

Polymorphisms and allele frequencies of glutathione *S*-transferases A1 and P1 genes in the Polish population

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ABSTRACT. Glutathione *S*-transferases (GST) A1 and P1 are crucial enzymes involved in the biotransformation of drugs, carcinogens, and toxins, and their activity may influence drug response, susceptibility to diseases, and carcinogenesis. The genes encoding these enzymes, *GSTA1* and *GSTP1*, have been examined in many studies because of their genetic variability, which may affect enzymatic activity. The goal of this study was to determine the distribution of the alleles *GSTA1* *A/*B and *GSTP1* *A, *B, and *C in the Polish population. A total of 160 subjects from the Polish population were genotyped for 2 polymorphisms

(I105V and A114V) in the *GSTP1* gene using pyrosequencing. The promoter region of the *GSTA1* gene was screened using sequencing. The detected variants were subjected to haplotype analysis. We found that the distribution of the alleles *GSTA1**A/*B and *GSTP1**A, *B, and *C in the Polish population correspond to the results of studies in Caucasians. Furthermore, we identified additional single nucleotide polymorphisms, excluding 3 well-known changes (G-52A, C-69T, T-567G), which are linked to alleles *GSTA1**A/*B, that affect enzyme activity. A total of 4 haplotypes were identified in 160 Polish individuals.

Key words: Genetic variants; *GSTA1*; *GSTP1*; Haplotypes

INTRODUCTION

The glutathione *S*-transferases (GSTs) are a superfamily of phase II metabolic enzymes that play a principal role in the metabolism and detoxification of carcinogens, environmental toxins, products of oxidative stress, and a broad range of drugs by catalyzing the conjugation between reduced glutathione and these electrophilic compounds (Hayes and Pulford, 1995). Currently, 8 soluble cytosolic classes of GST enzymes have been identified in mammals: α , β , δ , ϵ , θ , μ , π , and ω . Each class shows specific substrate affinity and is encoded by 1 or several highly polymorphic genes located on different chromosomes (Oakley, 2005; Krajka-Kuźniak, 2007). Genetic variations in the genes coding for these xenobiotic-metabolizing enzymes can change the expression level of the protein product, thus influencing an individual's susceptibility to carcinogens and various diseases as well as affecting the toxicity and efficacy of some drugs. Therefore, they have been intensively studied (Hayes and Strange, 2000).

In this study, we examined 2 genes, *GSTA1* and *GSTP1*, representing class α and class π , respectively, of the GST enzymes, whose polymorphisms have gained substantial attention recently. Class α -GST is a dominant fraction of GST enzyme in the human liver, constituting 65-80% of the total amount, but this protein is also expressed in the kidneys, testes, adrenal glands, and small intestine. GST alpha 1 (GSTA1), the product of the *GSTA1* gene, is essential in the formation of the hepatocyte homodimer GSTA1-1 (van Ommen et al., 1990; Rowe et al., 1997; Wu and Dong, 2012). The unique properties of this enzyme make it a more specific marker for hepatocellular impairment than the routinely used aminotransferases (aspartate and alanine aminotransferases) (Knapen et al., 2000). Therefore, this indicator has been widely analyzed for the hepatotoxic effect of different drugs such as anesthetics, nicardypine, and cimetidine, *N*-acetylcysteine (Ray et al., 1989a,b; Yousif et al., 2009; Beyaz et al., 2011).

