and *Kir6.2* (Benlier et al., 2011) in Turkish populations have also been reported to be similar to Caucasian populations.

In conclusion, this study confirms that the genotype

Table 2. *CYP2E1*5B* genotype frequencies compared with previously published data in European Caucasian populations.

Population	Number (n)	c1/c1 (%)	c1/c2 (%)	c2/c2 (%)	*P*	Reference
France	172	91.6	4.7	0	0.757	Bouchardy et al. (2000)
Germany	373	94.3	5.7	0	0.851	Brockmoller et al. (1996)
Germany	298	95.3	4.7	0	0.736	Farker et al. (1998)
Germany	297	94.9	4.4	0.7	0.600	Neuhaus et al. (2004)
Italy	114	91.0	9.0	0	0.192	Ingelman-Sundberg et al. (1993)
Serbia	177	90.4	9.0	0.6	0.113	Brocic et al. (2011)
Turkey	153	96.1	3.9	0	0.518	Omer et al. (2001)
Turkey	206	96.1	3.9	0	0.461	Ulusoy et al. (2007)
UK	155	96.8	3.2	0	0.317	Yang et al. (2001)
Turkey	302	94.7	5.3	0		This study

Table 3. *GSTM1* and *GSTT1* null frequencies compared with previously published data in European Caucasian populations.

Population	GSTM1				GSTT1				Reference
	n	Positive (%)	Null (%)	*P*	n	Positive (%)	Null (%)	*P*	
Denmark	537	46.4	53.6	0.779	358	87.1	12.9	0.011*	Garte et al. (2001)
Finland	482	53.1	46.9	0.035*	385	87.0	13.0	0.000*	Garte et al. (2001)
France	1184	46.6	53.4	0.696	512	83.2	16.8	0.223	Garte et al. (2001)
Germany	734	48.4	51.6	0.379	487	80.5	19.5	0.813	Garte et al. (2001)
Germany	143	49.0	51.0	0.479	143	67.9	32.1	0,006*	Zirbs et al. (2012)
Italy	810	50.6	49.4	0.119	553	83.7	16.3	0.194	Garte et al. (2001)
Poland	220	49.0	51.0	0.400	220	91.0	9.0	0.001*	Wlodarczyk and Nowicka (2012)
Slovenia	102	48.0	52.0	0.639	102	74.5	25.5	0.261	Garte et al. (2001)
Spain	192	50.6	49.4	0.263	192	80.8	19.2	0.801	To-Figueras et al. (1997)
Spain	338	50.0	50.0	0.241	338	84.3	15.7	0.136	Ibarrola-Villava et al. (2012)
Sweden	544	44.1	55.9	0.727	423	87.0	13.0	0.009*	Garte et al. (2001)
UK	1112	42.2	57.8	0.321	922	79.5	20.5	0.911	Garte et al. (2001)
Turkey	121	54.5	45.5	0.088	121	82.6	17.4	0.504	Toruner et al. (2001)
Turkey	204	56.9	43.1	0.011*	204	74.0	26.0	0.127	Ates et al. (2005)
Turkey	136	57.0	43.0	0.020*	136	84.0	16.0	0.320	Guven et al. (2007)
Turkey	128	49.2	50.8	0.464	128	93.0	7.0	0.001*	Altayli et al. (2009)
Turkey	142	53.5	46.5	0.109	149	83.2	16.8	0.385	Taspinar et al. (2012)
Turkey	202	65.3	34.7	0.000*					Aktas et al. (2001)
Turkey	206	82.0	18.0	0.000*					Pinarbasi et al. (2003)
Turkey					240	80.0	20.0	0.954	Oke et al. (1998)
Turkey	302	45.4	54.6		302	77.8	22.2		This study

*Significantly different when compared to this study (P<0.05).

Table 4. *GSTP1* exon 5 genotype frequencies compared with previously published data in European Caucasian populations.

Population	Number (n)	Ile/Ile (%)	Ile/Val (%)	Val/Val (%)	*P*	Reference
Denmark	268	43.3	47.8	9.0	0.005*	Sorensen et al. (2004)
Germany	127	55.0	36.0	9.0	0.950	Steinhoff et al. (2000)
Germany	143	47.9	41.7	10.4	0.248	Zirbs et al. (2012)
Poland	142	46.0	41.0	13.0	0.110	Whyatt et al. (2000)

Table 4. Continued.

