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RESEARCH PAPER

Glutathione S-Transferase Mu 1 and Glutathione S-transferase theta 1 Genes Polymorphism and Susceptibility to Chronic Myeloid Leukemia in Erbil-Iraq Kurdistan Region

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A B S T R A C T:

Chronic myeloid leukemia (CML) result from many reactions of heredity non-heredity factors. The null genotype for glutathione S-transferase (GSTM1 or GSTT1) is regarded a risk agent leukemia, especially on CML in various inhabitants. The current study focused on evaluating association of two polymorphic identified genes Glutathione S-Transferase Mu 1 and glutathione S-transferase null genotypes that respect to CML patients from Erbil province, hence this work was performed a case-control study that composed of 51 samples (62% males, 39% females) with CML included and 45 healthy controls (22% male and 78% females) have participated. Multiplex PCR was used to ascertain GSTM1 and GSTT1 null genotypes. The chi-square test was done to show any link between GSTM1 and GSTT1 null genotypes that might be occurred in CML. There are significant statistical differences between incidence of GSTM1 null genotypes among CML cases and the increased CML risk was showed in patients bearing any of the GSTM1 null genotypes (OR = 2.196, 95%CI = (0.6017-6.806), P-value = 0.2108). While there is no statistical relation of GSTT1 null genotype with the risk of CML and exhibited lower risk initiation of CML occurrence (OR: 0.391, 95% CI: 0.1741-0.9033, P-value = 0.0304). Our findings demonstrate that GSTM1 null genotype is linked with the risk of CML patient development. The statements are helpful for formulating different investigation including GSTM1, GSTT1 variation genes and comparing research outputs with geography zone diverse in Iraq.

KEY WORDS: GSTM1; GSTT1; Gene polymorphism; CML; Multiplex PCR.
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1. INTRODUCTION

Chronic myelogenous leukaemia (CML) belong to blood cancer specifically formed due to chromosome called Philadelphia resulting by reciprocal translocation t (9; 22) (q34; q11) or BCR-ABL gene fusion that lead to the constitutive activation BCR-ABL tyrosine kinase which increase blood cells proliferation and malignancy. CML prevalence yearly accounts one to two cases per hundred thousand people and fifteen percentage leukaemia type in mature individual (Faderl, Talpaz et al. 1999, Deininger, Goldman et al. 2000, Al-Attar and Qader 2017).

Most of the cancers, including CML and stomach formed by a massive environmental interference, for instance, exposing to ionizing and nonionizing radiation, exist cancer leading agents in the habitat like benzene, alcochol, smoke and pesticides. This mutagenic substance refers to genotoxic and have act on the biotransformation of xenobiotics. It leads to genetic alteration in haemogenesis which rise the susceptibility of cancer like CML (Bhat, Bhat et al. 2012, Kassogue, Dehbi et al. 2015, Sulaiman 2016).

The DNA damages eliminated by activation and detoxification of carcinogens repair of genomic mistake errors and program cell death for mutant cells, apoptosis (Hayes and Pulford

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1995, Belitsky and Yakubovskaya 2008, Fang, Wang et al. 2013).

Several metabolic cancer susceptibility genes show DNA polymorphisms in the germline. These genes encode enzymes that have a role in exogenous and endogenous toxic substances and xenobiotics metabolism (Taioli 1999). Glutathione S-transferases (GSTs) are enzymes of phase II, have role in xenobiotics metabolism which share in cell detoxification by changing the activated carcinogenic metabolites of phase I enzymes (cytochrome P450) to inactivated metabolites and soluble glutathione, ease executable. There are eight categories of GSTs have been founded such as alpha (GSTA), mu (GSTM) theta (GSTT), pi (GSTP), zeta (GSTZ), sigma (GSTS), omega (GSTO) and kappa (GSTK) (Mannervik, Awasthi et al. 1992, Jancova, Anzenbacher et al. 2010, Rabab 2013). There are many studies on the assigned locus of GSTM1 and GSTT1 genes on chromosome 1p13.3 and 22q11.2 respectively. The long-term exposure to urban air pollution increase chromosome aberration like gap and break in human somatic cells (Pearson, Vorachek et al. 1993, Webb, Vaska et al. 1996, Knudsen et al. 1999).

