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CYP1A1, GST gene polymorphisms and risk of chronic myeloid leukaemia

Mehmet Taspinar[a], Sena Erdogan Aydos[a], Omer Comez[a], Atilla Halil Elhan[b], Halil Gurhan Karabulut[c], Asuman Sunguroglu[a]

[a] Ankara University Faculty of Medicine, Department of Medical Biology, Ankara, Turkey
[b] Ankara University Faculty of Medicine, Department of Biostatistics, Ankara, Turkey
[c] Ankara University Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey

Summary

Principles: Associations between polymorphisms for genes encoding enzymes involved in biotransformation of xenobiotics and susceptibility to several cancers have been shown in several studies**.** The aim of the present study is to investigate the influence of cytochromes P450 (CYP450) 1A1*2C and Glutathione S-transferases (GSTs) (T1 and M1) gene polymorphisms in susceptibility to chronic myeloid leukaemia (CML).

Methods: The frequency of CYP1A1 Ile/Val alleles and of GSTT1 and GSTM1 homozygous deletions was examined in 107 patients with CML and 132 healthy controls by PCR and/or PCR-RFLP methods using blood samples.

Results: The frequency of CYP1A1 Val allele was found to be 19.2% in CML patients and 4.4% for controls, indicating that persons carrying this allele had an increased risk of CML (OR = 5.10, 95% CI: 2.60–9.97). The frequency of individuals carrying the GSTT1 null genotype was higher among CML patients (40.2%) compared to controls (19.2%) (OR = 2.82, 95% CI: 1.58–5.05; p <0.001). Therefore, GSTT1 present genotype may be a protective factor for CML. Although GSTM1 null genotype frequency was slightly higher in the patient group (44.9%) than in the controls (42.3%), this difference was not statistically significant (OR = 1.11, 95% CI: 0.66–1.86; p = 0.693). Individuals with GSTM1 null genotypes without the T allele have a 5.981 higher risk for CML than those who have the T allele.

Conclusions: This data suggests that polymorphic CYP1A1 and GSTT1 genes appear to affect susceptibility to CML.

Key words: CYP1A1; GSTT1; GSTM1; polymorphisms; CML

Introduction

Xenobiotics are chemical substances that are foreign to the biological system. They include naturally occurring compounds, drugs, environmental agents and carcinogens. Adverse effects of xenobiotics are exerted via covalent interactions between intermediate metabolites and genetic materials or proteins and their related metabolites. In order to avoid accumulation of lipophilic xenobiotics in cells and tissues, enzymatic reactions of xenobiotic metabolism that can be divided into two distinct phases are needed [1, 2]. The key enzyme systems catalyzing phase I oxidative metabolism are enzymes of the cytochrome P450 (CYP) superfamily. During these reactions, toxic metabolites are generated which might be processed by phase II enzymes [3].

The family of genes for Phase I cytochrome P450 (CYP450) is involved in the detoxification of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents and reactive oxygen species. The CYP1A1 gene is a polymorphic gene and encodes for the CYP1A1 enzyme that catalyzes the bioactivation of polycyclic aromatic hydrocarbons [3, 4]. CYP1A1 gene polymorphisms have been extensively studied, especially in relation to cancer susceptibility [4–9]. One of the most well known CYP1A1 gene polymorphism (CYP1A1*2C polymorphism) is 2455A→G mutation at the exon 7 region leading to Ile/Val replacement in the catalytic region of the CYP1A1 protein [10, 11]. The frequency of this polymorphic allele exhibits significant interethnic differences [12–14]. An increased enzyme activity in Ile/Val and Val/Val variants of

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CYP1A1 is associated with a higher level of adduct formation and increased risk of certain types of cancers, including leukaemia [15].

Phase II enzymes catalyze the conjugation of glutathione or glucuronide with reactive electrophiles and thus detoxify procarcinogens and carcinogens [16]. Glutathione S-transferases (GSTs) belong to the group of phase II enzymes. These are widely expressed in mammalian tissues and have a broad substrate specificity. GSTs are polymorphic genes and involved in the metabolism of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents and reactive species. The frequencies of GSTs polymorphic alleles especially GSTT1 and GSTM1 have been reported in various cancers [11, 17–22, 24–26].