Poland	220	52.0	38.0	10.0	0.643	Wlodarczyk and Nowicka (2012)
Spain	332	52.4	40.2	7.1	0.346	Ibarrola-Villava et al. (2012)
Turkey	121	68.6	27.3	4.1	0.035*	Toruner et al. (2001)
Turkey	265	50.6	37.4	12.1	0.353	Aynacioglu et al. (2004)
Turkey	204	44.1	36.3	19.6	0.001*	Ates et al. (2005)
Turkey	128	48.4	45.3	6.3	0.102	Altayli et al. (2009)
Turkey	302	56.0	34.8	9.3		This study

*Significantly different when compared to this study (P<0.05).

Table 5. *GSTP1* exon 6 genotype frequencies compared with previously published data in European Caucasian populations.

Population	Number (n)	Ala/Ala (%)	Ala/Val (%)	Val/Val (%)	*P*	Reference
Denmark	266	84.2	14.3	1.5	0.990	Sorensen et al. (2004)
Spain	1007	91.1	8.4	0.5	0.001*	Garcia-Closas et al. (2005)
Spain	338	94.6	5.4	0	0.000*	Ibarrola-Villava et al. (2012)
Turkey	302	84.4	14.2	1.0		This study

*Significantly different when compared to this study (P<0.05).

frequencies of the *CYP2E1*5B*, *GSTM1*, *GSTT1*, *GSTP1* exon 5 and *GSTP1* exon 6 polymorphisms in a Turkish population are similar to European Caucasian populations. These results may be useful for future studies to investigate the role of these polymorphisms in the inter-individual variability in drug response, drug-xenobiotic interactions or disease development.

ACKNOWLEDGEMENT

This study was supported by the Research Fund of Ankara University, Grants: 2006-08-03-002HPD and 10A3336002.

REFERENCES

Abdel-Rahman SZ, el-Zein RA, Anwar WA, Au WW (1996). A multiplex PCR procedure for polymorphic analysis of GSTM1 and GSTT1 genes in population studies. Cancer Lett., 107(2): 229-233.

Aktas D, Ozen H, Atsu N, Tekin A, Sozen S, Tuncbilek E (2001). Glutathione S-transferase M1 gene polymorphism in bladder cancer patients: a marker or invasive bladder cancer? Cancer Genet. Cytogenet. 125(1):1-4.

Ali-Osman F, Akande O, Antoun G, Mao JX, Buolamwini J (1997). Molecular cloning, characterization and expression in Escherichia coli of full-length cDNAs of three human glutathione Stransferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J. Biol. Chem. 272(15):10004-10012.

Altayli E, Gunes S, Yilmaz AF, Goktas S, Bek Y (2009). CYP1A2, CYP2D6, GSTM1, GSTP1, and GSTT1 gene polymorphisms in patients with bladder cancer in a Turkish population. Int. Urol. Nephrol. 41(2):259-266.

Ates NA, Tamer L, Ates C, Ercan B, Elipek T, Ocal K, Camdeviren H (2005). Glutathione S-Transferase M1, T1, P1 Genotypes and Risk for Development of Colorectal Cancer. Biochem. Genet. 43(3-4):149-163.

Aynacioglu AS, Nacak M, Filiz A, Ekinci E, Roots I (2004). Protective role of glutathione S-transferase P1 (GSTP1) Val105Val genotype in patients with bronchial asthma. Br. J. Clin. Pharmacol. 57(2):213-217.

Benlier N, Erdogan M, Ozkur M, Yildiz O, Nacak M, Yamak B, Aynacioglu AS (2011). Association of E23K polymorphism of Kir6.2 gene with coronary artery disease Afr. J. Pharm. Pharmacol. 5(4):554-558.

Bolt HM, Roos PH, Thier R (2003). The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int. Arch. Occup. Environ. Health 76(3):174-185.

Bouchardy C, Hirvonen A, Coutelle C, Ward PJ, Dayer P, Benhamou S (2000). Role of alcohol dehydrogenase 3 and cytochrome P-4502E1 genotypes in susceptibility to cancers of the upper aerodigestive tract. Int. J. Cancer 87(5):734-740.