The various research found that there is a link between enzyme inactivity in GSTM1 and GSTT1 and the susceptibility to form many sorts of malignancy like stomach, bladder and chronic myeloid leukemia (Bajpai, Tripathi et al. 2007, Ma, Zhuang et al. 2013, Sharma, Jain et al. 2013). The GSTM and GSTT genes are multifunctional enzymes groups that have a role in antioxidant activity interfere in cell differentiation drug detoxification, and anticancer drug resistance (Marchewka, Piwowar et al. 2017). The present study focuses on two polymorphic identified genes GSTM1 and GSTT1 null genotypes that respect to CML patients. Illustration the frequencies of these polymorphisms in Kurdish people from Erbil province, Kurdistan Region of Iraq and compare it to other population has benefit to show the exact role of GST genes in cancer formation.

2. MATERIALS AND METHODS

2.1. Sample Collection:

Three ml of blood samples were collected in EDTA tube of fifty-one CML patients collected from Nanakali Hospital, which was diagnosed by physicians. The age of patient suffered CML ranged (9-80) years, 62% were male, and 39% were female, and forty-five control group age ranged from 16 to 60 years, 22% male and 78% of samples were female.

2.1.1 Molecular Technique Analysis

2.1.2 Genomic DNA Extraction from blood sample

The genetic material was isolated from blood specimens in College of Science-Salahaddin University, using the Genomic DNA kit (GenetBio, Korea), depending on the manufacturer's instructions. Glutathione -S-Transferase genes polymorphisms identified by running multiplex polymerase chain reaction.

2.2. Genotyping of GSTM1 and GSTT1 Polymorphism

The total of 25 µl volume of PCR master mix reaction performed containing 3µl of template, 12.5 µl of 2X Go*Taq*Green PreMix (Promega, USA) and 1µl was added for each forward and reverse primers of both GSTM1, GSTT1 genes, GSTM1:forward5'GAACTCCCTGAAAAGCTAAAGC3',GSTM1:reverse5'GTTGGGCTCAAATATACGGTGG3',GSTT1:forward5'TTCCTTACTGGTCCTCACATCTC-3' and GSTT1 reverse 5'-TCACCGGATCATGGCCAGCA-3' Albumin forward 5'-GCCCTCTGCTAACAAGTCCTAC-3'Albumin:reverse5'GCCCTAAAAAGAAAATCGCCAATC-3'(Sharma et al., 2012) then the mixture was completed by adding 3.5µl DNase free water.

The target gene amplification was don using PCR started by initial denaturation at 95°C for 5 min, continued by 35 cycles at 94°C for 1 min, 56°C for 1 min, 72°C for 1 min and eventually elongation at 72°C for 7 minutes. After PCR amplification, the PCR amplicon separated on two percentage agarose then the separated bands were stained with ethidium bromide to visualize under UV light (Brown 2016). The bands of (219, 459 and 350) base pair mean the appearance of GSTM1, GSTT1 gene polymorphism and albumin respectively. The existence of albumin without GSTT1 or GSTM1

means its deletion and used as a control (Sharma et al., 2012).

3. Statistical Analysis

The graph pad prism 8.0.1 used. The chi-square test was done to illustrate the risk between GSTM1 and GSTT1 null genotypes and incidence of CML, corresponding the genotype distribution between cancer and healthy inhabitants. A *p*-value of lower than 0.05 reflected statistically significant. Odds ratio (OR) with a confidence interval (CI) of 95% was counted.

GST Polymorphism	CML N=51 (%)	Control N=45 (%)	Genetic Models	OR 95% CI	P Value
GSTM1	Recessive				
Present	9(17.7)	4(8.9)		1	-
Null	42(82.3)	41(91.1)		2.196 (0.6017-6.806)	**0.2108**
GSTT1	Recessive				
Present	13(25.5)	21(46.7)		1	-
Null	38(74.5)	24(53.3)		0.391 (0.1741-0.9033)	**0.0304**

4. RESULTS AND DISCUSSION

The current work consists of fifty-one CML patients from 9 to 80 years' age, (62% males, 39% females) and healthy blood cases collected from forty-five (22% males, 78% females; age ranged from 16 to 60 years).

In the present study, we found frequency of GSTM1 and GSTT1 genotypes in CML and control group, and CML risk belong to the effect of GST polymorphism as illustrated in Table 1.

