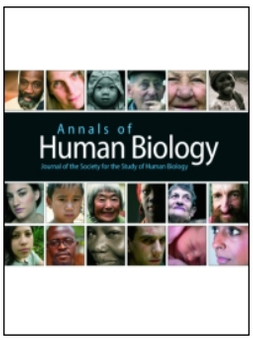

Annals of Human Biology

ISSN: 0301-4460 (Print) 1464-5033 (Online) Journal homepage: http://www.tandfonline.com/loi/iahb20

Gene polymorphism profiles of drug-metabolising enzymes GSTM1, GSTT1 and GSTP1 in an Argentinian population

Natalia Weich, Alejandro Roisman, Belén Cerliani, Hilda V. Aráoz, Lilien Chertkoff, Silvina M. Richard, Irma Slavutsky, Irene B. Larripa & Ariela F. Fundia

To cite this article: Natalia Weich, Alejandro Roisman, Belén Cerliani, Hilda V. Aráoz, Lilien Chertkoff, Silvina M. Richard, Irma Slavutsky, Irene B. Larripa & Ariela F. Fundia (2016): Gene polymorphism profiles of drug-metabolising enzymes GSTM1, GSTT1 and GSTP1 in an Argentinian population, Annals of Human Biology, DOI: 10.1080/03014460.2016.1259429

To link to this article: http://dx.doi.org/10.1080/03014460.2016.1259429

Published online: 28 Nov 2016.

ANNALS OF HUMAN BIOLOGY, 2016
http://dx.doi.org/10.1080/03014460.2016.1259429

HUMAN BIOLOGICAL SURVEY

Gene polymorphism profiles of drug-metabolising enzymes GSTM1, GSTT1 and GSTP1 in an Argentinian population

Natalia Weich[a], Alejandro Roisman[b], Belén Cerliani[c], Hilda V. Aráoz[d], Lilien Chertkoff[d], Silvina M. Richard[c], Irma Slavutsky[b], Irene B. Larripa[a] and Ariela F. Fundia[a]

[a]Hematological Genetics Laboratory, Instituto de Medicina Experimental, CONICET-Academia Nacional de Medicina, Ciudad de Buenos Aires, Argentina; [b]Laboratory of Genetics of Lymphoid Malignancies, Instituto de Medicina Experimental, CONICET-Academia Nacional de Medicina, Ciudad de Buenos Aires, Argentina; [c]Laboratory of Cytogenetics and Mutagenesis, IMBICE, CCT-La Plata-CONICET, Buenos Aires, Argentina; [d]Laboratory of Molecular Biology, Genetics Department, Hospital de Pediatría 'Prof. Juan P. Garrahan', Ciudad de Buenos Aires, Argentina

ABSTRACT

Background: Glutathione S-transferases (GSTs) are drug-metabolising enzymes involved in biotransformation of carcinogens, drugs, xenobiotics and oxygen free radicals. Polymorphisms of GST genes contribute to inter-individual and population variability in the susceptibility to environmental risk factors, cancer predisposition and pharmacotherapy responses. However, data about GST variability in Argentina are lacking.

Aim: The purpose was to determine the prevalence of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms in the general population from a central region of Argentina and to perform inter-population comparisons.

Subjects and methods: *GSTM1* and *GSTT1* gene deletions and *GSTP1* c.313A > G were genotyped by PCR assays in 609 healthy and unrelated Argentinians.

Results: The frequencies of variant genotypes in Argentinians were *GSTM1*-null (45%), *GSTT1*-null (17%) and *GSTP1*-GG (11%). *GSTM1*-present genotype was significantly associated with *GSTP1*-AG or *GSTP1*-GG variants ($p = 0.037$; $p = 0.034$, respectively). Comparison with worldwide populations demonstrated that the GST distributions in Argentina are similar to those reported for Italy and Spain, whereas significant differences were observed regarding Asian and African populations ($p < 0.001$).