Numerous genetic polymorphisms have been reported for CYP and GST genes, indicating a lack of functional protein [27] or causing either increased or reduced metabolic activity [28]. These polymorphisms may alter the ability of enzymes to metabolize the chemical carcinogens and mutagens. It has been suggested that these differences in the ability to metabolize carcinogens and mutagens may influence the susceptibility of individuals to cancer [5]. Thus, there may be an association between polymorphisms in genes encoding for xenobiotic-metabolizing enzymes and susceptibility to cancer.

Chronic myelogenous leukaemia (CML), also known as chronic myeloid [29] or chronic myelocytic leukaemia, [30] is a malignant cancer of the myeloid line of cells in the bone marrow that results in uncontrolled growth of white blood cells in bone marrow, blood and body tissues. CML affects males more than females and usually occurs in middle-aged adults [31]. It is known that the environmental exposures to cytotoxic and genotoxic agents, particularly those derived from benzene and ionizing radiation, may be associated with increased risk of CML [32].

In order to find some reproducible associations with either genetic or environmental factors other than benzene and radiation, we aimed to analyze the association of CYP1A1*2C and GST gene polymorphisms in CML patients among the Turkish population.

Materials and methods

Cases and controls

Our analysis included 107 patients diagnosed with CML (43 females (40.2%), 64 males (59.8%), with a mean age of 40.6 ± 13.3) and 135 healthy controls (45 females (33.3%), 90 males (66.7%), with a mean age of 34.3 ± 9.7). The Institutional Ethical Committee of Ankara University, Faculty of Medicine approved the study (The acceptation number: 61–1522) and written informed consents of all the patients who participated were obtained. The control group consisted of healthy unrelated volunteers without a medical history of cancer or other chronic diseases. All patients and controls were of Turkish ethnicity.

DNA isolation

Venous blood samples (10ml) were collected in heparin containing vacutainers. Genomic DNA used for polymorphic analysis was extracted from lymphocytes of donors by a standard method [33]. Isolated DNA was stored at –20 °C till use.

Genotyping

CYP1A1 polymorphism

The genetic polymorphism analysis for CYP1A1*2C was determined by using the polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) method described by Krajinovic et al. [34]. The primer pairs used were F-5' CTG TCT CCC TCT GGT TAC AGG AAG C-3' R-5' TTC CAC CCG TTG CAG CAG GAT AGC C-3' for Ile/Val. The PCR conditions for Ile/Val polymorphism: initial denaturation at 94 °C for 5 minutes was followed by 35 cycles of 30 seconds at 94 °C, 1 minute at 60 °C, 1 minute at 72 °C and a final extension of 10 minutes at 72 °C. The amplified products for Ile/Val polymorphism were subjected to restriction enzyme analysis with BsrDI (Fermentas). Three banding patterns were observed by RFLP analysis: 149 and 55 bp bands that corresponded to the *AA* (Ile/Ile, homozygous wild type genotype), 204, 149 and 55 bp bands that corresponded to the *AG* (Ile/Val, heterozygous genotype) and 204 bp band that corresponded to the *GG* (Val/Val, homozygous mutant genotype).