Genetic polymorphisms in the *GSTA1* gene, particularly in the promoter region, have been described: G-52A, C-69T, C-115T, A-513G, T-567G, G-631T, A-1066T, G-1142C, G-1245A, and a silent substitution in exon 5 (A375G) (Coles et al., 2001; Tetlow et al., 2001). The promoter variants are characterized by 2 alleles *GSTA1**A (-52G, -69C, -567T) and *GSTA1**B (-52A, -69T, -567G), associated with differential hepatic expression (Coles et al., 2001). The nucleotide change at position -52 is known to prevent binding of the Sp1 transcription factor, reducing *GSTA1**B promoter activity by 4-fold (Morel et al., 2002). However, the variant -115A decreases enzyme activity by 5-fold (Coles et al., 2001). These alleles are strongly associated with the variable efficiency of metabolism and detoxification of numerous compounds, as well as drug therapy and susceptibility to diseases. For example, *GSTA1**B is asso-

ciated with colorectal cancer because it causes inefficient detoxification of 2-amino-1-methyl-6-phenylimidazo[4,5-b]-pyridine (Sweeney et al., 2002). In Caucasians, the *GSTA1***B* allele has been observed at a frequency of 38-50% (Coles et al., 2001).

The *GSTP1* gene, which codes for the GSTP1-1 protein of the π -GST fraction, is widely expressed in most tissues, particularly in the lung, esophagus, and placenta (Moscow et al., 1989). The variable expression level of π -GST has been used in multiple studies as an indicator of, for example, preeclampsia, lung and breast cancer, response to chemotherapy, drug hepatotoxicity, Parkinson disease, and pre-neoplastic tumors (Eger et al., 1997; Watson et al., 1998; Canto et al., 2008; Bai et al., 2012; Zhong et al., 2013). The polymorphic nature of the *GSTP1* gene is responsible for the genetic variability of π -GST. Three polymorphic alleles of the *GSTP1* gene have been identified, including *GSTP1***A*, *GSTP1***B*, and *GSTP1***C*. Allele *GSTP1***A* is characterized by isoleucine (Ile) at codon 105 and alanine (Ala) at codon 114, allele **B* is characterized by the substitution Ile105Val, while allele **C* is defined by 2 amino acid variations: Ile105Val and Ala114Val (Board et al., 1989). Both amino acid substitutions in codons 105 (c.313A>G) and 114 (c.341C>T) are located in the active site of the GSTP1-1 protein and thus decrease the enzyme's catalytic activity by 4-fold (Harries et al., 1997). In contrast, studies have shown that the Ile105Val substitution significantly reduced protein activity in the lungs in a Caucasian population (Watson et al., 1998).

Differences in the frequency of single nucleotide polymorphisms (SNPs) in the *GSTA1* and *GSTP1* genes between populations and ethnic groups have been reported (Harries et al., 1997; Watson et al., 1998; Tetlow et al., 2001; Morel et al., 2002).

The aim of our study was to identify polymorphisms, allele frequencies, and haplotypes in the *GSTA1* and *GSTP1* genes within a Polish population. There have been no previous studies examining the *GSTA1* gene in the Polish population.

MATERIAL AND METHODS

Human DNA samples

In the present study, 160 healthy unrelated Polish individuals (89 males and 71 females) were examined. Genomic DNA of all subjects was obtained from peripheral blood according to standard procedures with guanidine isothiocyanate treatment. Blood samples were collected after obtaining written informed consent in collaboration with the Department of Anesthesiology and Intensive Therapy, Regional Hospital in Poznan, Poland. The study was approved by the Ethics Committee of the University of Medical Sciences in Poznan, Poland.

Analysis of *GSTP1* polymorphisms

The *GSTP1* gene is located on chromosome 11q13. Both polymorphisms, located at exon 5 at codon 105 and at exon 6 at codon 114, characterizing *GSTP1***A*, *GSTP1***B*, and *GSTP1***C* alleles were analyzed using pyrosequencing, a rapid genotyping method. A set of specific primers for each substitution was designed using the Pyrosequencing PSQ Assay Design Software (Qiagen GmbH, Hilden, Germany). Primer sequences are shown in Table 1. Regions of interest containing substitutions were amplified by polymerase chain reaction (PCR) performed in 30- μ L reaction mixtures consisting of 96 ng DNA, 3.0 μ L 10X PCR buffer, 2.4 μ L dNTP mix (2.5 mM of each dNTP), 1.6 mM MgCl₂, 0.75 U FirePol[®] DNA Polymerase,