Conclusion: This study has determined, for the first time, the normative profile of three pharmacogenetically relevant polymorphisms (*GSTM1*, *GSTT1* and *GSTP1*) in the largest Argentinian cohort described to date, providing the basis for further epidemiological and pharmacogenetic studies in this country.

ARTICLE HISTORY
Received 15 April 2016
Revised 19 October 2016
Accepted 2 November 2016

KEYWORDS
Glutathione S-transferases; polymorphisms; pharmacogenetic markers; human variability; Argentinian population

Background

Pharmacoethnicity, or population diversity in drug response or toxicity, is a key factor accounting for inter-individual variation in anti-cancer drug responsiveness and is associated with population differences in the frequencies of germline polymorphisms within many important drug-related genes (O'Donnell & Dolan, 2009). Genetic polymorphisms in genes encoding drug metabolising enzymes that affect gene expression or protein function lead to a marked inter-individual and population variability in drug response, toxicity, disease predisposition and susceptibility to environmental chemicals (Karaca et al., 2015; Umamaheswaran et al., 2014). Glutathione S-transferases (GSTs) constitute the most relevant superfamily of phase II detoxification enzymes involved in cellular protection against xenobiotics, carcinogens, toxins and by-products of oxidative stress (Hayes et al., 2005). In addition, as non-enzymatic proteins, GSTs can modulate signalling pathways that control cell proliferation, cell differentiation and apoptosis (Laborde, 2010; Tew et al., 2011) and other processes. Genetic polymorphisms in *GSTM1*, *GSTT1* and *GSTP1* genes result in loss of or reduced catalytic activity and detoxification capacity of the enzyme (Ali-Osman et al., 1997; Harries et al., 1997). Intra-population and inter-population differences in the frequency of GST polymorphic genotypes have been demonstrated worldwide (Di Pietro et al., 2010; Garte et al., 2001; Piacentini et al., 2011). However, there is partial and scarce information about Argentina, whose population is the result of a long-standing process of admixture between several human groups shaped by several immigration waves and a differential geographic contribution of Amerindian ancestry inhabitants (Avena et al., 2012; Catelli et al., 2011; Corach et al., 2010). Therefore, the aim of this study was to determine the prevalence of GST polymorphisms in a large cohort of healthy unrelated Argentinians and to perform a correlation with the genotype distributions reported worldwide.

Sample

The study population consisted of 609 unrelated individuals (mean age =41.87 ± 1.64 years; range =3–89 years) recruited from Buenos Aires city and the Buenos Aires metropolitan area, which are the largest urban areas in Argentina.

CONTACT Ariela Fundia affundia@hematologia.anm.edu.ar, arielafundia@hotmail.com Hematological Genetics Laboratory, Instituto de Medicina Experimental, CONICET - Academia Nacional de Medicina, Pacheco de Melo 3081, Ciudad de Buenos Aires - 1425, Argentina

Exclusion criteria were clinical signs of infection at time of blood draw, the presence of cancer, genetic, haematologic or immunologic disorder, osteoporosis, transfusions or chronic diseases. Peripheral blood samples from these individuals were evaluated at three different laboratories, two of them (Hematological Genetics Laboratory, IMEX, CONICET-ANM and Laboratory of Molecular Biology, Genetics Department, Hospital de Pediatría "Prof. Juan P. Garrahan") located in Buenos Aires city. The other one (Laboratory of Cytogenetics and Mutagenesis, IMBICE, CCT-La Plata-CONICET, CICPBA) was from La Plata city in Buenos Aires Province. All subjects included in this study were Argentinian citizens, and most of them self-reported European descent, although, as reported by Avena et al. (2012), some admixture of Amerindian and African ancestry is to be expected. All individuals provided their informed consent according to the experimental research protocol, approved by the Institutional Ethical Committees of all participating centres. The study was performed in accordance with the Declaration of Helsinki.

