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RESEARCH PAPER

Association between Glutathione-S-transferase (GSTT1 and GSTM1) Genetic Variations with Risks of both Acute and Chronic Myeloid Leukaemia.

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A B S T R A C T:

Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) are caused by an imbalance between carcinogen exposure and the capability of several enzyme systems involved in the activation or detoxification of xenobiotic compounds. The glutathione S-transferase (GSTT1 or GSTM1) null genotype is thought to be a risk factor for leukemia. Glutathione S-transferases (GST) regulate the effects of cytotoxic and genotoxic chemicals, including those linked to an elevated risk of AML and CML. The current study aims to look into the role of GSTT1 and GSTM1 gene polymorphisms in AML and CML susceptibility. In this case-control research GSTM1 and GSTT1 analyses, 50 AML patients, 50 CML patients, and 30 controls were enrolled. The current study found that null GSTT1 genotypes were found in 32% of AML and 20% of CML cases, compared to 23% of control subjects. In AML and CML, the statistical results were (OR=0.6467, 95% CI: 0.2505 - 1.82; p-value =0.407), and (OR=1.217, 95% CI: 0.4380 - 3.566; p-value =0.7242), respectively. Individuals with GSTM1 null genotypes were found in 50% of AML cases, 44% of CML cases, and 50% of control participants. The outcomes for AML and CML were (OR=1.0, 95% CI= 0.4229-2.365; p-value=>0.9999), and (OR=0.7858, 95% CI: 0.3294-1.86; p-value=>0.6023), respectively. GSTT1 and GSTM1 null genotypes may not be considered protective factors for AML and CML. This study suggests there is no association between GSTT1 and GSTM1 susceptibility to AML and CML.

KEY WORDS: AML, CML, GSTT1, GSTM1, and gene polymorphisms.
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1. INTRODUCTION :

Clonal hematopoietic stem cell diseases are including acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). AML progresses quickly as immature cells drive out normal cells in the bone marrow, but CML progresses more slowly, with CML cells multiplying uncontrollably (Healy et al., 2021, Marcucci et al., 2011). The risk of developing AML and CML has been linked in several studies to genetic changes in the precursor hematopoietic cells. DNA mutations that dramatically enhance a person's probability of developing particular types of cancer can be inherited from their parents (Desai et al., 2018, Yang et al., 2022). Numerous genetic modifications, including single nucleotide mutations, deletions or insertions, translocations, copy number variations, and loss of heterozygosity, are present in AML (Chun et al., 2018). However, the Philadelphia (Ph) chromosome was the main contributor to CML. The BCR-ABL (Breakpoint cluster region-Abelsone) fusion gene arises from a balanced reciprocal translocation between chromosomes 9 and 22, and its protein product has tyrosine kinase activity and drives uncontrolled proliferation of the myeloid cells (Minciacchi et al., 2021).

AML and CML are complex diseases that result from a combination of inherited and environmental factors. Reactive oxygen species-induced DNA damage in hematopoietic precursor cells is believed to be one of the mechanisms that contribute to the development of these diseases. Reactive oxygen species play a significant role in

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the pathogenesis of several hematological malignancies, including AML and CML. The interplay between genetic factors and environmental stress, particularly oxidative stress, is a critical factor in the initiation and progression of AML and CML (Zhou et al., 2013, Abdalhabib et al., 2021). Cancer susceptibility may be significantly influenced by those who have inherited genetic variations in detoxifying enzymes. Numerous research has looked into the functions of the whole-gene deletions of the GST-θ1 (GSTT1) and GSTμ-1 (GSTM1) in predisposing people to cancer, including AML and CML (Delmond et al., 2021, Nasr et al., 2015, Baba et al., 2021a).

The detoxifying enzyme Phase II is made up of 16 genes that encode glutathione S-transferases (GSTs), which are divided into eight classes: α (GSTA), μ (GSTM), ω (GSTO), π (GSTP), ς (GSTS), θ (GSTT), ζ (GSTZ), and K (GSTK). GSTT1 and GSTM1 deletion polymorphisms, which correspond to the Theta and Mu classes, are the most prevalent in humans (Singh, 2015, Baba et al., 2021b, Abdalhabib et al., 2021, Idris et al., 2020). The GSTT1 gene is found on chromosome 22q11.2, while the GSTM1 gene can be found on chromosome 1p13.3(Lee et al., 2022, Matejcic et al., 2011).