Brocic M, Supic G, Zeljic K, Jovic N, Kozomara R, Zagorac S, Zlatkovic M, Magic Z (2011). Genetic polymorphisms of ADH1C and CYP2E1 and risk of oral squamous cell carcinoma. Otolaryngol. Head Neck Surg. 145(4):586-593.

Brockmoller J, Cascorbi I, Kerb R, Roots I (1996). Combined analysis of inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1, microsomal epoxide hydrolase, and cytochrome P450 enzymes as modulators of bladder cancer risk. Cancer Res. 56(17):3915-3925.

Choi JY, Abel J, Neuhaus T, Ko Y, Harth V, Hamajima N, Tajima K, Yoo KY, Park SK, Noh DY, Han W, Choe KJ, Ahn SH, Kim SU, Hirvonen A, Kang D (2003). Role of alcohol and genetic polymorphisms of CYP2E1 and ALDH2 in breast cancer development. Pharmacogenetics 13(2):67-72.

Eklund BI, Moberg M, Bergquist J, Mannervik B (2006). Divergent activities of human glutathione transferases in the bioactivation of azathioprine. Mol. Pharmacol. 70(2):747-754.

Farker K, Lehmann MH, Oelschlagel B, Haerting J, HoVmann A, Janitzky V, Schubert J (1998). Impact of CYP2E1 genotype in renal cell and urothelial cancer patients. Exp. Toxicol. Pathol. 50:425-431.

Garcia-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M,

Hein DW, Tardon A, Serra C, Carrato A, Garcia-Closas R, Lloreta J, Castano-Vinyals G, Yeager M, Welch R, Chanock S, Chatterjee N, Wacholder S, Samanic C, Tora M, Fernandez F, Real FX and Rothman N (2005). NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. Lancet 366:649-659.

Garte S, Gaspari L, Alexandrie AK, Ambrosone C, Autrup H, Autrup JL, Baranova H, Bathum L, Benhamou S, Boffetta P, Bouchardy C, Breskvar K, Brockmoller J, Cascorbi I, Clapper ML, Coutelle C, Daly A, Dell'Omo M, Dolzan V, Dresler CM, Fryer A, Haugen A, Hein DW, Hildesheim A, Hirvonen A, Hsieh LL, Ingelman-Sundberg M, Kalina I, Kang D, Kihara M, Kiyohara C, Kremers P, Lazarus P, Le Marchand L, Lechner MC, van Lieshout EM, London S, Manni JJ, Maugard CM, Morita S, Nazar-Stewart V, Noda K, Oda Y, Parl FF, Pastorelli R, Persson I, Peters WH, Rannug A, Rebbeck T, Risch A, Roelandt L, Romkes M, Ryberg D, Salagovic J, Schoket B, Seidegard J, Shields PG, Sim E, Sinnet D, Strange RC, Stücker I, Sugimura H, To-Figueras J, Vineis P, Yu MC, Taioli E (2001). Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol. Biomarkers Prev. 10(12):1239-1248.

Griese EU, Ilett KF, Kitteringham NR, Eichelbaum M, Powell H, Spargo RM, LeSouef PN, Musk AW, Minchin RF (2001). Allele and genotype frequencies of polymorphic cytochromes P4502D6, 2C19 and 2E1 in aborigines from western Australia. Pharmacogenetics, 11(1): 69-76.

Guven M, Unal M, Sarici A, Ozaydin A, Batar B, Devranoglu K (2007). Glutathione-S-transferase M1 and T1 genetic polymorphisms and the risk of cataract development: a study in the Turkish population. Curr. Eye Res. 32(5):447-454.

Hayashi S, Watanabe J, Kawajiri K (1991). Genetic polymorphisms in the 5'-flanking region change transcriptional regulation of the human cytochrome P450IIE1 gene. J. Biochem. 110(4):559-565.

Ibarrola-Villava M, Martin-Gonzalez M, Lazaro P, Pizarro A, Lluch A, Ribas G (2012). Role of GSTs in Melanoma Susceptibility: Association with rs1695 GSTP1 Polymorphism. Br. J. Dermatol. Jan 17. doi: 10.1111/j.1365-2133.2012.10831.x.

