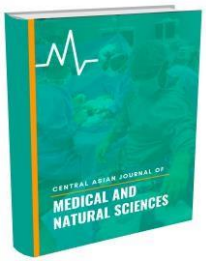

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Article

Glutathione S Transferase Impact on Acute Myeloid Leukemia Recurrence

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Abstract: The superfamily of glutathione S transferase enzymes (GSTs) were collected from several enzymes by an important polymorphic functional variance signal. GSTs remove toxins that may cause genetic mutations, then toxic and interacting with DNA, and which include the metabolites of many chemotherapy administrators, which some suspects are human carcinogens. To report how changes in human goods and services tax affect enzyme expressions in carcinogenic susceptibility, diagnosis, then treatment. This study included 60 patients with AML, as well as 50 healthy volunteers, with genotyping of GSTP 1, GSTM 1, and then GSTT 1 polymorphic gene were utilizing polymerase chain reaction and restriction polymorphic fraction (PCR - RFLP), then conventional PCR. The GSTP 1313 A→G polymorphism (GSTP1 Ile105Val), that the wild genotype (AA) among the control subjects was significantly higher (P value = 0.0377) it was established, while the incidence of the mutant genotype (AG) then was the mutant G allele (GG + AG) significantly elevated amid patients (P-value = 0.050, P-value = 0.026, in contrast). Targeting GSTM1 and then GSTT1gene, highlighted a significantly higher incidence among patients with respect to homozygous gene removal (P-value = 0.001). Creating the action of antioxidant enzymes may be the way cancer cells protect themselves in contrast to increased oxidative stress.

Keywords: Acute myeloid leukemia, Glutathione S transferase, Polymerase chain reaction

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1. Introduction

Cancer has impacted almost 42 million people worldwide, more than doubling its rate since 1990 [1]. Since 70% of deaths in developed countries are attributable to cancer, developing countries with high cancer incidence have a substantial impact on those nations. On the other hand, lung cancer has one of the highest global death rates [2]. Nonetheless, tobacco smoke is regarded as one of the leading causes of lung cancer [3]. In the world's population about 30% is unprotected from cancer caused by tobacco smoke [4]. Many investigations have discovered that additional mutation sources may contribute to lung cancer in nonsmokers as well. Many other factors include workplace pollution, heavy metals, second-hand smoking exposure, interaction with industrial pollutants such as radon and asbestos, and the air contamination which caused by fossil fuels such that polycyclic aromatic hydrocarbons [5], [6], [7], found that alcoholic intake components influenced cancer kinds.

The lung, as a respiratory organ, has always been unprotected from oxygen peripheral contamination, which then grounds other pollutants in the surrounding environment. There are two steps to fixing these carcinogens, antioxidant defense systems, according to

the recommendations. The first stage is when the enzymes cytochrome P450 (CYPs) work together to change the structure of substances by oxidizing and hydrolyzing them, as well as biotic organisms by reducing them.

Glutathione S transferases are used in the second stage to inactivate these chemicals by combining them with glutathione [8], [9], [10]. By limiting oxidative stress-causing chemicals, glutathione S transferases prevent tissue damage and maintain cell structural integrity. Glutathione S transferases are very susceptible to polymorphism damage in their primary components because its function as sensitive in oxidative stress mitigating [11], [12]. The effects of polymorphisms in GSTT1 and GSTp1 on glaucoma disease that caused by oxidative stress was investigated [13]. However, as the tobacco smoking prevalence and the incidence of lung cancer were increased in Iraq [14].

The polymorphism distribution in the GSTT1 and GSTp1 genes in patients with lung cancer and healthy controls were increased singly and in combination. In a community referral sample, researchers looked at a variety of lung cancer types to see if any of the polymorphisms increased the likelihood of lung cancer developing. Lung cancer is very common in Iraq.

