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# Polymorphism in Glutathione Transferases (GST) association with risk of childhood acute lymphoblastic leukemia Najaf province

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***Abstract***---Total sample number 90 were 60 children diagnosed with Acute lymphoblastic leukemia (ALL) collect form Center Tumor cancer in Najaf , and select 30 children normal heath ( control) from Amir al-Muminin Hospital and study conduct with molecular lab biology in the Department of Biology / Faculty of Science – University of Kufa, during the period from November 2021 to April 2022. The results of This study show *GSTM1* and *GSTT1* genotypes in 60 children with ALL and 30 healthy controls were compared, Patients and healthy who carried present *GSTM1*ella allele about ( 26.6% , 40%) respectively , who are of them null *GSTM1* (73.3% , 60% ) respectively ,also this study showed the significantly in null *GSTT1*ella when compared between patients and control ($p < 0.00$ ). as well as presence the heterozygous ella (*GSTT1*$^{-}$ *GSTM* 1$^{-}$ / *GSTM1*$^{-}$ *GSTT*1$^{+}$ & *GSTM*1$^{+}$ *GSTT*1$^{-}$ ) in patient and control about ( 13.3% , 40% , 33.3%) and (6.6% 53,3% ,6,6%) respectively.

***Keywords***---polymorphism, glutathione transferases, childhood, acute, lymphoblastic leukemia.

## Introduction

Several studies have described cancer as the third primary cause of death in children aged between 1 to 4 years, and it is also the most leading cause of death among children between 5 to 14 years. Detecting cancer in the early stages and given patients the best treatment (Siegel *et al.,* 2021). Can contribute to improvement of children's conditions, and treatment varies depending on the stage and type of cancer (Saeed *et al.,* 2021). Therapy of childhood acute

lymphoblastic leukemia (ALL) has been successful during the last decades due to improvements in intensive combination chemotherapy and supportive care (National cancer institute, 2021) The most successful strategy to reduce the burden of cancer during childhood and improve outcomes is to focus on early diagnosis followed by evidence-based therapy with tailored supportive care (WHO, 2021b). With the increasing incidence of childhood cancer, the role of parents especially mothers became more and more important (Siyu, 2020).

Worldwide, around 240,000 new cases of childhood acute leukemia are diagnosed each year. Acute lymphoblastic leukemia (ALL) is the most common type of leukemia among pediatric patients with 75% of cases occurring in developing countries. It represents 76% of leukemias in under 15-year-old patients and 30% of all kinds of cancer in this age group.( Jaime-Pérez *et al.*,2019). The survival rate of pediatric ALL patients in industrialized countries has improved to approximately 90% in recent years, (Hunger *et al.*, 2015; Jaime *et al.,* 2020) with a 93% overall survival recently reported in the United States ( Pui *et al.*,2009). However, in low- and middle-income nations overall survival varies from 50% to 75% (Jaime-Pérez, *et al.,* 2016). Risk stratification is pivotal for ALL prognosis and individualized therapy (Liu *et al.*, 2011). The association of GST polymorphisms and childhood ALL was in 1997 by Chen *et al* first reported the linkage between *GSTT1* polymorphism and incidence of childhood acute leukemia among both black and white children.( Ma *et al* ., 2019). Deletion polymorphisms of *GSTM1* and *GSTT1* genes and the single nucleotide polymorphism lead to the absence or reduced detoxification capacity of the enzyme. Differences in GSTs activity may modify the risk of cancer development and also may impact on the heterogeneous responses to toxic substances or specific therapies (Hollman *et al.*, 2016).

**Materials and Methods**

In this study the patient group consist of 60 case of children diagnosed with Leukemia (ALL) and the matched healthy group (control ) consist of 30 case with no Leukemia I was collect my sample from tumor center in Al-Najaf Patient who have confirmed diagnosis of (ALL) in children age (1.5 -7) years regard gender and ether group and attended cancer center Exclusion infected children with chemotherapy , Non Iraq patient and those relation to participate in this study Blood sample collect venous blood sample (3-5 ml ) DNA primers were used : GSTM1: F-( 5/ - GAA CTC CCT GAA AAG CTA AAG C) R-( 5/ - GTT GGG CTC AAA TAT ACG GTG G ) GSTT1: F-( 5/ - TTC CTT ACT GGT CCT CAC ATC TC ) R-( 5/ - TCA CCG GAT CAT GGC CAG CA ) Initial denaturation at 95 oC for 3 min, 30 cycles in thermocycler ( Techne,Cambridge Ltd., England) as follow : 94 oC for1 min; 59 oC for1 min ; 72 oC for1 min and 5 min final extension for last cycle. The PCR products were analyzed on 2%Agarose gel electrophoresis to detect the absence or presences of these genes.