Ingelman-Sundberg M, Johansson I, Yin H, Terelius Y, Eliason E, Clot P, Albano E (1993). Ethanol-inducible cytochrome P4502E1: Genetic polymorphism, regulation, and possible role in the etiology of alcohol-induced liver disease. Alcohology 10(6):447-452.

Lieber CS (1997). Cytochrome P-4502E1: its physiological and pathological role. Physiol Rev. 77(2):517-544.

Liu Y, Meng XW, Zhou LY, Zhang PY, Sun X, Zhang P (2009). Genetic polymorphism and mRNA levels of cytochrome P450IIE1 and glutathione S-transferase P1 in patients with alcoholic liver disease in different nationalities. Hepatobiliary Pancreat. Dis. Int., 8(2): 162-167.

Lo HW, Ali-Osman F (2007). Genetic polymorphism and function of glutathione S-transferases in tumor drug resistance. Curr. Opin. Pharmacol. 7(4):367-374.

Mannervik B, Awasthi YC, Board PG, Hayes JD, Di Ilio C, Ketterer B, Listowsky I, Morgenstern R, Muramatsu M, Pearson WR, Pickett CB, Sato K, Widersten M, Wolf CR (1992). Nomenclature for human glutathione transferases. Biochem. J. 282(Pt 1):305-306.

Nakagawa K, Yokota J, Wada M, Sasaki Y, Fujiwara Y, Sakai M, Muramatsu M, Terasaki T, Tsunokawa Y, Terada M (1988). Levels of glutathione S transferase pi mRNA in human lung cancer cell lines correlate with the resistance to cisplatin and carboplatin. Jpn. J. Cancer Res. 79(3):301-304.

Nebert DW, McKinnon RA, Puga A (1996). Human drug-metabolizing enzyme polymorphisms: effects on risk of toxicity and cancer. DNA Cell Biol. 15(4):273-280.

Neuhaus T, Ko YD, Lorenzen K, Fronhoffs S, Harth V, Bröde P, Vetter H, Bolt HM, Pesch B, Brüning T (2004). Association of cytochrome P450 2E1 Polymorphisms and head and neck squamous cell cancer. Toxicol. Lett. 151(1):273-282.

Oke B, Akbas F, Aydin M, Berkkan H (1998). GSTT1 null genotype frequency in a Turkish population. Arch. Toxicol. 72(7):454-455.

Omer B, Ozbek U, Akkose A, Kilic G (2001). Genetic polymorphism of cytochrome P450 2E1 in the Turkish population. Cell Biochem. Funct. 19(4):273-275.

Park JY, Schantz SP, Stern JC, Kaur T, Lazarus P (1999). Association between glutathione S-transferase pi genetic polymorphisms and oral cancer risk. Pharmacogenetics 9(4):497-504.

Pemble S, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM, Ketterer B, Taylor JB (1994). Human glutathione S-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. Biochem. J. 300(Pt1):271-276.

Pinarbasi H, Silig Y, Cetinkaya O, Seyfikli Z, Pinarbasi E (2003). Strong association between the GSTM1-null genotype and lung cancer in a Turkish population. Cancer Genet. Cytogenet. 146(2):125-129.

Pinarbasi H, Silig Y, Pinarbasi E (2010). Microsomal epoxide hydrolase polymorphisms. Mol. Med. Report 3(4):723-727.

Smith CM, Kelsey KT, Wiencke JK, Leyden K, Levin S, Christiani DC (1994). Inherited glutathione-S-transferase deficiency is a risk factor for pulmonary asbestosis. Cancer Epidemiol. Biomarkers Prev. 3(6):471-477.

Sorensen M, Autrup H, Tjonneland A, Overvad K, Raaschou-Nielsen O (2004). Glutathione S-transferase T1 null-genotype is associated with an increased risk of lung cancer. Int. J. Cancer 110(2):219-224.

Steinhoff C, Franke KH, Golka K, Thieri R, Romeri HC, Rotzeli C, Ackermanni R, Schulzi WA (2000). Glutathione transferase isozyme genotypes in patients with prostate and bladder carcinoma. Arch. Toxicol. 74(9):521-526.

Stocco G, Martelossi S, Barabino A, Decorti G, Bartoli F, Montico M, Gotti A, Ventura A (2007). Glutathione-S-transferase genotypes and the adverse effects of azathioprine in young patients with inflammatory bowel disease. Inflamm. Bowel Dis. 13(1):57-64.