Data collection

Genomic DNA from peripheral blood samples was isolated by proteinase K/phenol/chloroform or salting out methods. PCR-based methods employed for GST genotyping including primer sequences and concentration, cycling conditions, enzyme restriction digestion and electrophoresis analyses are detailed in previously published studies. *GSTM1* and *GSTT1* gene deletions were genotyped by multiplex PCR including a housekeeping gene as an internal control of amplification in both laboratories of Buenos Aires city (Aráoz et al., 2014; Weich et al., 2015). DNA samples from La Plata city were analysed by two different PCRs for *GSTM1* (Pavicic et al., 2009) and *GSTT1* (Baranova et al., 1999), including a housekeeping gene as an internal control of each PCR reaction. *GSTP1* c.313A > G (rs1695, p.105 Ile > Val) genotypes were determined in 309 samples from both centres of Buenos Aires city by a RFLP-PCR protocol using *Alw*261 restriction enzyme as previously reported (Harries et al., 1997). The laboratory of La Plata city did not evaluate *GSTP1* gene polymorphism. For quality-control purposes, two reviewers independently scored all genotypes, and 10–20% of the samples were randomly re-analysed, yielding identical results.

Data management and statistical analysis

Differences in the distribution of GST genotype and allele frequencies and deviation from Hardy-Weinberg equilibrium (HWE) were determined using the χ^2 or Fisher exact tests. The comparison of GST genotype frequencies defined in the present study with other human populations was done by contingency table analyses using the χ^2 or Fisher exact tests considering the number of individuals with wild type or variant genotypes/alleles. The distributions of *GSTM1*-null and *GSTT1*-null frequencies established in this cohort were compared with those described by Garte et al. (2001), because this is the largest study (15 000 individuals) reported up to now. For *GSTP1*-G allele frequency, we used data from the 1000 genomes browser (http://browser.1000genomes.org). All analyses were performed using GraphPad Prism 6.01 (2014). Values of $p < 0.05$ were considered statistically significant.

Results

The distribution of genotype and allele frequencies of GST polymorphisms established in the healthy Argentinian individuals is summarised in Table 1. Deletion of *GSTM1* and *GSTT1* genes was observed in 45% and 17% of 609 individuals, respectively. *GSTP1* c.313A > G genotyping performed on 304 samples showed no deviation from Hardy-Weinberg equilibrium (Chi-square goodness-of-fit test: $p > 0.05$). The frequencies observed for *GSTP1* gene were the following: 44% homozygous wild type (AA), 45% heterozygous (AG) and 11% homozygous variant (GG) genotypes. The analysis of *GSTP1* allele distribution performed by direct counting revealed that 66.5% of the population exhibited the wild type allele (A), whereas the remainder of the subjects (33.5%) presented the variant G allele (Table 1). The distribution of genotype frequencies in controls showed no significant differences when stratified by gender or when comparing paediatric vs adult individuals (all $p > 0.07$). Moreover, the distribution of GST genotype frequencies stratified according to seven age strata showed some differences between groups, but statistical analysis revealed no significant differences (data not shown).

Given that different GST enzymes are involved in the detoxification of similar activated carcinogens, we analysed the distribution of combined double and triple GST genotypes in our cohort (Table 2). Regarding double combinations, 45.1% of individuals were *GSTM1*-present/*GSTT1*-present, while 6.6% exhibited a concurrent lack of both genes. Other comparisons showed that the most frequently combined genotypes were *GSTM1*-present/*GSTP1*-AG (27.7%) and *GSTT1*-present/*GSTP1*-AG (39.1%), whereas the less common combinations were *GSTM1*-null/*GSTP1*-GG (3.1%) and *GSTT1*-null/*GSTP1*-GG (1.6%). The analysis of the triple

Table 1. Distribution of GST genotype and allele frequencies among Argentinians.