and 0.2 μM specific primers. Amplification was carried out in a 2720 Thermal Cycler (Applied Biosystems, Foster City, CA, USA) with an initial denaturation for 95°C at 3 min and then 50 cycles as follows: 30 s at 95°C, 30 s at 60°C, 60 s at 72°C, and a final elongation for 7 min at 72°C. All PCR reagents were obtained from Solis BioDyne (Tartu, Estonia). The PCR products were analyzed by 2% agarose gel electrophoresis and then used as a template for pyrosequencing using the PSQ™ 96MA System (Qiagen) and Pyro-Mark™ Gold Q96 Reagents (Qiagen) as described by the manufacturer.

Table 1. Sequences of PCR primers used for *GSTP1* and *GSTAI* analysis.

Gene	Primer	Primer sequence (5'-3')	Primer location	Product size (bp)
<i>GSTP1</i>	I105V_for	AATGACGGCGTGGAGGAC	Exon 5	75
	I105V_revBiot	CCTGGTGCAGATGCTCACATAG		
	I105V_seq	CTCCGCTGCAAATAC		-
	A114V_for	CTGGGAGGGATGAGAGTAGGA	Exon 6	107
	A114V_revBiot	CAGGGTCTCAAAGGCTTCAGT		
<i>GSTAI</i>	A114V_seq	GGTGTCTGGCAGGAG		-
	A1_longF/fr1_for	ACCGTCTGGCTCGACAA	Exon 1	1671
	A1_longR/fr5_rev	AAATGCCTATGACCAGATTTAGTT	Promoter	
	A1_longF/fr1_for	ACCGTCTGGCTCGACAA	Exon 1	366
	A1_fr1_rev	TCTCCAGCTATGCTCACA	Promoter	
	A1_fr2_for	TTTTCATGAGTTGGGTGCAA	Promoter	387
	A1_fr2_rev	TGCAATTGATGAATCCAGGT	Promoter	
	A1_fr3_for	ACCTGGATTCAATGCA	Promoter	363
	A1_fr3_rev	AATCCTCCCTGCGTCTCT	Promoter	
	A1_fr4_for	AGTCCAGAAAGGCCAAGAGC	Promoter	340
	A1_fr4_rev	CAGTTTTGTAAGGGGTGAGGA	Promoter	
	A1_fr5_for	AGGGTGGGTCTGTTTGCTCT	Promoter	403
	A1_longR/fr5_rev	AAATGCCTATGACCAGATTTAGTT	Promoter	

Analysis of *GSTAI* polymorphisms

Mutation screening of the *GSTAI* gene located on chromosome 6p12.1, including the detection of *GSTAI**A/*B alleles, was conducted by analyzing the promoter nucleotide sequence (from bp -1561 in the promoter to bp 109 in the first exon) using Sanger sequencing. The strategy to determine the selected region in the *GSTAI* gene without the pseudogene and homologous sequences was achieved using a 2-step PCR with specific primers (Table 1) (Bredschneider et al., 2002). The first round of PCR amplified the 1.67-kb promoter fragment and was performed in a total volume of 25 μL with 80 ng DNA, 2.5 μL 10X PCR buffer containing MgCl₂ (DyNAzyme EXT Optimized Buffer; Thermo Scientific, Waltham, MA, USA), 2.5 μL dNTP mix (2.5 mM of each dNTP), 0.5 μM primers, and 0.3 U DyNAzyme EXT DNA Polymerase (Thermo Scientific). The program started with an initial denaturation at 94°C for 2 min and then 35 cycles as follows: 15 s at 94°C, 30 s at 60°C, 2 min at 72°C, and a final elongation for 7 min at 72°C. Next, 1 μL PCR product from the first round and 0.2 μM second-step primers were used for nested PCR, where 5 fragments covering the 1.67-kb promoter region were amplified in separated reactions. After purification of the final amplicons using the QIAquick™ PCR purification kit (Qiagen), sequencing reactions were performed. All PCRs were carried out in an Applied Biosystems 2720 Thermal Cycler (Applied Biosystems). Sequencing of all 5 fragments covering the promoter region of 160 subjects was performed bidirectionally on the MegaBACE™ 1000 DNA Analysis System (Amersham Biosciences, Buckinghamshire, UK) using DYEnamic™ ET Dye Terminator technology.

