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Polymorphisms in glutathione *S*-transferases in French vinyl chloride workers

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Abstract

The authors have recently demonstrated a significant gene–environment interaction between vinyl chloride exposure and polymorphisms in the DNA repair protein XRCC1 on the occurrence of mutant p53 biomarkers of vinyl chloride-induced genetic damage. The aim of this study was to examine the polymorphisms in the glutathione *S*-transferases (GSTs) as potential modifiers of this relationship, since these enzymes may be involved in the phase II metabolism of the reactive intermediates of vinyl chloride. A cohort of 211 French vinyl chloride workers was genotyped for common polymorphisms in GSTM1, GSTT1 and GSTP1. Although no independent, statistically significant effect of these polymorphisms on the occurrence of the mutant p53 biomarker was found, the null GSTM1 and null GSTT1 polymorphisms were found to interact with the XRCC1 polymorphism to increase the occurrence of the biomarker such that, for example, workers with at least one variant XRCC1 allele who were null for both GSTM1 and GSTT1 had a significant odds ratio for the biomarker (OR = 8.4, 95% CI = 1.3–54.0) compared with workers who were wild-type for all alleles, controlling for potential confounders including cumulative vinyl chloride exposure.

Keywords: *Metabolism, gene–environment interaction, mutations, p53, DNA repair.*

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Introduction

Gene–environment interactions are believed to play important roles in mediating the health effects produced by exposures to exogenous toxins (Miller et al. 2001). The present authors recently demonstrated a significant gene–environment interaction between a common polymorphism (codon 399 Arg →Gln) in the X-ray cross-complementing-1 protein (XRCC1), a key component of the base excision repair (BER) pathway, on the occurrence of mutant p53 biomarkers that result from vinyl chloride (VC) exposure in a cohort of French vinyl chloride workers (Li et al. 2003a).

This finding was consistent with the known molecular mechanisms responsible for VC-induced mutagenesis (Li et al. 1998). For example, following exposure, VC is metabolized primarily in the liver to the electrophilic metabolites chloroethylene oxide (CEO) and chloroacetaldehyde (CAA), which are believed to be responsible for the

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formation of etheno-DNA adducts, such as 1,N^6-ethenoadenine. These adducts are pro-mutagenic and can account for the mutations seen in the resultant angiosarcomas of the liver that occur in exposed workers, namely the A to T transversions in the p53 tumour suppressor gene that occur in a high proportion of these tumours (Hollstein et al. 1994). These mutations have been associated with over-expression of biomarkers of p53, including mutant p53 protein and anti-p53 antibodies, in VC-exposed workers with tumours (Trivers et al. 1995, Brandt-Rauf et al. 1996). Furthermore, these mutant p53 biomarkers have been found in a high proportion of VC-exposed individuals without any apparent disease in a highly statistically significant dose–response relationship, reinforcing the idea that generation of the biomarker is the direct result of the VC exposure (Smith et al. 1998). However, at any given level of exposure, some individuals are positive and some negative for these biomarkers, suggesting that there might be some genetically determined susceptibility to VC mutagenesis that could account for different biomarker outcomes with similar exposures.

As noted, one source for this variability derives from altered DNA repair capability for the removal of etheno-DNA adducts (Li et al. 2003a). The ethenoadenine adducts produced by VC are normally removed by the BER pathway, starting with methyl purine glycosylase, which recognizes and excises these adducts. The BER machinery contains several other proteins whose activities are coordinated by XRCC1, which acts as a scaffold for the other proteins and is necessary for regulating the steps of BER through interactions with them. A common polymorphism occurs in XRCC1 at codon 399 (Arg →Gln) in the BRCT1 domain, which is known to interact with other BER proteins, and, thus, this substitution could lead to decreased DNA repair capability, increased ethenoadenine adducts and increased mutant p53 biomarkers at any given level of VC exposure. In fact, our prior study showed that compared with workers who were XRCC1 homozygous wild-type (Arg-Arg), workers who were XRCC1 heterozygous (Arg-Gln) or XRCC1 homozygous variant (Gln-Gln) had elevated odds ratios for the occurrence of the mutant p53 biomarker (OR = 1.73, 95%CI = 0.93–3.22 and OR = 3.95, 95%CI = 1.68–9.28, respectively), even after controlling for other sources of variability including cumulative VC exposure, with a highly statistically significant trend for the biomarker with increasing variant allele dosage ($p = 0.002$) (Li et al. 2003a).

