Carcinogenesis vol.19 no.2 pp.275–280, 1998

Human glutathione *S*-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution

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The association between glutathione *S*-transferase (GST) activity as measured by 1-chloro-2,4-dinitrobenzene (CDNB) conjugation and genotype at exon 5 and exon 6 of the human *GSTP1* gene was investigated in normal lung tissue obtained from 34 surgical patients. These samples were genotyped for previously identified polymorphisms in exon 5 (Ile105Val) and exon 6 (Ala114Val) by PCR-RFLP and direct sequencing. GST enzyme activity was significantly lower among individuals with the 105 Val allele. Homozygous Ile/Ile samples ($n = 18$) had a mean cytosolic CDNB conjugating activity of 74.9 ± 3.8 nmol/mg per min; heterozygotes ($n = 13$) had a mean specific activity of 62.1 ± 4.2 nmol/mg per min and homozygous Val/Val ($n = 3$) had a mean specific activity of 52.5 ± 4.5 nmol/mg per min. The CDNB conjugating activity measured for the Ile/Ile genotype group was significantly different from that observed in the Ile/Val group ($P = 0.03$), and from Ile/Val and Val/Val genotypes combined ($P = 0.009$). Mean GST activity values were consistently lower in individuals with genotypes containing the 105 valine allele, regardless of smoking exposure. Genotypes at codon 114 were also assessed but the mean GST activity was not significantly lower in individuals with the 114 valine allele. A new haplotype, present in two samples who were homozygous 105Ile and had a 114Val, was identified and proposed as *GSTP1D. Frequencies of the exon 5 and exon 6 polymorphisms were determined in samples obtained from European-Americans, African-Americans and Taiwanese. The differences observed were highly significant suggesting the possibility of *GSTP1* genotype-associated, ethnic differences in cancer susceptibility and chemotherapeutic response.**

Introduction

Glutathione transferases (GSTs*) consist of a super-family of dimeric phase II metabolic enzymes that catalyze the conjugation of reduced glutathione with electrophilic groups of a wide variety of compounds. In general, the reactions catalyzed by GSTs are considered detoxifying, and serve to protect cellular macromolecules from damage caused by cytotoxic and carcinogenic agents (1,2). In some cases, however, glutathione conjugation can result in chemical intermediates that may be more reactive than the parent compounds (3). Biochemical characteristics separate the cytosolic GST isozymes into four major classes: alpha, mu, theta and pi (4). Different classes of GSTs have distinct substrate specificities, although some substrates, such as 1-chloro-2,4-dinitrobenzene (CDNB), are conjugated by several classes (2). GST composition varies among tissues and the particular combination of GSTs expressed in a tissue may influence detoxifying capability (2). There is evidence to suggest that GSTs are involved in the metabolism of chemotherapeutic agents, and that they are over-expressed in tumors that are refractory to treatment (5). GST isoforms have been shown to be polymorphic (GSTM1 and GSTT1) resulting in reduced enzyme activity (6–8), and may confer an increased risk for developing specific types of cancer (9–13).

GSTP1-1 is widely expressed in normal human epithelial tissue (14) and is particularly abundant in the lung, esophagus and placenta (15). As much as 10-fold inter-individual variation in GST activity has been reported in normal and tumor tissues (16,17). GSTP1-1 is commonly over-expressed in tumors, and elevated levels have been found in stomach, colon, bladder, oral, breast, skin and lung tumors compared with normal matched tissues (15–23). In some cancer model systems, GSTP1-1 expression is considered a pre-neoplastic tumor marker (24). Increased levels of GSTP1-1 in tumors may account for part of the inherent drug resistance observed in many tumors, although the mechanism remains unknown (5). This evidence suggests that genetic polymorphisms in *GSTP1* could be an important factor in cancer etiology and therapy.