The ratio of GSTM1 and GSTT1 genotypes revealed in 51 chronic myelogenous leukemia and 45 healthy persons. There are significant statistical differences between incidence of GSTM1 null genotypes among CML cases and the increased CML risk was showed in patients bearing any of the GSTM1 null genotypes (OR = 2.196, 95%CI = (0.6017-6.806), *P-value* = 0.2108). While there is no any statistical relation of GSTT1 null genotype with the risk of CML and exhibited lower risk initiation of CML occurrence (OR: 0.391, 95% CI: 0.1741-0.9033, *P*-value = 0.0304).

There was a statistically significant relation between GSTM1 null genotype and CML incidence. Forty-two percentage of the CML cases and 41 % of health belong to homozygous deletion in the *GSTM1* referring a high variation with an (OR, 95% CI, 2.196, 0.6017-6.806; *P*-value = 0.2108). Although GSTT1 null genotypes exhibited a reduce risk producing CML cancer incidence, it was statistically not significant (OR: 0.391, 95% CI: 0.1741-0.9033, *P*-value = 0.0304). The DNA Polymorphisms did not show a significant association with CML disease when disposes oddly, an association may appear when CML genotypes of these various polymorphisms are fused. Hence we examined the combination of GSTM1 versus GSTT1 their relation with CML occurrence as in Table 1.

Table (1). The Distribution of GSTM1 and GSTT1 genotypes in CML patients and healthy controls and evaluation of the risk of CML.

Abbreviations: CML: Chronic Myelogenous Leukemia; **P* value < 0·05; OR: Odds ratio; CI: Confidence interval.

Two percentage agarose gel electrophoresis illustrating multiplex PCR genotyping of DNA samples for identifying of GSTM1 and GSTT1 gene deletion (null genotype). The (219, 459 and 350) base pair bands mean the existence of GSTM1, GSTT1 (non-null alleles) and albumin consecutively. The lake of GSTM1 or GSTT1 represents homozygous null genotype of that gene shown in Figure 1.

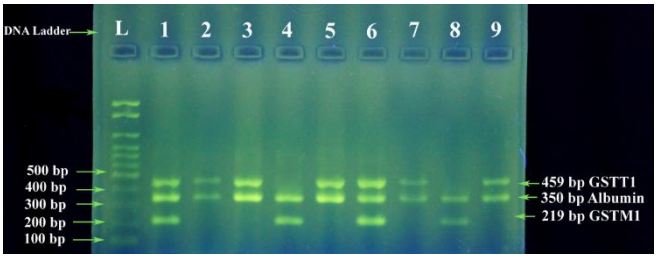

Figure 1. Agarose gel electrophoresis (2%) illustrating multiplex PCR genotyping of human genomic DNA samples for detection of GSTM1 and GSTT1 gene deletion (null genotype). The 219 bp, 459 bp and 350bp means the presence of GSTM1, GSTT1 (non-null alleles) and Albumin respectively. The absence of 219 bp band shows GSTM1 null genotype; absence of 459 bp band shows GSTT1 null genotype; albumin co-amplified in all samples. Absence of GSTM1 or GSTT1 product represents homozygous null

genotype of that gene. Lanes 1, 4, 6, and 8 GSTM1 and GSTT1 positive genotypes (non-null alleles). Lanes 2, 3, 5, 7,9: GSTM1 null genotypes. L: 100 bp DNA ladder.

Chronic myeloid leukemia is one the most of common studied human malignancy, and it is a myeloproliferative disturbance. Still, precise mechanism leading to this carcinogenesis is yet to be understood the risk of CML (Deininger, Goldman et al. 2000, Bhat, Bhat et al. 2012). The unequilibrium between expose to carcinogens (endogenous and exogenous) consequence lead to development of cancer and the ability of different enzymes involved in activation or in detoxification of xenobiotics (Kassogue, Dehbi et al. 2015). Metabolizing enzymes have role in cancer development of inter-individual genetic variation in xenobiotics. The genetic variation and level of expression of these carcinogen metabolizing enzymes are important in identifying the susceptibility of cancer initiation (Bhat, Bhat et al. 2012).