However, altered DNA repair capacity clearly does not account for all of the interindividual variability in this cohort. Another potential contributor to susceptibility could be due to genetically determined variation in the metabolism of VC, particularly the removal of the reactive electrophilic intermediates responsible for the formation of the etheno-DNA adducts. For example, it is believed that CAA undergoes phase II metabolism to non-genotoxic products via aldehyde dehydrogenase 2 (ALDH2). Low-activity variants of ALDH2 have been identified (ALDH2-2) that could be associated with increased DNA adducts at any given exposure level, and VC workers in Taiwan with this variant genotype have been found to be at increased risk for biomarkers of mutagenic damage, namely increased sister chromatid exchanges (Wong et al. 1998). However, in our French cohort, we have not found any workers with this variant ALDH2 allele (Li et al. 2003b). It is also believed that CEO undergoes phase II metabolism to non-genotoxic products via the glutathione *S*-transferases (GSTs), a superfamily of five enzyme groups (A, M, P, T, Z) that conjugate glutathione to various carcinogenic compounds to facilitate their excretion

from the body (Miller et al. 2001). Low GST activity may arise from various genetic polymorphisms, including the relatively common GSTM1 null, GSTT1 null and GSTP1b (codon 105 Ile →Val) alleles, which could be associated with increased DNA adducts at any given exposure level, and VC workers in Taiwan with the GSTT1 null genotype have been shown to vary in their biomarkers for liver damage and biomarkers of mutant p53 (Huang et al. 1997, Wong et al. 2002). Therefore, the purpose of this study was to determine if GST polymorphisms could account for additional genetic susceptibility in our cohort of French vinyl chloride workers, either alone or in conjunction with the XRCC1 polymorphism.

Materials and methods

A group of 211 subjects with available lymphocyte samples for DNA extraction were selected from a cohort of VC-exposed workers in France who had been characterized as to cumulative VC exposure and mutant p53 biomarkers, as described (Smith et al. 1998). The workers were all white males with an average age of 56 years (range = 35–74 years) and average cumulative VC exposure of 5871 ppm-years (range = 6–46702 ppm-years); 39% were current or former smokers, 20% were current drinkers, and 44.5% were positive for the mutant p53 biomarker. Positivity for the mutant p53 biomarker had been determined by analysis of serum samples for mutant p53 proteins and/or anti-p53 antibodies using enzyme-linked immunosorbent assays, as described (Smith et al. 1998); these assays have been shown to be sensitive, specific and reproducible, yielding results consistent with western immunoblotting on the same samples. XRCC1 genotype had been determined by polymerase chain reaction-restriction fragment length polymorphism analysis of lymphocyte DNA, as described (Li et al. 2003a).

DNA was isolated from lymphocytes, amplified by polymerase chain reaction (PCR) and analysed for the GSTM1, GSTT1 and GSTP1 polymorphisms, as described (Ford et al. 2000, Wiencke et al. 1995, Zielinska et al. 2004). Briefly, for GSTM1, 20 ng DNA was added to the PCR reaction mixture containing 10 mM Tris-HCl, 50 mM KCl, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 0.25 units Taq polymerase, 20 ng GSTM1 primer pairs (5′-GAACTCCCTGAAAAGCTAAAGC-3′ and 5′-GTTGGGCTCAAATATACGGTGG-3′) and 10 ng γ-globin primer pairs (5′-CAACTTCATCCACGTTCACC-3′ and 5′-GAAGAGCCAAGGACAGGTAC-3′), used as an internal control. The reaction mixture was denatured at 94°C for 4 min and then subjected to 34 cycles of 94°C for 25 s, 55°C for 30 s and 72°C for 1 min, followed by a final extension at 72°C for 5 min. The PCR products were examined by 2% agarose gel electrophoresis with ethidium bromide staining. A 273 bp band (γ-globin gene) and a 219 bp band (GSTM1 gene) were identified in individuals who were GSTM1 wild-type, while the latter was missing in those individuals who were GSTM1 null.