Polymorphisms in exon 5 (Ile105Val) and exon 6 (Ala114-Val) of *GSTP1* were first reported by Board *et al.* (25) and these changes appear to be within the active site of the GSTP1-1 protein (26,27). *In vitro* cDNA expression studies suggest that the Ile105Val substitution reduces enzyme activity (26). However, no studies have compared enzyme activities in tissue samples with the presence of these polymorphisms. In this study, we investigated whether polymorphisms within exons 5 and 6 of the *GSTP1* gene could account for the inter-individual variation seen in GST activity in normal lung tissue. We initially screened for the exon 5 polymorphism by using single-strand conformation polymorphism (SSCP) analysis and then developed a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method for rapid detection. We report the association of *GSTP1* polymorphisms with lower CDNB conjugating activity in human lung tissue and provide data on the frequency of *GSTP1* polymorphism among samples collected from individuals with European, African and Asian ancestry.

Materials and methods

Subjects

Sections of peripheral lung tissue (13–108 g), devoid of macroscopically visible tumors, were obtained from surgical patients at Kingston General

***Abbreviations:** Ile, isoleucine; Val, valine; GST, glutathione *S*-transferase; CDNB, 1-chloro-2,4-dinitrobenzene; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSCP, single-strand conformation polymorphism; GSTP1-1a, 105 isoleucine form of the GSTP1 protein, GSTP1-1b, 105 valine form of the GSTP1 protein; BSA, bovine serum albumin.

Table I. Primer sequences

Exon 5 sequencing	PiF2537	CCA ACC CCA GGG CTC TAT G
and SSCP	PiR205	GGG GTG AGG GCA CAA GA
Exon 5 RFLP	PiF2306	GTA GTT TGC CCA AGG TCA AG
(Ile105Val)	PiR2721	AGC CAC CTG AGG GGT AAG
Exon 6 RFLP	PiF3402	GGG AGC AAG CAG AGG AGA AT
(Ala114Val)	PiR3800	CAG GTT GTA GTC AGC GAA GGA G

Hospital, Kingston, Ontario, Canada, during clinically indicated lobectomy. Samples were obtained following informed consent and in accord with Queen's University Research Ethics Board guidelines. In order to minimize any loss of GSTP1-1 activity, immediately after removal, each tissue section was placed in 0.9% NaCl and kept on ice. Time between surgical resection and tissue processing was ~20 min. Tissues were homogenized and cytosols prepared by differential centrifugation as described previously (28). Cytosolic fractions were then snap frozen in liquid N_2 and stored at –70°C until use. Following thawing, protein concentrations were measured by the method of Lowry *et al.* (29), and glutathione *S*-transferase (GST)-catalyzed conjugation of 1-chloro-2,4-dinitrobenzene (CDNB) (Sigma Corporation, St Louis, MO) was measured as described by Habig *et al.* (30). DNA was isolated from frozen sections of peripheral lung by proteinase digestion followed by phenol:chloroform extraction and ethanol precipitation (31). Patients were characterized with respect to diagnosis leading to surgery, drug treatment prior to surgery, smoking status, possible occupational exposure to carcinogens, sex, age and race. Patients were considered former smokers if smoking cessation was >2 months prior to surgery. This period coincides with the time others have found necessary for loss of smoking-related effects on GST- and cytochrome P450-mediated biotransformation activities in human lung tumors (32,33).

Blood samples from African-American and European-American subjects were obtained from a community-based sample of 424 healthy, unrelated volunteers from Durham and Chapel Hill, North Carolina, who were recruited by newspaper advertisement. Taiwanese DNA samples were obtained from 116 unrelated full-term maternity patients with uncomplicated pregnancies at the Chang Gung Memorial Hospital, Taiwan and were kindly provided by Dr L.L.Hsieh. These samples were extracted from placental tissue as described in Hsieh and Hsieh (34). The population samples have been utilized in several studies from this laboratory and are used only for estimating approximate gene frequencies (9,13,35,36). Comparison of gene frequency data (*GSTM1, NAT2, CYP2E1*) derived from these samples with other published and unpublished data on European-American, African-American and Asian populations suggest that in general, these population samples display gene frequencies that approximate regional, national and international trends.