Statistical analysis

The agreement of genotype distribution of the *GSTP1* and *GSTAI* polymorphisms with Hardy-Weinberg equilibrium was evaluated using the calculator available on the following website: <http://ihg.gsf.de/cgi-bin/hw/hwa2.pl>. Based on the threshold P value ($P > 0.001$), the SNPs were classified for haplotype analysis using the Haploview v.3.11 software (Khrunin et al., 2009).

RESULTS

A total of 160 subjects from the Polish population were genotyped for polymorphisms (c.313A>G, rs1695 and c.341C>T, rs1138272) in the *GSTP1* gene using pyrosequencing and screened for genetic variants in the 1.67-kb promoter region of the *GSTAI* gene using Sanger sequencing.

In *GSTP1*, we found both single nucleotide changes, c.313A>G and c.341C>T in both heterozygous and homozygous status with variant allele frequencies of 34.7 and 10.9%, respectively (Table 2). Our haplotype analysis confirmed strong linkage disequilibrium ($D' = 1$) between these SNPs (Figure 1), and showed that alleles *GSTP1**A (c.313A, c.341C), *B (c.313G, c.341C), and *C (c.313G, c.341T) were observed with frequencies of 65.3, 23.8, and 10.9%, respectively (Table 3).

Table 2. Frequencies of *GSTP1* and *GSTAI* gene variants in 160 individuals of the Polish population.

Gene	SNP	Genotypes			Variant allele frequency (%)	HWE ^a (P value)
		Homozygous wild type	Heterozygous	Homozygous mutant		
<i>GSTP1</i>	A313G	67 (41.8%)	75 (46.8%)	18 (11.4%)	34.7	0.66
	C341T	129 (80.6%)	27 (16.9%)	4 (2.5%)	10.9	0.09
<i>GSTAI</i>	G-52A	54 (33.7%)	74 (46.3%)	32 (20%)	43.1	0.47
	C-69T	54 (33.7%)	74 (46.3%)	32 (20%)	43.1	0.47
	A-513G	148 (92.5%)	8 (5%)	4 (2.5%)	5.0	<0.001
	T-567G	54 (33.7%)	74 (46.3%)	32 (20%)	43.1	0.47
	G-631T	94 (58.8%)	47 (29.4%)	19 (11.8%)	26.5	0.0017
	A-1066T	137 (85.6%)	19 (11.9%)	4 (2.5%)	8.4	0.0034
	G-1142C	53 (33.1%)	54 (33.8%)	53 (33.1%)	50.0	<0.001
	G-1245A	137 (85.6%)	19 (11.9%)	4 (2.5%)	8.4	0.0034

^aHWE (Hardy-Weinberg equilibrium, threshold P value is 0.001).



Figure 1. Associations between polymorphisms in the *GSTP1* gene (pairwise linkage disequilibrium analysis).

Table 3. Observed frequency of *GSTP1* alleles among 160 Polish individuals.

