

Combined GSTT1 Null, GSTM1 Null and XPD Lys/Lys Genetic Polymorphisms and Their Association with Increased Risk of Chronic Myeloid Leukemia

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Purpose: Glutathione *S*-transferases (GSTT1 and GSTM1) are instrumental in detoxification process of activated carcinogens. Nucleotide excision repair is carried out by DNA helicase encoded by xeroderma pigmentosum group D (XPD) genes and aberrations in the *XPD* gene predisposes to increased risk of cancer. The present study aimed to investigate GSTT1, GSTM1 and XPD polymorphisms in newly diagnosed chronic myeloid leukemia (CML) patients and to examine the association of these polymorphisms with the risk of developing CML.

Patients and Methods: This case-control study was carried out from June 2019 to August 2021 involving 150 newly diagnosed patients with CML and an equal number of randomly selected age- and sex-matched healthy individuals. A multiplex-PCR assay was used to genotype GSTT1 null and GSTM1 null polymorphisms. XPD gene polymorphism was detected by PCR-RFLP using predesigned gene-specific primers.

Results: GSTT1 and GSTM1 null polymorphisms were detected in 42.7% and 61.3% of cases, respectively, compared to 18% and 35.3% for controls. The combination of both GST null polymorphisms revealed a significant association with CML. Frequencies of XPD Lys751Gln genotypes in cases were 62.7% heterozygous Lys/Gln, 24% homozygous Lys/Lys and 13.3% homozygous Gln/Gln, while in the controls were 74.7%, 20%, and 5.3%, respectively. Significant differences were also noted regarding the combination of GSTT1/GSTM1 null with XPD Lys/Lys, and GSTM1 null with XPD Lys/Lys.

Conclusion: In conclusion, GSTT1 null, GSTM1 null and XPD polymorphisms showed positive association with the risk of development of CML. Furthermore, age and gender did not exhibit any association with the studied polymorphisms, while CML phases were associated with GSTT1 null polymorphism.

Keywords: GSTT1 null polymorphism, GSTM1, XPD, chronic myeloid leukemia

Introduction

Chronic myeloid leukemia (CML) is a clonal neoplastic hematological stem cell disorder typically results from specific reciprocal chromosomal translocation $t(9;22)(q34;q11)$, which produces BCR-ABL aberrant oncogene.¹ Expression of BCR-ABL aberrant gene plays a critical role in transformation of hematopoietic stem cells, which results in relentless neoplastic proliferation of myeloid cells.² Various genetic disorders are known to be associated with cancer predisposition. Additionally, neoplastic cells are predisposed to acquire a number of genetic

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abnormalities over time, resulting in disease progression.³ It has been suggested that cancer susceptibility and carcinogen metabolism are associated with polymorphisms in detoxification enzymes, which are essential for the elimination of these toxic substances and protect the cells from developing cancers by hydrolysis, reduction, and/or oxidation of activated carcinogens.^{4–6}

Glutathione *S*-transferases (GSTs) are oxidative stress detoxification metabolic enzymes that carry out a wide range of functions in cell proliferation, apoptosis, neoplastic transformation, and tumor metastasis.⁷ In order to attain the xenobiotic detoxification function, GSTs catalyze the conjugation of xenobiotic substrates to the reduced glutathione (GSH).^{8,9} In the human genome, the GST encoding genes have been categorized into eight classes, including GSTT1 which encodes GST theta 1 and GSTM1 that encodes GST mu 1.¹⁰ Polymorphism GST encoding genes have been associated with reduced GST activity, which is implicated in developing different cancers, including hematologic malignancies and varied anti-neoplastic drug resistance.¹¹