2. Materials and Methods

From January to April 2021, the current study included 60 patients with AML who were referred to nuclear medicine and then to an oncology unit by patient follow-up, as well as 50 healthy volunteers. (WHO) criteria were used to identify cases. AML was diagnosed using morphological and then phenotypic data. The patients were divided into two groups: 30 before treatment and 30 after treatment, with ages ranging from 19 to 65. And 50 healthy subjects as a control group. These people were volunteers who had not gotten any medical treatment for cancer or any other illness and were not in any way connected to the patients. The participants' ages range from 18 to 56. Laboratory and clinical findings were reviewed in the patients, which included a thorough bet, clinical examination, laboratory investigations, and abdominal ultrasonography to detect lymphadenopathy. After the patients have been exposed to cytochemistry, immuno-phenotypic analyses should be carried out to confirm the diagnosis and partition the individuals into subgroups. Both patients and controls were genotyped to detect GSTP1, GSTM1, and then polymorphism GSTT1. All study participants had 3 milliliters of blood taken into a sterile EDTA filter. To extract DNA from whole blood a DNA extraction kit was used conform to the manufacturer's instructions. To confirm the diagnosis and assign the patients to their subtypes, cytochemical analyses and later immunological phenotypic analyses were performed on the patients.

Protocols for genomic DNA were isolated

Deoxyribonucleic acid purification in EDTA from fresh whole blood, no deleterious effects on further DNA manipulation, including polymerase chain reaction, were observed (PCR). Anticoagulant blood samples can be preserved for up to 2 months at 2-8 °C, however DNA generation decreases as storage duration increases.

GSTP1313 A → G polymorphism

We employed the polymorphic fraction length restriction (PCR - RFLP) approach to study the GSTP1 polymorphism. PCR was approved using a total volume of 25 l containing 12.5 mL of Master mix, 2 mL front foundation (20 pmole), 2 mL reverse primer (20 pmole), 3.5 mL of Nuclease-free water, and 5mL of DNA extracted from the genome, as stated in Table 1. The PCR cycling conditions are as follows: a 5-minute denaturation stage at 95 °C, followed by 30 cycles of 94 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s. To finish the elongation operations, at 72 °C for 5 minutes a last extension phase was done. The

products of PCR (20 L) with 5 units of BsmAI were incubated (New England Biolabs, Hertfordshire, UK) for 4 hours at 37 °C and finally loaded onto a 2.5% of agarose gel stained with ethidium bromide. The wild type (313AA) showed at 176 bp a single range. The presence of the "G" allele introduces a restriction site. Three groups of 176, 91, and 85 bp heterozygotes (313AG) were seen. GSTM1 homozygous deletions, ensuing in no specific enzymes using conventional polymerase chain reaction (PCR) technology were studied. Including the BCL-2 housekeeping gene as an internal control. The prefixes used as shown in Table 1.

Table 1. Sequences of the primer

Primer sequence		Annealing
GSTM1 forward	((5'-GAACTCCCTGAAAAGCTAAAGC-3'))	62 degrees Celsius
GSTM1 reverse	((5'-GTTGGC TCAAATATACGGTGG-3')).′	
GSTP1 forward	((5'- TTCCTTACTGGTCCTCACATCTC-3 '))	61 degrees Celsius
GSTP1 reverse	((5'- TCACCGGACATGGCCAGCA-3 '))	
GSTT1 forward	5'- GGA ATG GAG AAC CAG GTC TT- 3 '	62 degrees Celsius
GSTT1 reverse	5'- GCA TGT CTT TGG GAT GTG GA- 3 '	

Statistical Analysis

For data entry, a pre-designed Package for Social Science version 17 file (SPSS and IBM SPSS soft) was utilized, followed by analysis. The data was presented in the form of a mean value with a standard deviation (SD). The t-test was used for measure statistically significant the differences among multiple experimental groups. The unpaired t-test with 95 percent confidence intervals (95 percent CI) and the odds ratio to attain t by a given allele and genotype were employed in the following experiments. A significant AP value is less than 0.05.

3. Results

The genomic DNA was isolated

With a DNA concentration chain of 60-500 ng/L, the isolated DNA was put onto an agarose gel. After electrophoresis, the isolated DNA was stained with ethidium bromide to show that it had migrated to the same DNA locus as the standard chain. There was only one well-defined strand with no streaks, indicating that there was no DNA fragmentation. At a final concentration of 60 ng/L, the DNA concentration was measured using the concentration chain. The absorbance at 260 and 280 nm was measuring and calculating the 260/280 nm ratio, DNA purity was established. The ratio is 1.8, which is within the necessary range of 1.7-2.0 for DNA utilized in further molecular diagnostics.