Genes	Genotypes/Alleles	All subjects, *n* (%)	Paediatrics, *n* (%)	Adults, *n* (%)	Females, *n* (%)	Males, *n* (%)
GSTM1	present	337 (55)	25 (66)	312 (45)	153 (52)	174 (57)
(*n* = 609)	Null	272 (45)	13 (34)	259 (55)	140 (48)	129 (43)
GSTT1	present	507 (83)	33 (86.8)	474 (83)	236 (80)	258 (85)
(*n* = 609)	Null	102 (17)	5 (13.2)	97 (17)	57 (20)	45 (15)
GSTP1	AA	136 (44)	12 (42.1)	124 (44,7)	61 (50)	65 (38)
(*n* = 309)	AG	139 (45)	18 (47.4)	123 (44.5)	50 (40)	87 (50)
	GG	34 (11)	4 (10.5)	30 (10.8)	11 (10)	21 (12)
	A	411 (66.5)	50 (65.8)	371 (67)	172 (70.5)	217 (62.7)
	G	207 (33.5)	26 (34.2)	183 (33)	72 (29.5)	129 (37.3)

combined GST genotypes demonstrated that 24.7% of individuals were *GSTM1*-present/*GSTT1*-present/*GSTP1*-AG and only one exhibited the triple variant genotype *GSTM1*-null/*GSTT1*-null/*GSTP1*-GG. The statistical analysis of combined genotypes revealed that only double combined polymorphisms of *GSTM1*-present plus *GSTP1*-AG or *GSTP1*-GG genotypes were significantly associated ($p = 0.037$; $p = 0.034$, respectively) (Figure 1).

Table 2. Distribution of double and triple combined GST genotypes.

Combined genotypes		*n*	%
GSTM1/GSTT1	+/+	275	45.1
(*n* = 609)	+/−	62	10.2
	−/+	232	38.1
	−/−	40	6.6
GSTM1/GSTP1	+/AA	65	24.1
(*n* = 304)	+/AG	87	27.7
	+/GG	24	8.2
	−/AA	66	21.7
	−/AG	52	16.9
	−/GG	10	3.1
GSTT1/GSTP1	+/AA	110	36.1
(*n* = 304)	+/AG	119	39.1
	+/GG	29	9.5
	−/AA	21	6.9
	−/AG	20	6.6
	−/GG	5	1.6
GSTM1/GSTT1/GSTP1	+/+/AA	52	17.1
(*n* = 304)	+/+/AG	75	24.7
	+/+/AG	20	6.6
	+/−/AA	13	4.3
	+/−/AG	12	3.9
	+/−/GG	4	1.3
	−/+/AA	58	19.1
	−/+/AG	44	14.5
	−/+/GG	9	3
	−/−/AA	8	2.6
	−/−/AG	8	2.6
	−/−/GG	1	0.33

+: Presence of *GSMT1* or *GSTT1* genes; −: Null genotype *GSMT1* or *GSTT1*.

Inter-population comparisons among Argentinians and different populations were performed (Table 3). GST frequencies in our cohort are similar compared to previously reported studies evaluating smaller samples of subjects from different geographical regions from Argentina (Bailliet et al., 2007; Galván et al., 2011; Moore et al., 2004). The prevalence of *GSTM1*-null variant found in our study (45%) showed a significantly lower-frequency value with respect to Western Eurasian populations (53%) ($p = 0.001$). However, when compared with different European populations, we found that *GSTM1*-null frequency was in agreement with Spaniards (50%) and Italians (49%), whereas significant differences were seen in relation to Denmark (53.6%), France (53.4%), Germany (51.6%), Sweden (55.9%) and the UK (57.8%) (Garte et al., 2001). No significant differences were found between the frequencies for *GSTT1*-null genotype and *GSTP1*-G variant allele in our cohort and those reported for Western Eurasian populations. In our sample, frequencies of *GSTM1*-null and *GSTT1*-null genotype were significantly lower ($p = 0.0015$ and $p = 0.0001$, respectively), whereas the incidence of *GSTP1*-G allele was increased ($p = 0.0001$) compared to Asian populations. In addition, compared to African populations, our cohort displayed a higher frequency of *GSTM1*-null genotype ($p = 0.0001$) and a lower incidence of *GSTT1*-null genotype as well as *GSTP1*-G allele ($p = 0.0001$).