Defect in the DNA repair system is considered a crucial event in leukemogenesis, which causes chromosomal aberrations and genomic instability.^{12,13} The xeroderma pigmentosum group D (XPD) gene also known as ERCC2 which encodes a DNA helicase, functionally involved in the nucleotide excision repair (NER) pathway, is instrumental for nucleotide excision repair. Mutations in the XPD gene lessen the activity of DNA helicase, consequently causing defects in the NER pathway.¹⁴ XPD Lys751Gln (XPD 2251A>C, rs13181) polymorphisms in homozygous form downregulate the DNA repair capacity for UV DNA damage and benzo(*a*) pyrene adducts.^{15,16} Polymorphism's status of DNA repair genes is varied in ethnic and geographic distanced populations.¹⁷ Several studies have explored the effects of XPD Lys751Gln polymorphism in different hematological malignancies, including CML.^{18–21} However, these results are inconsistent in different populations. It is interesting to note that while some studies suggest strong association of leukemia with XPD gene polymorphism, others found relatively weak correlation; yet some negate this association.²² The present study aimed to investigate GSTT1, GSTM1 and XPD polymorphisms in newly diagnosed CML patients and to examine the association of these polymorphisms with the risk of developing CML.

Materials and Methods

This case–control study involving 150 patients with CML and an equal number of randomly selected healthy

individuals was carried out from June 2019 to August 2021. Newly diagnosed patients with CML were recruited from the Radiation and Isotope Centre Khartoum (RICK), Khartoum, Sudan. Patients were diagnosed by at least two hematopathologists according to WHO guidelines. All patients were positive for Ph chromosome. Patients with a history of other malignancies were excluded from the study. Age- and gender-matched healthy controls were recruited during their regular examination. All subjects were Sudanese and older than 18 years. Ethic committee of Alneelain University, Khartoum, Sudan, gave the ethical approval of this study. Guidelines of the Declaration of Helsinki were followed in this study. Written informed consents were signed by all study participants.

Venous blood samples were collected in EDTA-anticoagulated vacutainers from all participants. QIAamp[®] DNA Mini kit (Qiagen GmbH, Hilden, Germany) was used for the extraction of genomic DNA from the peripheral blood samples of patients and controls according to the manufacturer's instructions. Aliquots of the extracted DNA samples were stored at –20°C until molecular analysis. A multiplex-PCR assay was used to genotype GSTT1 and GSTM1 null polymorphisms. Briefly, for each 25 µL of reaction volume of genomic DNA (100–150 ng) a 10× PCR buffer of 1.5 µM MgCl₂, 0.5 units of Taq polymerase, and 200 µM dNTPs were mixed. The primers and PCR conditions were the same as described by Agrawal et al.²³ The β-Globin primers were used as a positive control (5'-CAA CTT CAT CCA CGT TCA CC-3' and 5'-GAA GAG CCA AGG ACA GGT AC-3'). The amplified products were analyzed by banding patterns on agarose gels electrophoresis. PCR product at 268 bp indicated a successful amplification. Genotyping of the GSTT1 and GSTM1 is revealed by the presence or absence of a band at 480 and 215 bp, respectively. XPD gene polymorphism was detected by PCR-RFLP using predesigned gene-specific primers. The primers and PCR conditions for XPD polymorphism were the same as described by Mervat et al.²⁴ The amplified PCR products of XPD were subjected to restriction digestion with respective enzyme (PstI). The digested products were run on 3% agarose gel electrophoresis and stained using ethidium bromide. The identification of genotypes was based on the banding patterns. PCR product of XPD polymorphism contained an internal PstI site, resulting in products of 290 and 146 bp in the 751 Lys/Lys (AA) allele. While the PstI site in the Gln allele, results in 272/146/63 bp for Gln/Gln (CC), and 290/227/146/63 bp products for Lys/Gln (AC) genotypes.