All samples were obtained with informed consent and under NIH approved human subject protocols. DNA was extracted from whole blood with conventional phenol:chloroform extraction methodology following lysis and nuclei pelleting using the Applied Biosystem Inc. protocol on the ABI 340A DNA Extractor (ABI, Foster City, CA).

Single-strand conformation polymorphism

Using published sequence data, primers were designed using the Oligo program (National Biosciences, Inc., Plymouth, MN) to amplify exon 5 of the *GSTP1* gene. Two consecutive PCR reactions were performed. Briefly, 100 ng of genomic DNA from frozen sections of peripheral lung was added to a mix containing 25 pmol of primers PiF2537 and PiR205 (Table I), 200 μM deoxynucleoside triphosphates, 1 U of Taq polymerase (Promega Corp., Madison, WI), 1.6 mM $MgCl_2$, and a PCR buffer containing 16.6 mM $(NH_4)_2SO_4$, 50 mM β-mercaptoethanol, 6.8 μM EDTA, 67 mM Tris (pH 8.8) and 80 μg/ml bovine serum albumin (BSA), in a final volume of 30 μl. A 'hot start' was used to prevent non-specific priming in the first cycle of PCR. Following an initial denaturation step at 94°C for 3 min, five cycles of PCR were carried out (cycle 1: 94°C for 15 s, 64°C for 30 s, 72°C for 60 s) in which the annealing temperature decreased by 1°C each cycle. This was followed by 25 cycles of amplification at 94°C for 15 s, 59°C for 30 s and 72°C for 1 min in a Perkin–Elmer 9600. Aliquots of 1 μl of the initial PCR reaction were added to a subsequent PCR containing 25 pmol of each SSCP primer, 2 μCi [α-^{33}P]dATP (Amersham Corp., Arlington Heights, IL), 2 μM dNTPs, 2.5 mM $MgCl_2$, 1 U Taq Polymerase and $(NH_4)_2SO_4$ PCR buffer in a final volume of 20 μl and amplified for an additional 15 cycles at 94°C for 15 s, 59°C for 30 s and 72°C for 1 min. Products were diluted and added to a formamide stop solution, heat denatured, placed on ice and loaded on to a 6% acrylamide gel containing 10% glycerol. Samples were electrophoresed for 5.5 h at 35 W and 4°C. The gel was dried and autoradiographed overnight at room temperature.

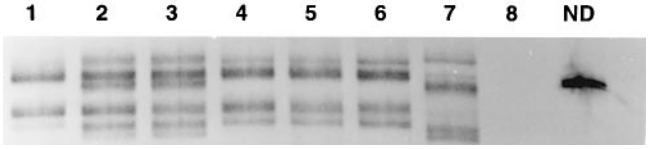

Fig. 1. SSCP analysis of exon 5 revealed three distinct fragment patterns. Direct sequencing of these samples determined samples 2 and 3 were heterozygous and sample 7 was homozygous for a G→A transition at nucleotide 313 of *GSTP1*.

Sequencing

Phenotyped samples screened by SSCP were directly sequenced in order to elucidate the basis for observed conformational changes detected. Samples were amplified prior to sequencing using primers PiF2537 and PiR205 for exon 5 (Table I). Cycling parameters were the same used in the SSCP protocol prior to the radioactive amplification, and both sense and anti-sense strands were sequenced. The PCR fragment from exon 6 was sequenced using the forward primer for the PCR-RFLP (PiF3402). The PCR product was purified with a Microcon 100 microconcentrator (Amicon Corp., Beverly, MA) and 5 μl was added to a sequencing mix and cycle sequenced using ABI Prism AmpliTaq DNA Polymerase FS (Perkin-Elmer Corp., Foster City, CA). Samples were again purified using Centri-sep columns (Princeton Separations, Adelphia, NJ) and analyzed on an ABI 373 Stretch Sequencer (ABI, Foster City, CA).