Glutathione S-transferases serve an important role in cellular detoxification by conjugating glutathione (GSH) to a wide range of exogenous and endogenous substances such as chemotherapeutic medicines, carcinogens, and pollutants. GSTs assist xenobiotic detoxification and clearance while protecting tissues from attack by reactive electrophiles that perform a variety of activities in cell proliferation, apoptosis, neoplastic transformation, and tumor metastasis (Singh, 2015). Smaller molecules are implicated in the metabolism of the GSTT1 polymorphism, whereas the metabolism of large hydrophobic electrophiles is functionally impacted by the GSTM1 polymorphism (Farasani, 2019). GSTs polymorphism variations may result in decreased intracellular enzyme concentration, impairing the enzyme's capacity for detoxification (Baba et al., 2021b, Abdalhabib et al., 2021, Idris et al., 2020).

Numerous types of research (Rostami et al., 2019, Idris et al., 2020, Delmond et al., 2021, Farasani, 2019, Ritambhara et al., 2019). looked into the relationship between GSTT1 and GSTM1 polymorphisms in the susceptibility to AML and CML, but their findings were inconclusive. Therefore, in the present study, we proposed that polymorphisms in GSTT1 and GSTM1 may be associated with metabolic variance and contribute to the interindividual variation of AML and CML patients. The current study was designed to investigate the aforesaid concept in patients from the Erbil province, Kurdistan Region of Iraq.

2. MATERIALS AND METHODS

2.1. Sample Collection

The study conducted blood collection in EDTA tubes from 50 patients diagnosed with AML and 50 patients diagnosed with CML by physicians at Nanakali Hospital in Erbil, Iraq, over a period from 8th September to 5th February. Table 1 provides additional information. AML patients varied in age from 9 to 81 years old (with a mean age of 43.56) and a male-to-female ratio of 56% to 44%, while CML patients ranged in age from 11 to 77 years old (with a mean age of 43.26) and a male-to-female ratio of 52% to 48%. The control group was composed of 30 individuals ranging in age from 9 to 72 years old (with a mean age of 42.17) and a male-to-female ratio of 53.3% to 46.7%. The study was approved by the Research Ethics Committee at the College of Science, Salahaddin University-Erbil, Iraq, and informed consent was obtained from all participants.

Table 1: Demographic characteristics of the AML and CML patients and control groups

	AML	CML	Control
Number	50	50	30
Sex [n (%)]			
Males	28 (56%)	26 (52%)	16 (53.3%)
Females	22 (44%)	24 (48%)	14 (46.7%)
Age (years)			
Mean ± SE	43.56 ± 2.986	43.26 ± 1.795	42.17 ± 3.111

2.2. Molecular Technique Analysis

2.2.1. Genomic DNA Extraction from the blood sample

The genomic DNA material was obtained from blood specimens at Salahaddin University Erbil Research Center (SURC) using the Genomic DNA kit (Jena Bioscience, Germany), as directed by the manufacturer. The quality, integrity and quantity of each DNA extracted sample were determined by NanodropTM 1000 spectrophotometer (Thermo Scientific, USA). The genomic DNA concentrations ranging by 10-2000ng/µl and purity ratio of absorbance at 260 and 280 nm is range (1.6-2.0) and Multiplex PCR was used to identify polymorphisms in the GSTs gene.

2.2.2. Genotyping of GSTM1 and GSTT1 Polymorphism

Multiplex PCR assay for detection of GSTM1 and GSTT1 Polymorphism that 20 µl of the mixture were prepared which consist of 10 µl of PCR Master Mix 2X (Ampliqon-Denmark), 3 µl of Genomic DNA as a template, and 2µ l for each of the forward and reverse primers for the GSTT1, GSTM1, and albumin genes (Table 2). The mixture was finished by adding 1 µl of DNase-free water. Multiplex-PCR was used to amplify the target gene. The process began with an initial denaturation at 95°C for 5 minutes, then progressed through 35 cycles at 94°C for 1 minute, annealing at 56°C for 1 minute, elongation at 72°C for 1 minute, and final elongation at 72°C for 7 minutes(Bhat et al., 2012). After PCR amplification, 2% agarose was used to separate the amplicon, and the separated bands were then dyed with a safe dye (Solarbio-China) for UV visualization (figure 1).