Alleles	313A>G	341C>T	Frequency
*A	A	C	65.3%
*B	G	C	23.8%
*C	G	T	10.9%

In the *GSTAI* gene promoter region, a total of 8 SNPs were detected, including G-52A (rs3957356), C-69T (rs3957357), A-513G (rs11964968), T-567G (rs 4715332), G-631T (rs4715333), A-1066T (rs3756983), G-1142C (rs58912740), and G-1245A (rs143523660). The genotype distributions and allele frequencies are shown in Table 2. The substitutions G-52A, C-69T, and T-567G, characterizing the 2 basic alleles *GSTAI**A (-52G, -69C, -567T) and *GSTAI**B (-52A, -69T, -567G), were observed with the same variant allele frequency of 43.1%. All SNPs, excluding 2 at positions -513 and -1142 bp that were not in Hardy-Weinberg equilibrium, were examined in haplotype analysis. The results indicated that 4 polymorphic sites, -52, -69, -567, and -631 bp, were in strong linkage disequilibrium, creating haploblock 1, as well as 2 changes, A-1066T and G-1245A, creating haploblock 2 (Figure 2). The haploblocks were inferred based on the threshold value of the pairwise linkage disequilibrium between SNPs of $D' > 0.7$. Finally, 4 *GSTAI* alleles defined as different SNP combinations were observed in our population (Table 4).

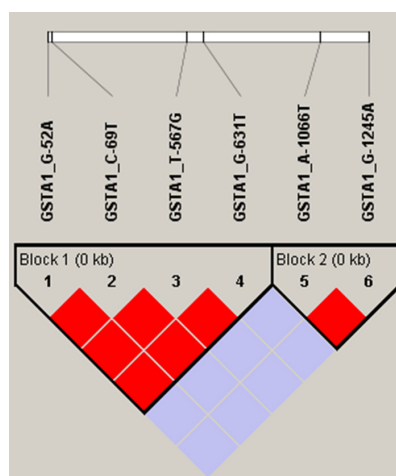


Figure 2. Associations between polymorphisms in the *GSTAI* gene (pairwise linkage disequilibrium analysis).

Table 4. *GSTAI* alleles defined as combinations of SNPs observed among 160 Polish individuals.

Alleles	-52	-69	-567	-631	-1066	-1245
*A1	G	C	T	T	A	G
*A2	G	C	T	G	A	G
*A3	G	C	T	G	T	A
*B1	A	T	G	G	A	G

The names *A1, A2, A3, B1 of *GSTAI* alleles were defined as combinations of SNPs found in this study: G-52A, C-69T, T-567G, G-631T, A-1066T, G-1245A.

DISCUSSION

GST enzymes A1 and P1 and their genetic variability have been examined in numerous studies because of their crucial role in toxin and drug metabolism, drug treatment response, susceptibility of a wide range of diseases, and hepatotoxicity detection. The alleles *GSTP1**A, *B, *C and *GSTA1**A, *B are known to be responsible for variable enzyme activity for specific substrates, which may have a clinical impact, and are observed at various frequencies among different populations and ethnic groups (Allan et al., 2001; Morel et al., 2002). We identified and evaluated the distribution of the polymorphisms characterizing these alleles in a Polish population.

Our results showed that the polymorphisms c.313A>G (p.Ile105Val) and c.341C>T (p.Ala114Val) in the *GSTP1* gene are present in the Polish population at allele frequencies of 34.7 and 10.9%, respectively, confirming the results obtained for Caucasians in the NCBI database: 33-50% for Val105 and 6-12% for Val114. Moreover, we found through haplotype analysis that both nucleotide substitutions are always linked, creating the alleles *GSTP1**A (c.313A, c.341C), *B (c.313G, c.341C), and *C (c.313G, c.341T) according to a study conducted by Ali-Osman et al. (1997), and were found in the Polish population with frequencies of 65.3, 23.8, and 10.9%. The genotype distribution as well as the frequency of the Ile105Val polymorphism observed in this study did not largely differ from those reported in another Central European population, the Czechs; the variant allele in this group has a reported frequency of 34.4%, and the heterozygote genotype was found to be associated with a decreased risk of colorectal cancer (Hezova et al., 2012). In contrast to our results, the frequency of this allele was higher in a Serbian population, reaching 37.6% (Suvakov et al., 2013). The genotype Ile105Ile frequency observed in our study (41.8%) was similar to that determined by Vichi et al. (2012) in a healthy Italian population (42%), where this genotype was found to be associated with a higher risk of endometriosis (frequency in cases, 48.6%). Polymorphism I105V was also studied by Burim et al. (2004) in the Brazilian population in association with cirrhosis or pancreatitis in alcoholics. A possible association was observed between the Val105Val genotype and increased susceptibility to these diseases in alcoholics (7.3% in healthy Brazilian vs 28.6% in pancreatitis cases) (Burim et al., 2004). Kaymak et al. (2008) found that heterozygous (*GSTP1* I105V) individuals in a Turkish population undergoing sevoflurane anesthesia showed an increased level of serum α -GST enzyme within 24 h after anesthesia. International studies have indicated that the Val105 allele is more common in African-Americans (42%), but less common among Chinese (22%), Taiwanese (18%), and Japanese (14%) populations compared to European-Americans (33%), while allele Val114 is less often observed in African-Americans (5%) than in European-Americans (9%) (Watson et al., 1998; Zhong et al., 2006).