**Results and Discussion**

GST's Function GST is a family of enzymes involved in the detoxification of reactive chemical species by bonding to the reduced form of glutathione. A recent development in the field of molecular biology has enabled scientists to study large-scale genome data, expressed sequence tags, and termination signals using

X-ray crystallography. Mammalian GST's have been extensively studied and been classified into various subclasses according to the given criteria but up to now, many GSTs in non-mammalian species have also been discovered. This discovery has led to the development of functions other than those that were described earlier only in mammalian species (James, *et al.,* 2020). These enzymes play a wide variety of functions such as removal of ROS, production of s-thiol containing proteins both of which are formed as a consequence of oxidative stress to the brain or any other cell of the body. Other generalized functions include catalysis of complexes formed because of conjugation with endogenous ligand species and in the processing of mechanisms involved in detoxification. In the case of their role in enzymatic detoxification, chemical compounds like xenobiotic and metallic species are major sources of toxicity when exposed to the human system. These toxic compounds may sometimes include phenols, aflatoxins, ROS such as superoxides, hydroxides, and superoxides. In addition to sequestration and binding, another biochemical transformation mechanism is an important pathway involved in getting rid of toxic chemical compounds (Mihalopoulos *et al.* 2015).

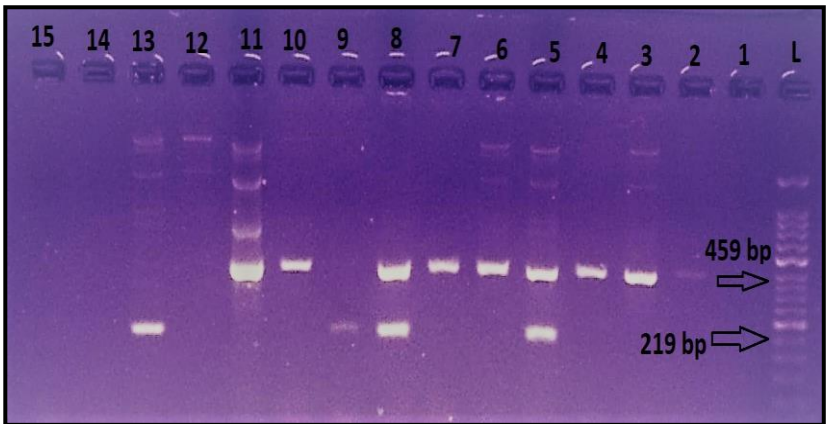


Figure 1. PCR products of *GSTT1* and *GSTM1* gene polymorphism in patient electrophorese on 2% agarose gel. Lane: 5, 8, Heterozygote both *GSTT1* and The *GSTT1* present. Lane: 2,3,4,5,6,7.8,9,11 determine the *GSTT1* and *GSTM1* gene polymorphism. Bands at 459 bp and 219 bp represent *GSTT1* and *GSTM1* respectively genotype

Most of these finding was compatible with recent studies of( Abdalhabib *et al.*, 2022; Moulik *et al.*, 2014 )Multiple studies have demonstrated that susceptibility to cancer is caused by a deficiency in xenobiotic-metabolism genes (*GSTT1* and *GSTM1* )were significantly higher in the cases groups compared to the control group (Aziz, 2010). Data demonstrated that GST frequent determined in Iraq population GST polymorphism have been related to different cancer some of may be direct associated with cancerogenic toxic factor.

Table 1
Genotypic frequency of *GSTT1* and *GSTM1* genotypes in control and lymphoblastic leukaemia patients

| Genotype | Patients N=60 (%) | Control N=30 (%) | OR | P |
|---|---|---|---|---|
| *GSTM1 (+)* | 16 (26.6) % | 12 (40) % | 0.54 | 0.05 |
| *GSTM1 (-)* | 44 (73.3) % | 18 (60) % | 1.83 | 0.00* |
| *GSTT1 (+)* | 32 (53.3) % | 28 (93.3) % | 0.08 | 0.05 |
| *GSTT1 (-)* | 28 (47) % | 2 (6.6) % | 12.5 | 0.00* |
| *GSTT1(+) & GSTM1 (+)* | 8 (13.8) % | 12 (40) % | 0.24 | 0.05 |
| *GSTM1 (-)&GSTT1 (+)* | 24 (40) % | 16 (53.3) % | 0.58 | 0.05 |
| *GSTM1 (+) & GSTT1 (-)* | 20 (33.3) % | 2 (6.6) % | 7.06 | 0.00* |
| *GSTT1(-) & GSTM1 (-)* | 8 (13.3) % | 2 (6.6) % | 2.17 | 0.00 |

* Significant differences at p- value 0.00, OR: odds ratio patient = 60, control =30

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