Table 2: Primer sequences and length of PCR products (Sharma *et al*., 2012)

Primer pair	Sequence 5'–3'	PCR product size(bp)
GSTT1 F GSTT1 R	TTCCTTACTGGTCCTCACATCTC TCACCGGATCATGGCCAGCA	459
Albumin F Albumin R	GCCCTCTGCTAACAAGTCCTAC GCCCTAAAAAGAAAATCGCCAATC	350
GSTM1 F GSTM1 R	GAACTCCCTGAAAAGCTAAAGC GTTGGGCTCAAATATACGGTGG	219

3. Statistical Analysis

The GraphPad Prism 8.4.3 program was used to conduct the statistical analysis. By using direct counting, genotype and demographic traits were computed. The chi-square test was used to assess differences in genotype and demographic traits between patients and controls. $p < .05$ was regarded as the threshold for statistical significance.

Table 3: The Distribution of GSTT1 and GSTM1 Genotypes in AML Patients and Controls

GST Polymorphism	AML N=50 (%)	Control N=30 (%)	OR 95% CI	P Value
GSTT				
Present	34 (68%)	23 (76.67)	0.6467	0.4070
Null	16 (32%)	7 (23.33%)	(0.2508 -1.820)	
GSTM				
Present	25 (50%)	15 (50%)	1.000	>0.9999
Null	25 (50%)	15 (50%)	(0.4229- 2.365)	

Table 4: The Distribution of GSTT1 and GSTM1 Genotypes in CML Patients and Controls

GST Polymorphism	CML N=50 (%)	Control N=30 (%)	OR 95% CI	P Value
GSTT				
Present	40 (80%)	23(76.67%)	1.217	0.7242
Null	10 (20%)	7 (23.33%)	(0.4380- 3.566)	
GSTM				
Present	28 (56%)	15 (50%)	0.7858	0.6023
Null	22 (44%)	15 (50%)	(0.3294-1.860)	

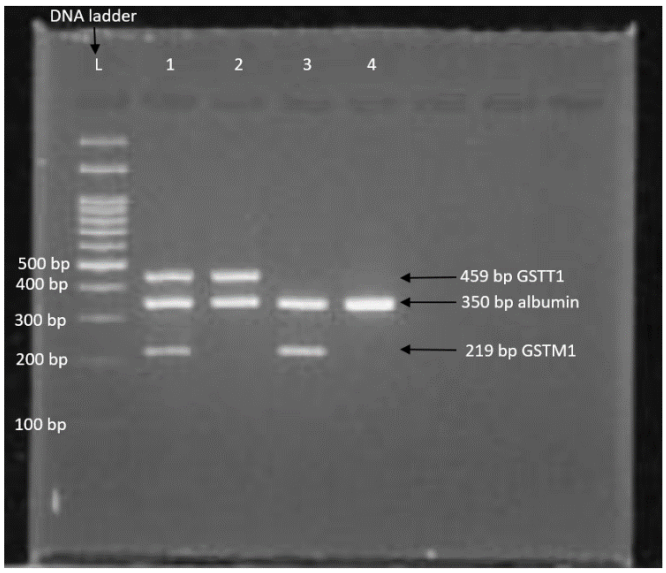

Figure 1: Multiplex PCR genotyping of human genomic DNA samples for detection of GSTT1 and GSTM1 gene deletion using agarose gel electrophoresis (2%). The presence of GSTT1, GSTM1, and Albumin is indicated by the presence of 459 bp, 219 bp, and 350 bp, respectively. GSTT1 null genotype is shown by the lack of the 459 bp band; GSTM1 null genotype is indicated by the absence of the 219 bp band; albumin was amplified in all samples as an internal control. The absence of GSTT1 or GSTM1 product indicates that the gene is a homozygous null allele. GSTT1 and GSTM1 positive genotypes are shown in Lane 1. Lanes 2 is GSTM1 null genotypes. Lane 3 contains a GSTT1 null genotype. Lane 4: GSTT1 and GSTM1 null genotypes. L: 100 bp DNA ladder.