GSTT1 and GSTM1 polymorphism

The polymorphic deletion of the GSTT1 and GSTM1 genes were genotyped using the multiplex PCR approach. The primers used for GSTT1 and GSTM1 amplification were F5'-TTC CTT ACT GGT CCT CAC ATC TC-3', R5'-TCA CCG GAT CAT GGC CAG CA-3' and F5'-GAA CTC CCT GAA AAG CTA AAG C-3'; R5'-GTT GGG CTC AAA TAT ACG GTG G-3', respectively [19]. The β-globin gene primer pairs were F5'-CAA CTT CAT CCA CGT TCA CC-3', R5'-GAA GAG CCA AGG ACA GGT AC-3' [34]. In the thermocycling procedure, initial denaturation at 94 °C for 4 minutes was followed by 35 cycles of 1 minute at 94 °C, 45 seconds at 55 °C, 1 minute at 72 °C and final extension was 10 minutes at 72 °C. Genotyping of the genes (null genotypes) is revealed by the absence of the 480 bp for GSTT1 and 219 bp for GSTM1 PCR products respectively, using the β-globin amplification (268 bp) as an internal positive control. PCR and RFLP products for the genotyping of polymorphisms were visualized by 2% agarose gel electrophoresis with ethidium bromide. The absence of β-globin amplification indicated a failure of PCR reaction.

Statistical analysis

Differences between the two groups for categorical variables were analyzed by Chi Square test, and odds ratios were calculated. Age was evaluated by Student's test.

The association between CML and CYP1A1, GSTT1, and GSTM1 polymorphisms was evaluated by multiple logistic regression analysis controlling for sex. Adjusted odds ratios and their confidence intervals were calculated. P-values less than 0.05 were considered significant. SPSS for Windows 15.0 was used for statistical analysis.

Results

This case/control study included 107 patients with CML and 135 normal controls. The distribution of the CYP1A1 Ile/Val polymorphism, GSTT1 and GSTM1 genotypes in CML patients and controls are shown in table 1.

The frequency for CYP1A1 Ile/Ile genotype was higher among controls (91.1%) when compared to CML patients (62.6%). On the other hand, the frequency for CYP1A1 Ile/Val genotype in CML patients (36.4%) was higher than that in controls (8.9%) (p <0.001). The CYP1A1 Val/Val genotype was only detected in one patient. The carriers of CYP1A1 Ile/Val (AG) genotype had an increased risk of developing CML (OR = 5.97, 95% CI: 2.93–12.16) (table 1).

The frequency of CYP1A1 Val allele was 19.2% in CML patients, and 4.4% for controls, indicating that persons carrying this allele had an increased risk of CML (OR = 5.10, 95% CI: 2.60–9.97) (table 1).

The frequency of individuals carrying the GSTT1 null genotype was higher among CML patients (40.2%) compared to controls (19.2%) (OR = 2.82, 95% CI: 1.58–5.05; p <0.001). Therefore, GSTT1 present genotype may be a protective factor for CML (table 1).

Although GSTM1 null genotype frequency was slightly higher in the patient group (44.9%) than that of the controls (42.3%), this difference was not statistically significant (OR = 1.11, 95% CI: 0.66–1.86; p = 0.693) (table 1).

A multiple logistic regression was performed to identify the independent variables that continued to show significant association in terms of CML in the presence of the others. The CYP1A1 Val/Val genotype was detected only in one CML patient, so Ile/Val and Val/Val genotypes were combined for the multiple logistic regression. The adjusted odds ratio for a person carrying the CYP1A1 Ile/Val and Val/Val genotypes was 6.0 (95% CI: 2.86–12.55) with compared to a person carrying the CYP1A1 Ile/Ile genotype. There was a significant interaction between GSTT1 and GSTM1 genotypes. This means that the association between the GSTT1 (or GSTM1) genotype and CML depends in some way on the level of the GSTM1 (or GSTT1) genotype. The GSTT1 null genotype was a significant risk factor among persons whose GSTM1 genotype was null with an adjusted odds ratio of 5.81 (95% CI: 2.16–15.59), whereas it was not a significant risk factor among persons whose GSTM1 genotype was present (table 2). The GSTM1 null genotype was not a significant risk factor irrespective of the GSTT1 genotype (table 2).

The positions of GSTT1 and M1 genotypes towards each other were investigated by logistic regression analyses as shown in table 2. This investigation showed that the GSTM1 null genotypes individuals who do not have T allele 5.81 times more risk to be CML than the ones with T allele.

Table 1

The distribution of the CYP1A1 Ile/Val, GSTT1 and GSTM1 genotypes in CML patients and controls.