For GSTT1, the PCR mixture as above contained 30 ng DNA, 0.4 units Taq polymerase, 30 ng γ-globin primer pairs and 30 ng GSTT1 primer pairs (5′-TT CCTTACTGGTCCTCACATCTC-3′ and 5′-TCACCGGATCATGGCCA GCA-3′). The reaction mixture was denatured at 94°C for 4 min and then subjected to 34 cycles of 94°C for 30 s, 60°C for 30 s and 72°C for 1 min followed by a final extension at 72°C for 5 min. The PCR products were examined by 1.8% agarose gel electrophoresis with ethidium bromide staining. A 273 bp band (γ-globin gene) and

a 480 bp gene (GSTT1 gene) were identified in individuals who were GSTT1 wild-type, while the latter was missing in those individuals who were GSTT1 null.

For GSTP1, genotyping analysis was modified to incorporate high-throughput methodology based on fluorescence polarization analysis. In this case, the PCR mixture as above contained 2 mM $MgCl_2$, 0.4 units Taq polymerase and 1.6 pmoles GSTP1 primer pairs (5′-CTCTATGGGAAGGACCAGCA-3′ and 5′-GAAGCCCCTTTCTTTGTTCA-3′). The reaction mixture was denatured at 94°C for 4 min and then subjected to 34 cycles of 94°C for 30 s, 61°C for 30 s and 72°C for 45 s followed by a final extension at 72°C for 7 min. After amplification, the primers were digested with shrimp alkaline phosphatase and *Escherichia coli* exonuclease I at 37°C for 45 min followed by incubation at 95°C for 15 min for inactivation of the enzymes. The resulting PCR product mixture was added to AcycloProme-FP mixture with 5 pmole GSTP1 polymorphism probe (5′-GAG-GACCTCCGCTGCAAATAC-3′), according to the instructions of the manufacturer (Perkin-Elmer, Boston, MA, USA). This mixture was denatured at 95°C for 2 min followed by 30–40 cycles of 95°C for 15 s and 55°C for 30 s, as described by the manufacturer. Fluorescence polarization was measured on a VICTOR 2 fluorescence polarization microplate reader (Perkin-Elmer), which provided clear separate clusterings of samples by homozygous wild-type (Ile-Ile), heterozygous (Ile-Val) and homozygous variant (Val-Val) GSTP1 genotypes.

The cohort was analysed for the differences in occurrence of the mutant p53 biomarker between individuals with the wild-type versus the variant genotypes for each of the GSTs individually by logistic regression, adjusting for age, smoking, drinking and cumulative VC exposure, to generate odds ratios and 95% confidence intervals. The analysis was repeated to incorporate combinations of GST genotypes with XRCC1 genotypes to examine potential gene–gene interactions.

Results and discussion

Of the 211 workers studied, 94 (45%) were GSTM1 wild-type and 116 (55%) were GSTM1 null, 182 (86%) were GSTT1 wild-type and 29 (14%) were GSTT1 null, and 97 (46%) were GSTP1 homozygous wild-type (Ile-Ile), 90 (43%) were GSTP1 heterozygous (Ile-Val) and 24 (11%) were GSTP1 homozygous variant (Val-Val). For GSTP1, the distribution of genotypes was consistent with a Hardy–Weinberg equilibrium ($\chi^2 = 0.2$). All genotype distributions were consistent with those reported in other similar populations (Habdous et al. 2004). There were no statistically significant differences in terms of the distribution of VC exposure levels among the different genotypes. Assigning an odds ratio of 1 to the lowest exposure group ($\leq$1000 ppm-years) and adjusting for age, smoking, drinking and genotype, there was a statistically significant trend for increasing prevalence of the mutant p53 biomarker in the medium (1001–4000 ppm-years; OR = 1.7, 95%CI = 0.8–3.8) and high ($>$4000 ppm-years; OR = 2.6, 95%CI = 1.1–61) exposure groups ($p = 0.03$ for trend), as has been previously observed (Smith et al. 1998).