Table 1 Demographic Characteristics of the Studied Subjects

Category	Cases (n=150)	Controls (n=150)	P-value
Gender			
Male	99(66%)	103(68.7%)	0.587
Female	51(34%)	47(31.3%)	
Age			
Mean \pm SD (years)	48.29 \pm 14.1	47.09 \pm 8.8	0.317
Range (years)	19–75	19–65	
<40 years, n(%)	38(25.3)	32(21.3)	0.363
>40 years, n(%)	112 (74.7)	118(79.7)	
Phase			
Chronic, n(%)	129 (86)	-	-
Accelerated, n(%)	12 (8)	-	-
Blast, n(%)	9 (6)	-	-

Statistical Analysis

Standard statistical tests were carried out using the Statistical Package for Social Sciences (SPSS) version 25 (SPSS for Windows, Chicago, IL, USA) to compute descriptive parameters including mean and frequencies. Inferential statistics including Student's *t*-test was used to evaluate the significance of the difference between the mean values of two continuous variables. Chi-square test (χ^2) test and Fisher-Freeman-Halton test were used to verify statistical significance in proportions categorical variables. Odds ratios (OR) with 95% confidence intervals (CI) calculated by logistic regression analyses were conducted to determine the relationship between the studied genotypes and the risk for CML. The level of confidence ($P < 0.05$) was considered as cutoff value for statistical significance.

Results

In this study, GSTT1 null, GSTM1 null and XPD Lys 751Gln polymorphisms were investigated in patients with

CML and healthy controls. Demographic features including age, gender, and phase of CML are presented in Table 1. Similar distribution of age and gender existed between cases and controls as depicted in Table 1. The male group constituted 66% (n=99), and 68.7% (n=103) of cases and controls, respectively. Among cases, 86% were diagnosed in the chronic phase, 8% accelerated phase, while 6% in the blast crisis phase.

In this study, GSTT1 null and GSTM1 null showed positive association with CML (Table 2). Genotype frequency of GSTT1 null polymorphism in cases was 42.7%, and for controls, it was 18%. Statistically significant difference was observed in the variant genotype frequencies between the cases and controls (OR=3.39, $P < 0.001$). Frequencies of GSTM1 null polymorphism in cases were 61.3% and, 35.3% for the controls. Statistically significant difference was observed in the variant genotype frequencies between the cases and controls (OR=2.9, $P < 0.001$).

The observed genotype frequencies of XPD Lys751Gln polymorphism in cases were 62.7% heterozygous Lys/Gln, 24% homozygous Lys/Lys and 13.3% homozygous Gln/Gln. As for the controls, genotype frequencies were 74.7%, 20%, and 5.3%, respectively, which revealed significant association between CML patients and controls (Lys/Lys; OR=1.43, $P = 0.027$, Gln/Gln; OR=2.98, $P = 0.013$).

We analyzed the combination of the studied polymorphism and their association with CML as shown in Table 3. The combination of both GSTs null polymorphism revealed a significant association with CML ($P < 0.001$), in which the frequency of GSTT1null/GSTM1 null/Gln/Lys was 29.3% in cases, and 6.7% in control group. Also, significant differences were noted regarding the combination of GSTT1 Null/GSTM1 null with XPD Lys/Lys ($P = 0.034$), and GSTM1 with XPD Lys/Lys ($P = 0.023$). However, the combinations of GSTT1 null/GSTM1 null with XPD Gln/Gln, GSTT1 with XPD Gln/Gln, and GSTM1 null with XPD Gln/Gln did not show

Table 2 Genotypes and Alleles Distribution in the CML Cases and Control Groups

SNP	Genotype/Allele	CML (N = 150)	Controls (N = 150)	Odds Ratio (95% CI)	P-value
GSTT1	Present	86 (57.3%)	123 (82%)	3.39 (2.0006 to 5.7450)	<0.001
	Null	64 (42.7%)	27 (18%)		
GSTM1	Present	58 (38.7%)	97 (64.7%)	2.9 (1.8160 to 4.6408)	<0.001
	Null	92 (61.3%)	53 (35.3%)		
XPD	Lys/Gln	94 (62.7%)	112 (74.7%)	1	
	Lys/Lys	36 (24%)	30 (20%)	1.43 (0.8194 to 2.4949)	0.027
	Gln/Gln	20 (13.3%)	8 (5.3%)	2.98 (1.2548 to 7.0713)	0.013