Taspinar M, Aydos S, Sakiragaoglu O, Duzen IV, Yalcinkaya A, Oztuna D, Bardakci H, Tutar E, Sunguroglu A (2012). Impact of genetic variations of the CYP1A1, GSTT1, and GSTM1 genes on the risk of coronary artery disease. DNA Cell Biol. 31(2):211-218.

To-Figueras J, Gene M, Gomez-Catalan J, Galan MC, Fuentes M, Ramon JM, Rodamilans M, Huguet E, Corbella J (1997). Glutathione S-transferase M1(GSTM1) and T1 (GSTT1) polymorphisms and lung cancer risk among Northwestern Mediterraneans. Carcinogenesis 18(8):1529-1533.

Toruner GA, Akyerli C, Ucar A, Aki T, Atsu N, Ozen H, Tez M, Cetinkaya M, Ozcelik T (2001). Polymorphisms of glutathione S-transferase genes (GSTM1, GSTP1 and GSTT1) and bladder cancer susceptibility in the Turkish population. Arch. Toxicol. 75(8):459-464.

Townsend D, Tew K (2003). Cancer drugs, genetic variation and the glutathione-S-transferase gene family. Am. J. Pharmacogenomics 3(3):157-172.

Ueno Y, Adachi J, Imamichi H, Nishimura A, Tatsuno Y (1996). Effect of the cytochrome P-450IIE1 genotype on ethanol elimination rate in alcoholics and control subjects. Alcohol Clin. Exp. Res. 20(1 Suppl):17A-21A.

Ueshima Y, Tsutsumi M, Takase S, Matsuda Y, Kawahara H (1996). Acetaminophen metabolism in patients with different cytochrome P-4502E1 genotypes. Alcohol Clin. Exp. Res., 20(1 Suppl): 25A-28A.

Ulusoy G, Arinc E, Adali O (2007). Genotype and allele frequencies of polymorphic CYP2E1 in the Turkish population. Arch. Toxicol. 81(10):711-718.

Wang Y, Spitz MR, Schabath MB, Ali-Osman F, Mata H, Wu X (2003). Association between glutathione S-transferase p1 polymorphisms and lung cancer risk in Caucasians: a case-control study. Lung Cancer 40(1):25-32.

Watson MA, Stewart RK, Smith GB, Massey TE, Bell DA (1998). Human glutathione S-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. Carcinogenesis 19(2):275-280.

Whyatt RM, Perera FP, Jedrychowski W, Santella RM, Garte S, Bell DA (2000). Association between polycyclic aromatic hydrocarbon-DNA adduct levels in maternal and newborn white blood cells and glutathione S-transferase P1 and CYP1A1 polymorphisms. Cancer Epidemiol. Biomarkers Prev. 9(2):207-212.

Wlodarczyk M, Nowicka G (2012). Common polymorphisms in CYP1A1, GSTM1, GSTT1, GSTP1 and XPD genes and endogenous DNA damage. Mol. Biol. Rep. 39(5):5699-5704.

Wormhoudt LW, Commandeur JN, Vermeulen NP (1999). Genetic polymorphisms of human N-acetyltransferase, cytochrome P450,

glutathione-S-transferase, and epoxide hydrolase enzymes: relevance to xenobiotic metabolism and toxicity. Crit. Rev. Toxicol. 29(1):59-124.

Yang B, O'Reilly DA, Demaine AG, Kingsnorth AN (2001). Study of polymorphisms in the CYP2E1 gene in patients with alcoholic pancreatitis. Alcohol., 23(2): 91-97.

Zimniak P, Nanduri B, Pikuła S, Bandorowicz-Pikuła J, Singhal SS, Srivastava SK, Awasthi S, Awasthi YC (1994). Naturally occurring human glutathione S-transferase GSTP1-1 isoforms with isoleucine and valine in position 104 differ in enzymic properties. Eur. J. Biochem., 224(3): 893-899.

Zirbs M, Purner C, Buters JT, Effner R, Weidinger S, Ring J, Eberlein B (2012). GSTM1, GSTT1 and GSTP1 gene polymorphism in polymorphous light eruption. J. Eur. Acad. Dermatol. Venereol., Jan 9. doi: 10.1111/j.1468-3083.2011.04431.x.