PCR-RFLP analysis

PCR was performed using the primers PiF2306/PiR2721 for exon 5 (Ile105Val), and PiF3402/PiR3800 for exon 6 (Ala114Val). The same cycling parameters were used as in the non-radioactive amplification of the SSCP protocol. Following PCR, the entire sample was digested for 2 h at 37°C with 5 units of Alw26I for exon 5, or AciI for exon 6 (New England Biolabs, Beverly, MA). Approximately 15 μl of the digest was electrophoresed on a 3% 3:1 NuSieve:agarose gel (FMC Bioproducts, Rockland, ME) containing ethidium bromide. While digestion with AciI identifies the polymorphism in exon 6 (Ala114Val), digestions with this enzyme were inconsistent. Optimized conditions could not be obtained and results reported for Ala114Val (Table IV) were confirmed by direct sequencing.

Statistics

Differences between means of two groups were tested using Student's *t*-test. For comparisons between group data that did not display normal distributions, non-parametric analysis was performed by Mann–Whitney rank sum test (SAS statistical package, SAS, Cary, NC). Analysis of variance (two-way) was carried out to test the relationship between smoking history (current versus former), *GSTP1* genotype and CDNB conjugating activity (SAS). Genotype and allele frequency differences were tested by chi-square analysis (SAS).

Results and discussion

SSCP screening of *GSTP1* exon 5 was undertaken at the outset of the study because the precise nature of the polymorphism was unclear from the published literature and the genome database. SSCP analysis revealed three distinct fragment patterns for exon 5 of *GSTP1* (Figure 1). From direct sequencing of the samples that exhibited mobility shifts, it was determined that samples 2 and 3 were heterozygous and sample 7 was homozygous for a G→A transition at nucleotide 313 of *GSTP1*. This change represents an amino acid substitution from isoleucine to valine at codon 105; as previously reported by Board *et al.* (25) and by Zimniak *et al.* (26). However, in the latter study the change was stated to be at codon 104. This polymorphism is located at an *Alw*26I restriction site and unambiguous identification of variants can be achieved by PCR-RFLP, as seen in Figure 2. The results obtained with the present method are equivalent to a recently published method (37); however, the approach used here provides a control cut site for the *Alw*26I restriction enzyme.

Table II shows mean GST activity after grouping samples by Ile105Val and Ala114Val genotype. GST enzyme activities in lung tissue were significantly lower among individuals

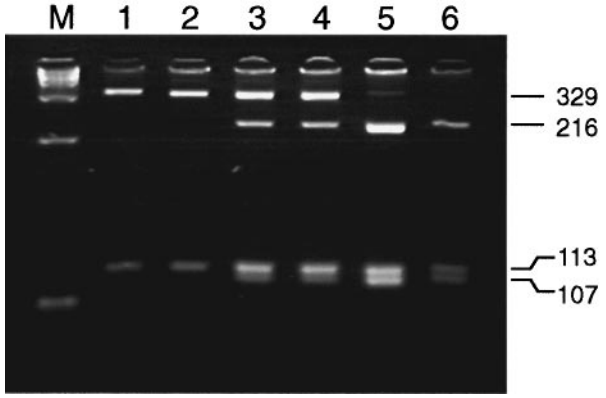

Fig. 2. PCR-RFLP patterns of the Exon 5 amplified fragment resulted in a band of 113 bp in all samples, which represents a control cut for confirmation of proper digestion. In the wild-type sequence (Ile/Ile), bands of 329 bp and 113 bp were generated, whereas in the homozygous mutant, (Val/Val), bands at 216 bp, 113 bp and 107 bp were produced. In the heterozygous Ile/Val, all four bands were present.