Table I–III show the differences in the prevalences of the mutant p53 biomarker for each of the GST genotypes. With an OR of 1 for the wild-type category in each case, the adjusted ORs for the prevalence of the biomarker were 1.2 (95%CI = 0.7–2.2) for the GSTM1 null genotype, 1.5 (95%CI = 0.6–3.3) for the GSTT1 null genotype, and 1.0 (95%CI = 0.6–1.7) for the combined Ile-Val and Val-Val GSTP1 genotypes.

Table I. Association between GSTM1 polymorphism and p53 biomarker in VC workers.

GSTM1 genotype (*n*)	p53 biomarker −	+	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Wild-type (*n* = 95)	55 (58%)	40 (42%)	1	1
Null (*n* = 116)	62 (53%)	54 (47%)	1.2 (0.7–2.1)	1.2 (0.7–2.2)

*Adjusted for age, smoking, drinking and cumulative VC exposure.

Thus, no GST genotype was found to have an independent, statistically significant effect on biomarker status, although there was evidence that, at least for GSTM1 and GSTT1, the null genotypes had some non-significant effects.

We have previously reported (Li et al. 2003a) that the most significant genetic effect on mutant p53 biomarker status was due to the codon 399 polymorphism in XRCC1, as noted above. We therefore examined whether GST genotype, specifically GSTM1 and/or GSTT1 null genotypes, had any effect on modifying the relationship between XRCC1 genotype and p53 biomarker status. The results are shown in Table IV. Assigning an OR of 1 to those individuals who were wild-type for XRCC1, GSTM1 and GSTT1, the adjusted ORs for the prevalence of the p53 biomarker were: 1.8 (95%CI = 0.7–5.0) for those who were homozygous wild-type for XRCC1 but null for either GSTM1 or GSTT1; 1.8 (95%CI = 0.3–9.3) for those who were homozygous wild-type for XRCC1 but null for both GSTM1 and GSTT1; 2.9 (95%CI = 1.1–7.8) for those who were heterozygous or homozygous variant for XRCC1 but wild-type for both GSTM1 and GSTT1; 3.2 (95%CI = 1.2–8.3) for those who were heterozygous or homozygous variant for XRCC1 but null for either GSTM1 or GSTT1; and 8.4 (1.3–54.0) for those who were heterozygous or homozygous variant for XRCC1 but null for both GSTM1 and GSTT1. A statistically significant trend was observed for p53 biomarker prevalence with increasing variant allele dosage ($p = 0.0037$). Furthermore, the combined effect of variant XRCC1 and GST genotypes appeared to be greater than the product of the OR for the homozygous wild-type XRCC1 and null GSTM1 and GSTT1 stratum times the OR for the heterozygous or homozygous variant XRCC1 and wild-type GSTM1 and GSTT1 stratum ($1.8 \times 2.9 = 5.2$). Therefore, although GST genotype apparently has no independently significant effect on p53 biomarker status in a cohort of this size, the GSTM1 and

Table II. Association between GSTT1 polymorphism and p53 biomarker in VC workers.

GSTT1 genotype (*n*)	p53 biomarker −	+	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Wild-type (*n* = 182)	103 (57%)	79 (43%)	1	1
Null (*n* = 29)	14 (48%)	15 (52%)	1.4 (0.6–3.1)	1.5 (0.6–3.3)

*Adjusted for age, smoking, drinking and cumulative VC exposure.

Table III. Association between GSTP1 polymorphism and p53 biomarker in VC workers.

GSTP1genotype (n)	p53 biomarker −	p53 biomarker +	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Ile-Ile ($n=97$)	54 (56%)	43 (44%)	1	1
Ile-Val+Val-Val ($n=114$)	63 (55%)	51 (45%)	1.0 (0.6–2.0)	1.0 (0.6–1.7)

*Adjusted for age, smoking, drinking and cumulative VC exposure.