Hence, in a genetic case-control study, the relation between xenobiotic metabolizing gene polymorphisms and susceptibility were examined to CML patients in Erbil Province, Kurdistan Region of Iraq. There are many studies that reported the role of GSTT1 and GSTM1 gene polymorphisms in the formation of carcinogenesis like CML (Kassogue, Dehbi et al. 2015)

Genetic differences that decrease the activity of the phase II glutathione transferase enzymes or increase the level of the phase I cytochrome P450 enzymes associated with elevating risk of cancer because polymorphism lead to stop enzymatic activity and inhibit the detoxification role for GSTs (Makhtar, Husin et al. 2017). Although polymorphisms in detoxification genes have essential role in determining cancer risk, relatively little is known about their genetics and expression. (Pearson, Vorachek et al. 1993).

Two DNA polymorphisms that comprise deletions in GSTM1 and GSTT1 were described that results in enzyme missing or absence activity (Kassogue, Dehbi et al. 2015), therefore, we analyzed and realize the association between the GSTs (GSTT1 and GSTM1) gene polymorphisms and CML intensively. Nowadays, several studies have suggested that susceptibility to Acute myeloid leukemia and Chronic myeloid leukemia may associate GSTT1 and or GSTM1 deletions (Souza, Barbosa et al. 2008).

The current results pointed out that polymorphic variants in the glutathione S-transferase (GSTs) are associated the CML cancer susceptibility. Moreover, regarding the GST genes, we noticed that GSTM1 null genotype people expose more at risk to be affected with CML by conceiving higher risk (OR= 2.196) for CML as compared to healthy controls as shown in table 1 and describing a statistically significant positive association with CML patients. Similarly, the results were also clearly reported about the elevated risk of CML for the GSTM1 null genotype by Al-Achkar et al. (2017), Bhat et al., (2012), and Lordelo et al. (2012) showed that the GSTM1 null genotype frequency was higher in CML than in control (Bhat, Bhat et al. 2012, Lordelo, Miranda-Vilela et al. 2012, Al-Achkar, Moassass et al. 2017, Rostami, Assad et al. 2019).

The concurring results from different populations depicted. Depending to the references, various epidemiological studies have represented the role of GSTM1 and GSTT1 null in predisposing individuals to different cancer types including CML. There are some studies elucidated that the GSTM1 null whether, alone or with GSTT1, increased disease risk in Indian, Brazilian and Syrian people (Al-Achkar, Moassass et al. 2017). Besides, Sharma et al., (2012) who stated that the existence of homozygous null GSTM1 genotype is substantially higher in Caucasians and Asians as compared to Indian population (Sharma, Pandey et al. 2012).

Disconcordance research are demonstrated in the relationship between GSTM1 null genotype and CML, and some studies remarked no association of the GSTM1 gene polymorphism with CML (Taspinar, Aydos et al. 2008, Özten, Sunguroğlu et al. 2012, Al-Achkar, Azeiz et al. 2014).

Alternatively, our analyses show that the GSTT1 gene deletion (null genotype) was not a significant association among CML patients with control sample. The findings of the current study are in accord with the previous investigation of Kassogue et al., (2015) who submit that the GSTT1 null genotype not found to be associated with the development of CML (Kassogue, Dehbi et al. 2015). Likewise, in the current study, Our results were similar to the results which concluded

by Rostami et al., (2019) consistent with Weich et al. (2016) report (Weich, Ferri et al. 2016, Rostami, Assad et al. 2019).

Furthermore, a research approved in Japan that did not report the association between GSTT1 null genotype and CML patient (Hishida, Terakura et al. 2005)a. In contrast, the conflicting results with an association were achieved such as the studies in Caucasian, Indian, Chinese Syrian populations that find an increase in the GSTT1null genotype in CML cases (Al-Achkar, Moassass et al. 2017). There is abundantly manifest and apparent that polymorphism in individual GST genes is important modulators of CML cancer susceptibility.

5. CONCLUSIONS

To the best of our comprehension and knowing, this is the first genetic variation in Kurdish people from Erbil Province, Kurdistan Region of Iraq for evaluating of association the risk of GSTM1 and GSTT1 null genotype carrier in the development of CML. This study has allowed determining the frequency of GSTM1 andGSTT1gene polymorphism in a sample of our population. Besides, we have distinguished that the GSTM1 null genotype is associated with the development of CML patients. These statements have role in study many populations including allele variation of GSTM1, GSTT1 genes and comparing the data with many geographical zones in Iraq.

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