Table II. CDNB conjugating activity in lung tissue cytosols in relationship to *GSTP1* genotypes

Exon 5 genotype (Ile105Val)	Specific activity mean (SEM)	Exon 6 genotype (Ala114Val)	Specific activity mean (SEM)
Ile/Ile (n = 18)	74.9 (3.8)[a]	Ala/Ala (n = 27)	70.5 (2.8)[b]
Ile/Val (n = 13)	62.1 (4.2)	Ala/Val (n = 6)	59.2 (10.3)
Val/Val (n = 3)	52.5 (4.5)	Val/Val (n = 1)	55.2

[a]Ile105Val tests, Ile/Ile versus Ile/Val, P = 0.014; Ile/Ile versus Val/Val, P = 0.05; Ile/Ile versus pooled Ile/Val and Val/Val, P = 0.005 (all Mann–Whitney rank sum test).
[b]Ala114Val tests, Ala/Ala versus Ala/Val, P = 0.36; Ala/Ala versus Ala/Val + Val/Val, P = 0.22 (all Mann–Whitney rank sum test).

with the 105 Val allele. The mean activities for the Ile/Val heterozygote group (62.1 ± 4.2 nmol/mg per min, P = 0.03) and Ile/Val and Val/Val genotypes combined (60.3 + 3.6 nmol/mg per min, P = 0.009) were significantly lower than for Ile/Ile genotypes (74.9 ± 3.8 nmol/mg per min).

Zimniak *et al.* (26) used *Escherichia coli* expression to compare Ile 105 and Val 105 alleles and found reduced (~30%) CDNB conjugating activity for the 105Val allele, and a recent paper by Ali-Osman and colleagues reproduced this finding (27). The reduced CDNB activities we observe in lung tissue samples with genotypes containing 105Val were consistent with these findings. Of note, heterozygote genotypes had lower mean CDNB conjugating activity than Ile/Ile homozygotes. This suggests the possibility that GSTP1a-1b heterodimers, which would be present in the cells of those with heterozygote genotypes, may have reduced activity.

Although CDNB is not a class specific GST substrate, a large proportion of human lung CDNB activity has been attributed to GSTP1-1 (38). Contribution to CDNB activity in the lung from other GST enzymes such as GSTM3 or GSTA1/A2 would tend to dilute the *GSTP1* genotype effect that we have observed. Thus the *GSTP1* 105Val genotype might have greater impact on other GSTP1-1 substrates. Interestingly, Zimniak *et al.* (26) found that the GSTP1-1 enzyme containing 105Val had higher rather than lower activity for ethacrynic acid and bromo-sulfophthalein conjugation; suggesting that the differences in activity reflect differences in binding of the electrophilic substrate to the hydrophobic binding site of GSTP1-1. It would be of interest to know how the polymorphism affects activity with regard to other GSTP1-1 substrates present in cigarette smoke, such as benzo[*a*]pyrene.

Table III. Smoking: *GSTP1* genotype and CDNB activity

Exon 5 GST genotype	Specific activity mean ± SEM of smoking status		
	Non-smoker (n)	Former (n)	Current (n)
All genotypes	77.9 ± 8.8 (2)	70.8 ± 5.5 (9)	58.9 ± 3.3 (23)
Ile/Ile	85.1 (1)	61.5 ± 4.2 (5)[a]	79.7 ± 4.0 (12)
Ile/Val or Val/Val	70.7 (1)	55.5 ± 8.9 (4)	61.1 ± 4.2 (11)

[a]To test the difference between current smokers and former smokers, analysis of variance was carried out with genotype as a covariate. The differences observed between current smokers and former smokers were not significant (P = 0.11). The presence of a 105Val allele was positively associated with lower CDNB activity (ANOVA, F = 4.48, P = 0.0086).

Due to limited availability of tissues, this study utilized healthy tissue from patients undergoing surgery (as opposed to healthy tissue from healthy patients). While disease state can sometimes influence expression of metabolizing enzymes in tumors, this has not been observed for GSTP1-1 in normal human lung tissue (41). The present study focuses on the effect of *GSTP1* genotype on GSTP1-1 activity levels in healthy lung tissue, and while the relationship between these variables could be influenced by disease state, this seems unlikely, given that these results are consistent with the biochemical data (26,27).