Comments

Pharmacogenetic studies have shown that GST genetic variability contributes to inter-individual and population differences in cancer risk, chemotherapy resistance and environmental exposure response. Moreover, GST polymorphisms have been associated with major consequences upon human exposure to distinct man-made chemicals (Bolt & Thier, 2006). We defined, for the first time, the genetic

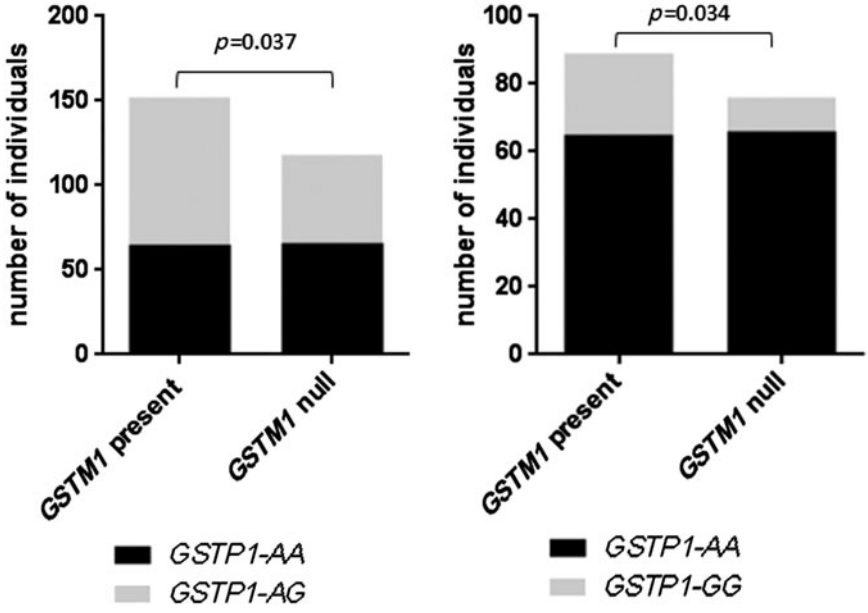

Figure 1. Contingency analysis of double GST genotypes: The double combination between different GST genotypes in our population showed that *GSTM1* and *GSTP1* genes exhibited a statistical association. The majority of the individuals carrying *GSTM1*-present genotype also have *GSTP1-AG* ($p = 0.037$) or *GSTP1-GG* ($p = 0.034$) variant genotypes.

Table 3. Comparison of GST variant genotype frequencies from Argentinians and worldwide populations.

	GSTM1-null frequency (*n*)	p^a	*GSTT1*-null frequency (*n*)	p^a	*GSTP1*-G frequency (n^b)	p^a
Our series	0.45 (609)		0.17 (609)		0.33 (618)	
Other Argentinian series						
Córdoba city	NE		NE		0.35 (204)[d]	ns
Córdoba rural	0.45 (109)[c]	ns	0.11 (109)[c]	ns	NE	
Amerindian	0.40 (90)[e]	ns	0.16 (90)[e]	ns	NE	
Western Eurasians	0.53 (10514)[f]	0.0001	0.20 (5577)[f]	ns	0.33 (1006)[g]	ns
Spain	0.50 (312)	ns	0.205 (312)	ns	0.36 (214)[g]	ns
Italy	0.49 (810)	ns	0.160 (553)	ns	0.29 (214)[g]	ns
Denmark	0.536 (537)	0.0001	0.129 (358)	ns	NE	
France	0.534 (1184)	0.0005	0.168 (512)	ns	NE	
Germany	0.516 (734)	0.01	0.195 (487)	ns	NE	
Sweden	0.559 (544)	0.002	0.130 (423)	ns	NE	
UK	0.578 (1122)	0.0001	0.205 (922)	ns	0.32 (182)	ns
Asians	0.53 (1511)[f]	0.0015	0.47 (575)[f]	0.0001	0.18 (1008)[g]	0.0001
Africans	0.27 (479)[f]	0.0001	0.41 (279)[h]	0.0001	0.48 (1322)[g]	0.0001