Table 3 Combination Effect of Studied Polymorphisms on the Risk of CML

GSTT1	GSTM1	XPD	Cases, n (%)	Controls, n (%)	Odds Ratio (95% CI)	P-value
Null	Null	Gln/Lys	44 (29.3)	10 (6.7)	5.8 (2.80 to 12.08)	<0.001
Null	Null	Lys/Lys	9 (6.0)	1(0.7)	9.5 (1.19 to 76.04)	0.034
Null	Null	Gln/Gln	5 (3.3)	0 (0.00)	11.4 (0.624 to 207.63)	0.1008
Null	Present	Lys/Lys	6 (4.0)	6 (4.0)	1.00 (0.32 to 3.17)	1.00
Present	Null	Lys/Lys	11(7.3)	2 (1.3)	5.9 (1.28 to 26.89)	0.023
Null	Present	Gln/Gln	5 (3.3)	1(0.7)	5.1(0.59 to 44.517)	0.1374
Present	Null	Gln/Gln	4 (2.7)	0 (0.00)	9.2 (0.493 to 173.261)	0.1369

statistically significant difference between cases and control groups ($P > 0.05$).

Distribution of XPD variants and GSTs null polymorphisms in patients stratified by age groups, gender, and CML phases is illustrated in Table 4. No statistically significant difference was found between the distribution of studied polymorphisms and age of CML patients at diagnosis. (P -values were >0.05). The studied polymorphisms also had no impact on the risk of CML with respect to patient's gender. No statistically significant differences were observed in genotypes frequencies within CML patients ($p > 0.05$). Statistically significant difference was observed in GSTT1 null genotype and phases of CML ($p = 0.012$) as shown in Table 4.

Discussion

GSTs are categorized into two families: membrane bound and the soluble or cytosolic GSTs. Cytosolic GSTs

including GSTT1 and GSTM1 are instrumental in detoxification process of activated carcinogens.²⁵ Nucleotide excision repair and basal transcription are carried out by helicase encoded by XPD genes and aberrations in the XPD gene predisposes to increased risk of cancer.²⁶

In this case-control study, genetic polymorphisms of GSTT1, GSTM1, and XPD Lys751Gln polymorphisms as risk for CML were investigated in Sudanese population. Literature shows contradictory results of these polymorphisms in a number of studies in different ethnicities and populations. In the current study, GSTT1 null polymorphism was observed in 42.7% patients with CML (OR = 3.39, 95% CI = 2.0 to 5.74, $p < 0.001$) as compared to control group (18%). Almost the same frequency of GSTT1 null polymorphism has also been reported in a local study,²⁵ while another has reported lower rate (34%) of GSTT1 in Sudanese population with CML.²⁷

Table 4 Distribution of the Studied Polymorphisms Among CML Patients According to Age Group, Gender, and CML Phase

Parameter	Category	GSTT1		GSTM1		XPD		
		Present	Null	Present	Null	Lys/Gln	Lys/Lys	Gln/Gln
Age groups	<40 years	18 (12%)	20 (13.3%)	16 (10.7%)	22 (14.7%)	23 (15.3%)	10 (6.7%)	5 (3.3%)
	>40 years	68 (45.3%)	44 (29.3%)	42 (28%)	70 (46.7%)	71 (47.3%)	26 (17.3%)	15 (10%)
Chi-square (P-value)		2.07 (0.151)		0.25 (0.614)		0.152 (0.926)		
Gender	Male	60 (40%)	39 (26%)	38 (25.3%)	61 (40.7%)	64 (42.7%)	24 (16%)	11 (7.3%)
	Female	26 (17.3%)	25 (16.7%)	20 (13.3%)	31 (20.7%)	30 (20%)	12 (8%)	9 (6%)
Chi-square (P-value)		1.27 (0.259)		0.01 (0.921)		1.27 (0.531)		
Phases	Chronic	69 (46%)	60 (40%)	46 (30.7%)	83 (55.3%)	82 (54.7%)	30 (20%)	16 (10.7%)
	Accelerated	10 (6.7%)	2 (1.3%)	8 (5.3%)	4 (2.7%)	8 (5.3%)	1 (0.7%)	3 (2%)
	Blast crisis	7 (4.7%)	2 (1.3%)	4 (2.7%)	5 (3.3%)	4 (2.7%)	5 (3.3%)	1 (0.7%)
Fisher's Exact (P-value)		8.5 (0.012)		4.5 (0.098)		6.7 (0.108)		