4. Results

The study successfully genotyped 50 AML patients, 50 CML patients, and 30 healthy people. AML patients were 28 men and 22 women, with a median age of 45 years (range 9-81 years). There were 26 men and 24 women among the CML patients and the median age are 43 (range 11-77). In addition, 30 people were roughly gender-matched, leukemia-free, healthy control subjects for GSTT1 and GSTM1 genotyping. Tables 4 and 5 show the frequency of GST genotypes in AML and CML cases and controls.

GSTT1 (Present) and GSTT1 null genotypes (individuals lacking the GSTT1 gene) were found in 68% and 32% of AML patients, respectively (tables 3 and 4). The control group had a slightly greater frequency of GSTT1 null genotypes, but this difference was not considered statistically significant. CML patients had 80% GSTT1 and 20% null alleles, and the results were deemed insignificant.

GSTM1 present and GSTM1 null genotypes were 50% and 50% in AML patients, respectively, while 56% and 44% in CML patients (tables 3 and 4). Furthermore, data analysis for AML and CML shows that the presence or lack of GSTM1 genotypes does not affect AML and CML.

5. Discussion

Both AML and CML are neoplasm myeloproliferative diseases, although the exact mechanisms underlying these cancers remain unknown. The recognized genetic aberration related to AML is present in the three most common driver mutations, *DNMT3A*, and *NPM1 FLT3*(Dunlap *et al*., 2019). While 90% of CML cases are linked to the current Philadelphia chromosome, which originates as a result of a reciprocal translocation between chromosomes 9 and 22, resulting in position-the juxta of the BCR-ABL gene (Kumar *et al*., 2018, Huang *et al*., 2021). The amount of expression of carcinogen-metabolizing enzymes as well as individual genotypic variations has a critical role in determining the susceptibility to developing various types of cancer (Waś *et al*., 2018, Hidaka *et al*., 2016).

The biotransformation of numerous toxic substances is carried out by the GSTT1 and

GSTM1 enzymes. The GSTs (GSTM1 and GSTT1) have been described in polymorphic forms, and the difference in genotype from the wild form may be relevant in predicting cancer risk. It has been discovered that people who have less effective phase II metabolizing enzymes are more likely to have cancer spacially AML and CML (Aronica *et al*., 2022, El-Deek *et al*., 2021). There has been a correlation between null mutations in the GSTT1 and GSTM1 genes and an increase in cancer cases, which is probably related to a greater vulnerability to environmental chemicals and carcinogens (Ritambhara *et al*., 2019).

The GSTT1 null genotype frequency was higher in AML patients (32%) compared to controls (23%), although it did not reach statistical significance, according to the current study (Table 4). These results concur with a study by (Farasani, 2019), which found no appreciable increase in the incidence of AML associated with the GSTT1 null genotype. Additionally, similar outcomes for ALL's GSTT1 gene polymorphism were also described by (Guven *et al*., 2015, Aali *et al*., 2020).

GSTM1 present and GSTM1 null genotypes were found in 50% of AML patients and 50% of CML patients, respectively, while they were found in 56% and 44% of CML patients.

Furthermore, data analysis for AML and CML were statistically insignificant when compared to controls and The supportive result was reported by (Idris *et al*., 2020, Masood *et al*., 2016).

This study focuses on the genetic predisposition to AML and CML caused by polymorphisms in the GSTM1 and GSTT1 genes in Erbil patients. The study's benefit is that it greatly contributes to our understanding of the role of polymorphism variants in several phase II metabolizing genes in regulating individual susceptibility to AML and CML in the Erbil.

6. Conclusion

The present study examined the association between GSTT1 and GSTM1 gene polymorphisms and the risk of developing AML and CML in the Erbil-Iraqi population. The findings of this study support the insignificant correlation, implying that GST gene polymorphisms may not be linked to AML and CML susceptibility.

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