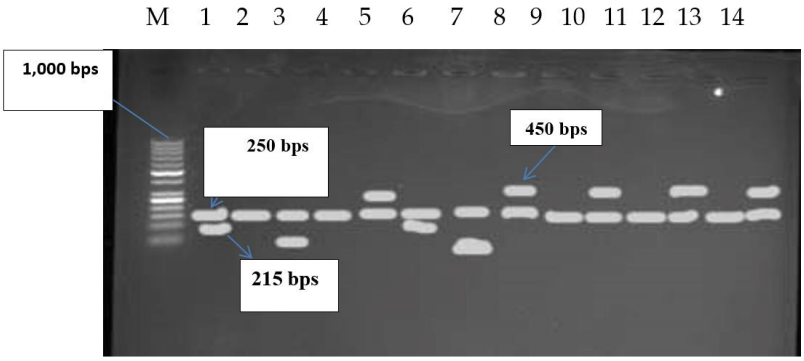

Figure 1. The products of PCR for GSTT1, GSTM1 and GSTP1 gene polymorph were amplified

The genotype was distributed

Regarding the PCR-RFLP results for GSTP1 313 A → G (GSTP1 Ile105Val) was polymorphic in the patient group, 25 patients (42%) had homozygous for the wild allele (105Ile / 105Ile) (AA), 21 patients (35%) heterozygous for the mutant allele (105Ile / 105Val) (AG), then 14 patients (23%) had the homozygous allele for the mutant (105Val / 105Val) allele (GG). For the control group, 32 cases (64%) had the AA genotype, 8 cases (16%) had the AG genotype, while 10 cases (20%) had the GG genotype. The wild (AA) genotype, it was found significantly higher than the control subjects P. value = 0.0377, while the frequency of the mutant (AG) genotype and then the mutated G allele (GG + AG) seem to be significantly higher among the patients (P = 0.050, P = 0.026 respectively). The deletion rate in the GSTM1 gene (GSTM1*0) in the patients was 23 (38%). For the control group, 7 subjects (14%) had a homologous genetic deletion with significantly higher frequency among patients (P-value = 0.0005). The results of the frequency of the genetic makeup are summarized in Table 2. In GSTT1 the control group, 4 subjects (8%) had a homologous genetic deletion with significantly higher frequency among patients (P = 0.0001). This meant that the frequency of deletions in the GSTM1 gene (GSTM1*0) was significantly higher among patients (P = 0.0005). A significantly higher frequency of deletions was also found in the GSTT1 gene (GSTT1*0) among patients (P = 0.0001).

Table 2. Genotyping and allele frequencies in Patients and GSTP 313 A - G, GSTM1 and GSTT1 gene deletion controls

Genotyping, alleles	Patients (N = 60) (%)	Controls (N = 50) (%)	P value
GSTP1			
AA	25 (42%)	32 (64%)	0.0377 [S]
AG	21 (35%)	8 (16%)	0.050 [S]
GG	14 (23%)	10 (20%)	0.70 [NS]
AA / AG	40 (67%)	40 (80%)	0.80 [NS]
GG / AG	35 (58%)	18 (36%)	0.026 [S]
GSTM1			
Not deleted	37 (62%)	43 (86%)	0.0005 [HS]
Symmetric deletion	23 (38%)	7 (14%)	0.0005 [HS]
GSTT1			
Not deleted	25 (42%)	46 (92%)	<0.0001 [HS]

he is	35 (58%)	4 (8%)	<0.0001 [HS]
Mozygous Delete (0)			

S Value: Significant [S] <0.05, Non-significant [NS]> 0.05, High significance [HS] <0.001

ST genotypes then initial treatment response: After chemotherapy, 35 patients (70%) completed while 15 patients (30%) only partially achieved 47 patients (94%) requiring red blood cells then platelet transfusions, while 3 patients (6%) did not require red blood cells nor platelet transfusions. Adverse drug reactions such as myeloma inhibition, infection or toxicity developed in 47 patients (94%).

Gene frequency in patients and control groups

In Table 3 with a higher frequency arrival, the GSTP1*105 allele was detected in both groups. It was significant, with a patient group individual ratio of 1.06 against 0.61 for the control groups (95 % CI: 0.43-0.77).

GSTT1*0 is only found in 1.26 single-patient groups. With a high individual ratio, the patient develops more frequently in the individual carrying the virus than in the bed with the allele frequency in individuals who lack it.