[a]Statistical analysis comparing our cohort with other populations was done by contingency table analyses with χ^2 or Fisher exact tests considering the number of individuals with wild type or variant genotypes or alleles.
[b]Number between parentheses shows the total number of alleles evaluated for *GSTP1*-G variant allele.
[c]Moore et al. (2004); [d]Galván et al. (2011); [e]Bailliet et al. (2007); [f]Garte et al. (2001); [g]1000 genomes Browser (last accessed: October 2015); [h]Piacentini et al. (2011).
NA: not evaluated.

profiles of drug-metabolising enzymes *GSTM1*, *GSTT1* and *GSTP1* in the largest cohort of healthy individuals from two important urban cities from Argentina. We demonstrated a significant association between *GSTM1*-present with *GSTP1*-AG or *GSTP1*-GG genotypes, suggesting a potential protective mechanism that involves the presence of GSTM1 protein to balance the reduced GSTP1 enzyme activity associated with *GSTP1*-AG or *GSTP1*-GG genotypes. In addition, the compensatory mechanism reported for GSTP1 when GSTM1 is lacking (Fuciarelli et al., 2009) supports our hypothesis. In fact, few studies demonstrated that double *GSTM1* and *GSTT1* null genotypes confer an increasing risk of development of numerous diseases such as cancer (Di Pietro et al., 2010). In addition, inter-population comparisons enable us to find differences with other human groups. The *GSTM1*-null frequency determined in our cohort exhibits significant differences compared to Denmark, France, Germany, Sweden and UK populations, but it resembles that of Spaniards and Italians. This finding could be related to the remarkable intra-population heterogeneity described for *GSTM1*-null genotype among northern and southern European countries (Garte et al., 2001) and also to the well-documented immigration flows landing in Argentina from Spain and Italy (Avena et al., 2006; Catelli et al., 2011; Corach et al., 2010). Moreover, we found that GST frequencies in our cohort significantly differ from those reported for Asians and Africans, which is probably related to the limited immigration flow from these countries (Avena et al., 2006, 2012).

Pharmacoethnic characterisation of gene polymorphisms is crucial to elucidate the genetic background underlying the differences in drug responses and is one of the main goals in future chemotherapy pharmacogenomics research. In low-resource settings, it will be of particular importance because sparse resources may be preferentially guided toward optimising chemotherapy. The establishment of geographical patterns of GST polymorphisms in different human populations may be of great value to understand population differences in disease risk and variable clinical responses to chemotherapy. Our results provide new insights for future association studies to define the potential role of GSTs in cancer risk and pharmacogenetic responses contributing to favourably impact the development of personalised medicine in the Argentinian population.

Acknowledgements

The author would like to thank all healthy individuals for their participation in this study.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This study was supported in part by grants from the National Research Council (CONICET-PIP0088), (CONICET-PIP 0634); the National Agency of Scientific and Technical Promotion (SECyT-PICT 0330), and the National Institute of Cancer.

References

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 S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem 272:10004–10012.

Aráoz HV, D'Aloi K, Foncuberta ME, Sanchez La Rosa CG, Alonso CN, Chertkoff L, Felice M. 2014. Pharmacogenetic studies in children with acute lymphoblastic leukemia in Argentina. Leuk Lymphoma 56:1370–1378.

Avena S, Via M, Ziv E, Pérez-Stable EJ, Gignoux CR, Dejean C, Huntsman S, et al. 2012. Heterogeneity in genetic admixture across different regions of Argentina. PLoS One 7:e34695. doi: 10.1371/journal.pone.0034695.

Avena SA, Goicoechea AS, Rey J, Dugoujon JM, Dejean CB, Carnese FR. 2006. Gene mixture in a population sample from Buenos Aires City. Medicina (B Aires.) 66:113–118.

Bailliet G, Santos MR, Alfaro EL, Dipierri JE, Demarchi DA, Carnese FR, Bianchi NO. 2007. Allele and genotype frequencies of metabolic genes in Native Americans from Argentina and Paraguay. Mutat Res 627:171–177.

Baranova H, Canis M, Ivaschenko T, Albuisson E, Bothorishvilli R, Baranov V, Malet P, Bruhat MA. 1999. Possible involvement of arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1 genes in the development of endometriosis. Mol Hum Reprod 5:636–641.