As shown in Table II, there was a non-significant trend toward lower mean GST activity among individuals with the 114 valine allele. Ali-Osman *et al.* (27) identified three variant cDNAs with the following haplotypes: (i) 105 Ile/114Ala (*GSTP1**A); (ii) 105Val/114Ala (*GSTP1**B), and (iii) 105Val/114Val (*GSTP1**C) (see Reference 39 for GST nomenclature). Precise haplotype frequencies could not be determined in the present study using PCR genotyping methods, but haplotypes can be estimated to occur in the order *GSTP1**A >> *GSTP1**B > *GSTP1**C. In addition, two samples had a 114 valine allele and were homozygous for 105Ile. Therefore, a fourth rare haplotype exists for *GSTP1* (105Ile/114Val, proposed as *GSTP1**D). There were not enough individuals in the study carrying this haplotype (*GSTP1**D) to assess if 114 valine had an independent association with enzyme activity levels. However, the mean conjugating activity for the two individuals carrying *GSTP1**D alleles was 87.9 nmol/mg per min, suggesting that the presence of a valine at position 114 had little impact on enzyme activity in whole tissue extracts.

Exposure to cigarette smoke can alter expression of some xenobiotic metabolism enzymes (32,33,40,41). Because we observed considerable variation for CDNB conjugating activity within *GSTP1* genotypes, we also tested to see if current smoking behavior influenced GSTP1-1 activity in lung tissue samples. There were two non-smokers, nine former smokers and 23 current smokers in the study. As seen in Table III, which displays stratification by smoking and also by smoking and genotype, there is no apparent relationship between smoking history and CDNB activity in these tissue samples. Mean activity levels for current smokers (68.5) were intermediate to non-smokers (87.9) and former smokers (62.5). Individuals

Table IV. *GSTP1* genotype and allele frequencies among Taiwanese, African-Americans and European-Americans

	Exon 5 Ile105Val					Exon 6 Ala114Val				
	n	Ile/Ile	Ile/Val	Val/Val	Allele frequency (valine)	*n*	Ala/Ala	Ala/Val	Val/Val	Allele frequency (valine)
Taiwanese	116	78 (67%)	35 (30%)	3 (3%)	0.18[a]	n.d.[e]	n.d.	n.d.	n.d.	n.d.
African-American	137	48 (35%)	63 (46%)	26 (19%)	0.42[b]	112	106 (95%)	6 (5%)	0 (0%)	0.05
European-American	287	119 (42%)	147 (51%)	21 (7%)	0.33[c,d]	114	93 (82%)	20 (18%)	0 (0%)	0.09

[a]Allele frequency Taiwanese versus African-Americans, chi-square test, $P < 0.0001$.
[b]Allele frequency African-Americans versus European-Americans, chi-square test, $P = 0.01$.
[c]Allele frequency Taiwanese versus European-Americans, chi-square test, $P < 0.0001$.
[d]The Hardy–Weinberg equilibrium test indicates an excess number of 105Val heterozygotes in this European-American population sample ($P < 0.05$). Other populations were in equilibrium. HW tests for other genes (*GSTM1, NAT2, NAT1, CYP2E1*) in these populations were all in equilibrium.
[e]n.d., not determined.

with the 105 valine allele tended to have lower activities in each smoking category; however, due to the small size of this study, differences observed in the stratified analysis are not statistically meaningful. Only *GSTP1* genotype appears to be a significant predictor of activity ($F = 4.48$, $P = 0.0086$). Other studies of GSTP1 and smoking have also been inconclusive. Nakajima *et al.* (41) found no significant differences in GSTP1-1 activity in lung tissue among samples from smokers and non-smokers, providing further evidence that tobacco may not be an effective inducer of GSTP1 in lung.