The second aim of the present study was to determine the distribution of alleles *GSTA1**A/*B in the Polish population based on 3 crucial polymorphisms at positions -52, -69, and -567 and to search for other SNPs in the promoter region, which may be linked to these alleles and contribute to the inter-individual variability of *GSTA1* expression. In the 1.67-kb promoter region (with exon 1 fragment) of the human *GSTA1* gene, we identified 8 SNPs, including G-52A, C-69T, A-513G, T-567G, G-631T, A-1066T, G-1142C, and G-1245A, confirming the results of Bredschneider et al. (2002) in Caucasians, except for the SNP that was only observed in our study at site -1245. The frequency of the *GSTA1**B allele containing 3 linked basic variants affecting gene expression (-52A, -69T, -567G) observed in our study among 160 individuals (43.1%) was slightly lower than that observed by Bredschneider et al.

(2002) among 48 subjects (47.9%), but showed some similarities, including genotype distribution, to the data of global studies in the Caucasian population (38-50%) (Coles et al., 2001; Spalletta et al., 2012; Suvakov et al., 2013). However, in African-American, Japanese, and Chinese subjects, the allele frequency was much lower, at 26, 16, and 12.9%, respectively (Coles et al., 2001; Matsuno et al., 2004; Ping et al., 2006). The lower transcriptional activity of the *GSTA1***B* allele compared to *GSTA1***A* is mainly responsible for a base substitution at position -52, altering the binding process of transcription factor Sp1 (Morel et al., 2002). Another observation from our study, confirming the results of previous research, was that the polymorphism at position -631 was linked to the alleles *GSTA1***A* (-631T/G) and **B* (-631G) and associated with lower hepatic expression (Coles et al., 2001; Bredschneider et al., 2002). Moreover, based on our haplotype analysis, we observed a remarkable association between SNPs A-1066T and G-1245A, and both were observed at a frequency of 8.4% (Figure 2). The 4 alleles containing various combinations of SNPs were in Hardy-Weinberg equilibrium and identified in all 160 subjects of the Polish population (Table 4). However, the single nucleotide substitutions A-513G and G-1142C were not included in the haplotype analysis, but were observed at frequencies of 5 and 50%, respectively, corresponding to the data in the literature. In contrast to our results, a study by Guy et al. (2004) indicated the presence of other changes and combinations in the *GSTA1* promoter region, and showed different haplotypes such as *GSTA1***A*, **C*, **D*, and **E* based on the SNPs G-52A, C-69T, G-115A, and A-513G.

This is the first study examining the *GSTA1***A*/**B* allele distributions in the Polish population. We not only identified the 3 well-known linked SNPs at positions -52, -69, and -567, but also identified other polymorphisms associated with these alleles, revealing haplotypes of the *GSTA1* gene. Determining the prevalence of the *GSTA1***A*/**B* alleles in various populations and ethnic groups is a valuable step for clinical and medical applications because the activity of the GSTA1 enzyme is involved in a wide range of important processes in the human body. Furthermore, our results regarding the *GSTP1* gene agree with those of previous studies performed on Caucasians and allowed for the determination of the *GSTP1***A*, **B*, and **C* allele frequencies in Polish individuals.

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