Table 3. The observed numbers and frequency rates gene in patients then controls

The gene	Patients		Controls	
	Individual Rate	95% CI	Individual Rate	95% CI
GSTP1*105 Allele	1.06	0.77-1.52	0.61	0.43-0.77
GSTM1*0	1.30	0.66-1.54	1.02	0.72-1.51
GSTT1*0	1.26	0.62-1.54	1.00	0.61-1.49

CI: Confidence Interval

4. Discussion

Phase II detoxifying enzymes, or GSTs, have been linked to the metabolism of anti-cancer drugs and carcinogens. They have also been shown to interact with kinase complexes in the course of stress-induced oxidative or chemical apoptosis. We sought to determine whether the polymorphic polymorphisms in these patients could account for their susceptibility to chemotherapy-induced differences in outcome. Subsequently, we examined three GST genes (GSTP1 / M1 / T1) in fifty healthy volunteers (as a control group) and sixty patients with (AML). Numerous studies have connected the polymorphism GSTT1 and the presence of GSTM1 to lymphocytic and then myeloid leukemia [15]. Although additional investigations have failed to confirm these findings [16], the GSTT1 deficient genotype has been shown to enhance the plastic myeloma syndrome and later acute leukemia [17]. A variety of devices have been created to preserve DNA from both internal and external damage.

GSTs are key components of the system that defends against reactive oxygen species, lipid breakdown, and DNA damage. Exposure to foreign compounds can increase GST levels in vivo, implying that they are part of the chemical stress adaption process. GST polymorphisms were a good candidate because leukemia genes were locus genes [18]. GSTs were involved in the metabolism of various carcinogens and then environmental pollutants, so polymorphisms in GST loci were a good candidate because leukemia genes were locus genes [19].

The patients were followed for 18 months to see how important GST genotypes are in the diagnosis of AML. There was no significant difference in RFS or OS between GSTM1 or GSTT1 null genotypes and normal genotypes, whereas patients with the GSTP1*105 Val mutant allele had superior and longer RFS and OS. Our findings were similar to those of [20].

These findings suggest that while the hereditary lack of the GSTT1 and then GSTM1 detoxification pathways may be linked to malignancy, it was not a significant driver of AML diagnosis. Patients with GSTM1 negative genotype had the same survival as those with at least one GSTM1 allele, whereas patients with GSTT1 negative genotype had the same survival as those with at least one GSTT1 allele, according to another study [21]. Consequences [22] that any genotype of GSTT1 or GSTM1 causes significant differences in OS, then adjust for other common variables like age, race, gender, cytogenetic in the group, previous cancer, FAB and WBC number, and blast rate, and the appearance of AML has no effect on HR estimates in a regression analysis [23]. Patients with GSTM1 null genotypes lived as long as those who had at least one GSTM1 allele. Given the limited size of the samples in many earlier investigations, these contradictory results could be due to chance. The dosage and then the type of chemotherapy regimen may also have an impact on the outcome. Patients with AML have previously been investigated [24].

When compared to patients with intact GST genes, those missing GSTM1, GSTT1, or both had a reduced chance of obtaining CR during induction therapy. The fundamental causes were discovered to be unknown. GST enzyme expression has been connected to in vitro chemotherapy and then to leukemic cells [25]. GST deficit produced by an empty genotype would be expected to result in a greater response to chemotherapy. It also demonstrated that GSTM1 null or GSTT1 null individuals had a lower risk of relapse in acute B-cell lymphocytic leukemia (ALL), whereas in the [26], [27]. GST genotypes had no effect on the patient's response to treatment or outcome. The disparity between our findings and those of others could indicate that gene polymorphism has very minor impacts, undermining many polymorphism research, particularly those with short follow-up periods Finally, we demonstrated that GSTM1null or GSTT1 null genotypes may be regarded separate variables for AML with no influence on prognosis, and that the GSTP1*105 genotype could be used as a predictive factor, providing additional independent information to the regular laboratory.

5. Conclusion

It was proved that GSTM1 null and otherwise GSTT1 null genotypes might be considered independent, it was factors for AML with no effect on the diagnosis, then the genotype GSTP1*105 was a prognostic factor, in addition to independent evidence to the laboratory of repeated parameters then cytogenetics then changes molecular structure of cancer cells.

6. Conflict of Interest

For this work there has been no conflict of interest of any kind with the authors.

7. Ethical Standard

The research plan of study was officially approved.

8. Informed Consent

Was taken before being enrolled in the study from all the participant patients.

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