In order to determine the distribution of genotypes in different populations, Ile105Val and Ala114Val polymorphisms were analyzed in samples obtained from European-Americans, African-Americans and Taiwanese populations. Table IV shows the frequencies of genotypes and alleles in these populations. The 105 valine allele was most common among African-Americans (0.42) and least common among Taiwanese (0.18) with European-Americans (0.33) intermediate between these groups. The allele frequency for European-Americans is not significantly different. These frequencies should be considered preliminary; in particular, the European-American sample displays an excessive number of heterozygotes. While the samples used to test frequency may not be truly representative of these racial groups, the differences observed were highly statistically significant, which suggests that the underlying allele frequencies in Europeans, Asians and African-Americans are likely to be different. Other data from our laboratory suggests that Asian populations, in general, may have a low 105 valine allele frequency: a Japanese population we have tested had a 0.14 allele frequency for 105 valine (D.A.Bell and T.Katoh, unpublished).

The Ala114Val polymorphism in exon 6 was less common than the Ile105Val in both European-Americans (0.09) and African-Americans (0.05) (Table IV). While the 105Val allele was more common in African-Americans than in European-Americans, the opposite was true for the 114Val allele. Thus, the *GSTP1**B haplotype must be the common variant allele in African-Americans. The differences in genotype and allele frequencies that we observed between groups suggests the possibility of differences in susceptibility to exposure to electrophilic toxicants, or in effectiveness of drugs that are inactivated by GSTP1-1-catalyzed biotransformation. For example GSTP1-1 is over-expressed in certain drug resistant tumor cell lines and GSTP1-1 activity may contribute to the drug resistant phenotype of these cells (42,43). It will be of interest if genetic polymorphism modulates GSTP1-1 tumor expression or drug resistance phenotype.

Other GST super-family genes are polymorphic (*GSTM1* and *GSTT1*) and variations within these genes have been associated with an increased risk for cancer, including bladder and lung (9–13). A recent report by Harries *et al.* (37) suggests that *GSTP1* genotype may also influence risk of cancer; individuals who were *GSTP1* valine 105 homozygotes had increased risk for bladder and testicular cancer, and decreased risk for prostate cancer. No information on epidemiological risk factors was available for subjects in the Harries *et al.* study, but the positive findings in that preliminary study suggest that more detailed studies might be worthwhile.

Levels of expression of the GSTP1-1 enzyme may be important for the efficiency of detoxification. Terrier *et al.* (14) used immunohistochemistry to examine GSTP1-1 expression in normal human tissue and found high levels of GST pi-class expression in respiratory, urinary and digestive tract epithelia. Thus, tissues that are the most likely to be exposed to exogenous chemicals from the environment also generally express GSTP1-1 at high levels. Hypothetically, these tissues may be the most 'at risk' of developing cancers among those individuals with genetically determined low activity GSTP1-1 phenotypes. Indeed, a very recent paper suggests that individuals with low activity alleles for *GSTP1* had higher levels of smoking related DNA adducts in lung tissue and higher risk of lung cancer (44). We are conducting follow-up case-control studies of cancer of the bladder, lung, colon, breast and prostate to determine if risk associated with environmental exposures is modulated by genetic polymorphism in the *GSTP1* gene.

In conclusion, the Ile105Val polymorphism in the *GSTP1* gene significantly alters catalytic activity of this phase II enzyme in lung tissue samples and this variation occurs frequently in human populations. *GSTP1* variability has potential implications for individual susceptibility to electrophilic carcinogen metabolites, as well as for expression of the drug resistant phenotype.

Acknowledgements

We thank L.L.Hsieh, Chang Gung Medical School for providing DNA samples from Taiwanese maternity patients. We also thank Patrick Herron, NIEHS for PCR optimizations, Lena Heung for photographs and Richard Morris, Analytical Science, Inc. for statistical analysis. This study was supported in part by Medical Research Council of Canada grant MT10382 to T.E.M. The authors wish to express gratitude to Drs Alan Conlan, Ken Reid and Dimitri Petsikas,

Department of Surgery, Queen's University for providing the human lung tissue and smoking histories. We also thank Sophia Ali and Patty Donnelly for assistance in tissue preparation.

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Received on July 30, 1997; revised on October 22, 1997; accepted on November 3, 1997