GSTT1 null genotypes appears to modify the effect of XRCC1 genotype on biomarker status, perhaps in a synergistic fashion. However, it should be noted that this study is limited by the relatively small numbers of subjects, both in the whole group and especially in some of the sub-groups. The power of the study is thus quite limited, especially for testing interactions of either the gene–environment or gene–gene nature. Therefore, it is difficult to make definitive conclusions until the remainder of the approximately 450 workers in the cohort are similarly tested, which is being planned for the near future.

Nevertheless, such an interaction as noted is consistent with the proposed mechanism of VC-induced mutagenesis in which GSTM1 and GSTT1 play a role in the phase II metabolism of the VC reactive intermediates. In this scenario, VC-exposed individuals with GSTM1 and/or GSTT1 null genotypes would have less efficient removal of CEO leading to higher levels of ethenoadenine adducts and subsequent mutations at any given level of VC exposure, which would be further exacerbated by deficient BER of the ethenoadenine adducts caused by polymorphic XRCC1. However, the fact that an independent effect for GSTM1 and GSTT1 genotypes on the prevalence of the biomarker could not be identified suggest that these GSTs may not play a dominant role in VC phase II metabolism. In fact as noted, CAA (which can form by spontaneous rearrangement of CEO) can undergo phase II

Table IV. Association between XRCC1/GSTM1/GSTT1 genotypes and p53 biomarker in VC workers.

XRCC1/GSTM1+GSTT1 genotypes (n)	p53 biomarker −	p53 biomarker +	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Arg-Arg/both wild-type ($n=31$)	23 (74%)	8 (26%)	1	1
Arg-Arg/either null ($n=47$)	29 (62%)	18 (38%)	1.7 (0.7–4.8)	1.8 (0.7–5.0)
Arg-Arg/both null ($n=8$)	5 (62%)	3 (38%)	1.7 (0.3–9.0)	1.8 (0.3–9.3)
Arg-Gln+Gln-Gln/both wild-type ($n=50$)	25 (50%)	25 (50%)	2.9 (1.1–7.6)	2.9 (1.1–7.8)
Arg-Gln+Gln-Gln/either null ($n=68$)	33 (49%)	35 (51%)	3.1 (1.2–7.7)	3.2 (1.2–8.3)
Arg-Gln+Gln-Gln/both null ($n=7$)	2 (29%)	5 (71%)	7.2 (1.3–39.5)	8.4 (1.3–54.0)

*Adjusted for age, smoking, drinking and cumulative VC exposure; for trend, $p=0.0037$.

metabolism via ALDH2, and, in studies of VC-exposed workers in Taiwan, the ALDH2-2 polymorphism has been found to play an important role in modifying VC-induced mutagenic damage (Wong et al. 1998, 2002). In this French worker population, no individuals with the ALDH2-2 allele have been identified so that all of these workers can be assumed to have intact CAA metabolism, which would serve to minimize the deleterious impact of GST polymorphisms rendering them non-significant in the absence of other genetic defects, as supported by the Taiwanese studies (Wong et al. 1998, 2002).

Interestingly, in the Taiwanese studies, the GSTT1 null genotype was associated with a decrease in the p53 biomarker, particularly due to the effect in the low VC exposure group ($<$40 ppm-years) (Wong et al. 2002), as opposed to the increase seen in this study. The Taiwanese studies had previously noted a similar effect of GSTT1 genotype on other biomarkers of VC-induced liver damage, namely, at low VC exposures the wild-type GSTT1 genotype was significantly associated with an increase in biomarkers, whereas at high VC exposures ($\geq$40 ppm-years), the wild-type GSTT1 genotype was significantly associated with a decrease in biomarkers (Huang et al. 1997). In this French cohort, the vast majority of workers (93%) would be considered to have high VC exposure by this definition, and thus an increase in biomarkers in the null genotype group would not be unexpected. In this cohort, there were too few workers with VC exposures $<$40 ppm-years to allow for separate analysis of genotype effect.

These results indicate that GST polymorphisms are not a major genetic determinant of inter-individual variability for VC-induced genetic damage. However, they suggest that GSTM1 and GSTT1 null genotypes can play a role in modifying the effects of other major genetic determinants of such inter-individual variability, such as polymorphisms in XRCC1-dependent BER, and thus need to be accounted for in such susceptibility analyses.

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