Similarly, the frequency of GSTT1 null phenotype has been found to be lower in other populations including India (9%),²⁸ Syria (17%),²⁹ Turkey (18%),³⁰ Brazil (23.8%),³¹ and Romania (24%).³² Frequencies of GSTM1 null polymorphism in cases were 61.3% and, 35.3% in controls. Statistically significant difference was observed in the variant genotype frequencies between the cases and controls (OR= 2.9, P = <0.001). Our results revealed a strong association between GSTT1 null and GSTM1 null polymorphisms and CML susceptibility. Similar results have been also reported in a local study²⁷ and, other populations as well.^{28,33} However, in contrast, other studies also suggest that GSTT1 null, and GSTM1 null may not be a predisposing risk factor for CML.^{32,34} Additionally, a local study also presents contradictory results reporting no association of GSTM1 null phenotype and risk of CML (OR = 0.975, P = 0.836).²⁵ Furthermore, several studies have described the influence of isolated GSTM1 gene polymorphism on CML risk, but no association of GSTT1 gene polymorphism was found in the same patients.^{35,36} Contrary to this, some reports show that GSTT1 gene polymorphism has association with increased risk for CML, whereas no association was observed in regards to GSTM1 gene polymorphism.^{6,37} The reasons for these contradictions and inconsistencies might depend on geographic and ethnic variations, among others.³⁵

The combined analysis performed in the current study illustrates that GSTT1 null genotype in combination with GSTM1 null genotype are considerable risk factors for CML development. A similar pattern of results have also been observed.^{25,30} The increased risk could be correlated with the synergistic effect of the enzymes encoded by GSTT1 and GSTM1 genes; instrumental in the cellular detoxification process. Genetic aberrations affecting the enzymatic activity of GSTT1 and GSTM1 make the DNA prone to damages leading to increased risk of developing CML.

Increased risk of cancer among individuals with XPD polymorphisms or other genes involved in the NER pathway has been observed.³⁸ Literature shows conflicting results of XPD polymorphism in patients with neoplasia. Some studies have reported a strong association between the XPD Lys751Gln polymorphism and increased leukemia risk,^{20,21,39} while one study found decreased risk of the leukemia.²⁶ In the current study, XPD Lys751Gln polymorphism was found to be associated with increased risk for CML. These results are in agreement with Bănescu et al.³⁹ To examine the effect of gene–gene interactions as

an estimation for CML risk in the present study, the relationship between dual gene–gene combinations was also analyzed. The results indicate that XPD Lys/Lys genotypes and GSTM1 null polymorphisms have an impact together on CML development and risk. No previous study has used this to investigate the effects of these polymorphisms on CML.

Distribution of XPD variants and GSTs null polymorphisms in patients stratified by age group and gender did not show statistically significant difference between the distribution of studied polymorphisms and age of CML patients at diagnosis (P > 0.05). The studied polymorphisms also had no impact on the risk of CML with respect to patient's gender. No statistically significant differences were observed in genotypes frequencies within CML patients (P > 0.05); this finding is also supported by other studies.^{27,35,40} However, these findings are contradictory to previous reports where the frequency of GSTM1 null genotype was lower in patients in the accelerated and/or blast crisis phase as compared to patients in chronic phase.⁴¹ Moreover, findings of this study show that GSTT1 polymorphism is associated with phase of CML. In the light of the above results and discussion, it is concluded GSTT1, GSTM1 and XPD null polymorphisms showed positive association with the risk of development with CML. Furthermore, age and gender did not exhibit any association with the studied polymorphisms, while CML phases were associated with GSTT1 null polymorphism.

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Disclosure

The authors report no conflicts of interest in this work.

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