Bolt HM, Thier R. 2006. Relevance of the deletion polymorphisms of the glutathione S-transferases GSTT1 and GSTM1 in pharmacology and toxicology. Curr Drug Metab 7:613–628.

Catelli ML, Alvarez-Iglesias V, Gómez-Carballa A, Mosquera-Miguel A, Romanini C, Borosky A, Amigo J, et al. 2011. The impact of modern migrations on present-day multi-ethnic Argentina as recorded on the mitochondrial DNA genome. BMC Genet 12:77. doi: 10.1186/1471-2156-12-77.

Corach D, Lao O, Bobillo C, van Der Gaag K, Zuniga S, Vermeulen M, van Duijn K, et al. 2010. Inferring continental ancestry of argentineans from Autosomal, Y-chromosomal and mitochondrial DNA. Ann Hum Genet 74:65–76.

Di Pietro G, Magno LA, Rios-Santos F. 2010. Glutathione S-transferases: an overview in cancer research. Expert Opin Drug Metab Toxicol 6:153–170.

Fuciarelli M, Caccuri A, De Francesca M, Ferazzoli F, Piacentini S, Porreca F. 2009. Modulation of the GSTT1 activity by the GSTM1 phenotype in a sample of Italian farm-workers. Arch Toxicol 83:115–120.

Galván CA, Elbarcha OC, Fernández EJ, Beltramo DM, Soria NW. 2011. Genetic profiling of GSTP1, DPYD, FCGR2A, FCGR3A and CCND1 genes in an Argentinian population. Clin Biochem 44:1058–1061.

Garte S, Gaspari L, Alexandrie AK, Ambrosone C, Autrup H, Autrup JL, Baranova H, et al. 2001. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev 10:1239–1248.

Harries LW, Stubbins MJ, Forman D, Howard GC, Wolf CR. 1997. Identification of genetic polymorphisms at the glutathione S-transferase Pi locus and association with susceptibility to bladder, testicular and prostate cancer. Carcinogenesis 18:641–644.

Hayes JD, Flanagan JU, Jowsey IR. 2005. Glutathione transferases. Annu Rev Pharmacol Toxicol 45:51–88.

Karaca S, Karaca M, Cesuroglu T, Erge S, Polimanti R. 2015. GSTM1, GSTP1, and GSTT1 genetic variability in Turkish and worldwide populations. Am J Hum Biol 27:310–316.

Laborde E. 2010. Glutathione transferases as mediators of signaling pathways involved in cell proliferation and cell death. Cell Death Differ 17:1373–1380.

Moore LE, Wiencke JK, Bates MN, Zheng S, Rey OA, Smith AH. 2004. Investigation of genetic polymorphisms and smoking in a bladder cancer case-control study in Argentina. Cancer Lett 211:199–207.

O'Donnell PH, Dolan ME. 2009. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res 15:4806–4814.

Pavicic WH, Laguens M, Richard SM. 2009. Analysis association between mitochondrial genome instability and xenobiotic metabolizing genes in human breast cancer. Mol Med 15:160–165.

Piacentini S, Polimanti R, Porreca F. 2011. GSTT1 and GSTM1 gene polymorphisms in European and African populations. Mol Biol Rep 38:1225–122530.

Tew KD, Manevich Y, Grek C, Xiong Y, Uys J, Townsend DM. 2011. The role of glutathione S-transferase P in signaling pathways and S-glutathionylation in cancer. Free Radic Biol Med 51:299–313.

Umamaheswaran G, Kumar DK, Adithan C. 2014. Distribution of genetic polymorphisms of genes encoding drug metabolizing enzymes & drug transporters: a review with Indian perspective. Indian J Med Res 139:27–65.

Weich N, Nuñez MC, Galimberti G, Elena G, Acevedo S, Larripa I, Fundia AF. 2015. Polymorphic variants of GSTM1, GSTT1, and GSTP1 genes in childhood acute leukemias: a preliminary study in Argentina. Hematology 20:511–516.