Locus	Genotype/Allele	Patients No. (%)	Controls No. (%)	OR	95% CI
CYP1A1	Ile/Ile	67 (62,6)	123 (91,1)	1	
	Ile/Val	39 (36,4)	12 (8,9)	5.97	2.93–12.16
	Val/Val	1 (0,9)	0 (0,0)	–	–
	Ile/Val + Val/Val	40 (37,4)	12 (8,9)	6.12	3.01–12.45
	Ile	173 (80,8)	258 (95,6)	1	
	Val	41 (19,2)	12 (4,4)	5.10	2.60–9.97
GSTT1	Present	64 (59,8)	105 (80,8)	1	
	Null	43 (40,2)	25 (19,2)	2.82	1.58–5.05
GSTM1	Present	59 (55,1)	75 (57,7)	1	
	Null	48 (44,9)	55 (42,3)	1.11	0.66–1.86

Table 2

Combined effects of GSTM1 and GSTT1 genotypes in CML risk.

Genotypes		Patients No. (%)	Controls No. (%)	OR*	95%CI
GSTM1	GSTT1				
Present	Present	40 (67,8)	57 (77,0)	1	
	Null	19 (32,2)	17 (23,0)	1.48	0.65–3.38
Null	Present	24 (50,0)	47 (85,5)	1	
	Null	24 (50,0)	8 (14,5)	5.81	2.16–15.59
GSTT1	GSTM1				
Present	Present	40 (62,5)	57 (54,8)	1	
	Null	24 (37,5)	47 (45,2)	0.69	0.35–1.36
Null	Present	19 (44,2)	17 (68,0)	1	
	Null	24 (55,8)	8 (32,0)	2.70	0.91–8.05

* Adjusted for sex

Discussion

In this study we report the role and importance of CYP1A1 Ile/Val and GST enzymes (T1 and M1) polymorphic variants for the risk of CML. In the previous studies, significant relations were found between CYP1A1 and GST polymorphisms in solid tumours and also in acute leukaemia [5, 17, 23–25, 34–36]. However, in most of the epidemiological reports CYP1A1 and GST genotypes were particularly involved in acute leukaemia and acute myeloid leukaemia [17, 19–20, 37].

Little is known about the role of genetic susceptibility and environmental factors on the development on CML. To our knowledge, there has been only one study, published as a letter to editor on the investigation of the CYP1A1 polymorphisms in CML. As it was mentioned in this letter, the aetiological role of chemical carcinogens in leukaemia is less obvious for many haematological malignancies in contrast to solid tumours [32]. The expression of the CYP1 family increases in lymphoblastic and myeloblastic cell lines [38] and plays a role in the detoxification of environmental factors. Therefore, CYP1A1 enzymes might be responsible for carcinogenesis in haematopoietic cells. Indeed, there is supporting evidence that increased frequency of CYP1A1 Val/Val genotype among ALL patients is a risk factor for developing ALL [36].

As seen in all such tumours, environmental and genetic factors might also be important in CML development. Since the relation between environmental and genetic factors and CML has not been shown clearly, the present study was planned to directly correlate these factors. There is a metabolic balance between CYP1A1 (Phase I) and GST (Phase II) enzymes. Procarcinogens that enter the cell are transformed into active carcinogens by the CYP1A1 enzyme. Formed active carcinogens are detoxified by GST enzymes involved in the detoxification processes by conjugating with glutathione, glucuronide or sulphate [39]. The difference in activity of these two enzymes causes accumulation of DNA adducts in cells. Increasing DNA adducts cause different kinds of mutations in tumour suppressor genes and oncogenes and thus cancer cell development may be triggered. Therefore, people with an altered ability to activate procarcinogens and detoxify carcinogens may have an increased risk of developing cancer [16].

In the presence of CYP1A1 Val allele, the enzyme activity and/or inducibility increases [40,41]. When a person who carries CYP1A1 Val allele is exposed to carcinogens, the carcinogenic effect of the carcinogens might be more powerful due to increasing enzyme activity. Therefore, in the presence of CYP1A1 Val allele and null genes of GSTT1 and GSTM1, DNA adducts that accumulate in the cell cause different kinds of mutations. This scenario might prove to be the cause of cancer formation in human cells [41].

In the study by Löffler et al. [32], no relation was found between the CYP1A1*2C, GSTT1 and GSTM1 null genes and CML in BCR-ABL + CML patients in the German population. In our study, we found that carrying CYP1A1 Val allele and also GSTT1 and GSTM1 null genes carried a 5.1 greater risk for CML [BCR-ABL(+) or (–)] ($p < 0.001$; 95% CI: 2.60–9.97). This result is in accordance with other studies, in which other cancers other than CML were studied. Due to the increasing activity of the enzymes in the presence of Val allele, this result is expected in cancer cases. In our study, people who carried the CYP1A1 Ile/Val genotype carried a greater risk for CML than the controls (95% CI for OR: 3.00–12.45).

Regarding the GST genes, we found that, T1 null genotype people were more at risk to be afflicted with CML. Therefore, it might be thought that the GSTT1 positive genotype is a protective factor against CML. Metabolization of oxygen products and carcinogens are reduced in GSTT1 null genotypes. Thus, GSTT1 null genotype may be a risk factor for cancer development. Similarly, in two studies, GSTT1 null genotype was associated with a significant increase in the risk of CML [42–43]. However, other studies on CML patients reported similar findings regarding GST genes in different populations [44–46]. In other studies, GSTT1 null genotypes were shown to be risk factors for both AML and ALL [47–48].

Although GSTM1 null genotype frequency was higher in the patients than the controls in this study, the difference was not statistically meaningful. In two different studies from India, similar results were reported, where GSTM1 null genotype frequency was higher than the controls but did not reach statistical significance in CML patients [42–43]. The differences between our results and those of Löffler et al. [32] might be attributed to polymorphism of the genes and ethnic differences. Löffler also suggested that genetic susceptibility and environmental effects might be additive in CML. Therefore, the results of our study showing the effects of CYP1A1 Ile/Val and GST genes polymorphisms provide further information on the development of different kinds of cancer.

It has been shown that the risk of ALL is doubled in patients who carry the GSTM1 deletion [17]. GSTM1 null genotype has also been suggested as a risk factor for different kinds of cancers [24–25, 49]. Carrying GSTM1 null genotype causes accumulation of DNA adducts and these increased levels of DNA adducts may result in mutations.

In our study, the frequencies of CYP1A1, GSTT1 and M1 variant in the control group are in accordance with those of the other studies

conducted among the Turkish population [12, 35, 49–51]. No relation was found between being a carrier of polymorphic alleles and gender in this study.

Using logistic regression analysis (95% CI for OR: 2.16–15.59), we have shown that GSTM1 null carriers, who are also null for GSTT1, are 5.81 times more at risk for CML than those who are GSTT1 positive. A combined analysis of variant genotypes was conducted to assess the roles of polymorphic variants on cancer risk.

This is a pilot study showing phase I and phase II enzymes to be important for CML as has been found for other cancers and also for AML and ALL. To our knowledge, this is the first study highlighting the combined effects of GSTT1 and GSTM1 polymorphisms and the risk for CML. Although a significant interaction between GSTT1 and GSTM1 polymorphisms was found in our study, this should be considered as preliminary result and must be confirmed in a larger series.

All our data may also support the theory that susceptibility to certain cancers may depend on ethnic-specific gene polymorphisms. Variable frequencies of xenobiotic metabolizing polymorphic alleles in different populations may reflect susceptibility to certain cancers. Further studies with different gene combinations in different populations are required in order to investigate the associations between gene-gene and gene-environment interactions.

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Correspondence:
Mehmet Taspinar
Research Assistant
Ankara University, Faculty of Medicine
Dept. of Medical Biology
06100 Ankara, Turkey
E-Mail: mtaspinartr@yahoo.com

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