

The Influence of Glutathione-S-Transferase M1 (*GSTM1*) Null Polymorphism in Acute Leukemia in Sudanese

Alaa Atef Hamid Yasin¹, Elfirdous Salah El-deen Ahmed Abdallah¹, Halima Ali Ibrahim Ali¹, Romisa Abd-Algadir Mohammed Ahmed Mohamed¹, Romisa Kamal Ahmed Alrehema¹, Mosab Nouraldein Mohammed Hamad² and Enaam Hussein Mohammed Ahmed Ali^{1*}

¹Department of Hematology and Immunohematology, Faculty of Medical Laboratory Sciences, University of Khartoum, Sudan

²Department of Medical Laboratory Sciences, Faculty of Health Sciences, Elsheikh Abdallah Elbadri University, Sudan

***Corresponding Author:** Enaam Hussein Mohammed Ahmed Ali, Department of Hematology and Immunohematology, Faculty of Medical Laboratory Sciences, University of Khartoum, Sudan.

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Abstract

Introduction: The glutathione S-transferase (GST) play a crucial role in detoxification of mutagens and carcinogens, including those associated with increased risk of the acute leukemia. Both GST M1 (*GSTM1*) and GST theta 1 (*GSTT1*) genes have a “null” variant allele, in which the entire gene is absent. Previous studies have revealed significant differences between populations for genotypic frequencies of glutathione S-transferase, including (*GSTM1*) polymorphisms in health and disease. Therefore, we aimed to test whether the *GSTM1* null genotype could alter the risk to develop acute leukemia in Sudan.

Method: Observational analytical retrospective case-control association study was conducted, over a period of five months. A total of 100 donors/patients were randomly enrolled from different hospitals in Khartoum, Sudan. For molecular analysis genomic DNA was extracted from EDTA blood samples and analyzed by allele specific PCR for demonstration of *GSTM1* gene.

Results: The data analysis revealed that *GSTM1* null genotype is demonstrated in 58% of cases (58% males and 42% females) and in 41% of control subjects (70% males and 30% females). It was observable that the *GSTM1* null genotype was higher in cases compared to controls (odd ratio = 1.915, 95% CI 0.8629 to 4.251). However, the difference showed no significant association between *GSTM1* Null and acute leukemia (P = 0.1085). The frequency of *GSTM1* null genotype in AML-subtype was significantly higher than ALL- subtype (P = 0.0015).

Conclusion: Our findings came up without statistical significant influence of *GSTM1* null genotype on the risk of developing acute leukemia in Sudanese, however, the influence cannot be ruled out, so further study with a larger sample size is recommended.

Keywords: *Glutathione-S-transferase M1; Polymorphism; Acute Leukemia, Sudan*

Background

Acute leukemia's are neoplasm of clonal widespread of blast in the blood, bone marrow and infiltrate to other organs. The origin of these blasts is hematopoietic stem cell, myeloid cells and precursor T, B-cell [1]. Acute leukemia is a cancer of blood cells and bone marrow that characteristically come on suddenly and lead to rapid increase in the number of immature blood cells [2]. Classified into Acute

myeloid leukemia (AML), also known as acute myelogenous leukemia or acute non lymphocytic leukemia, Acute lymphoblastic leukemia (ALL) or acute lymphoid leukemia [3].

Cancer is a main cause of death worldwide. An estimated 12,7 million new cancer cases occurred in 2008, of which about 715,000 new cancer cases resulted in 542,000 death in Africa [4]. These number are expected to nearly double to 1,28 million new cancer cases and 970,000 death by the year 2030. This increase in cancer cases in Africa is attributed to both aging and population growth and adoption of lifestyles associated with economic development, such as smoking, unhealthy dieting and a lack of physical activity [4,5].

Cancer continues to receive low public health priority in Africa, in general across the continent and specifically in Sudan [6]. In a recent, study from Sudan NCR. 6771 incident cancer cases were recorded among Khartoum State residents during 2009 - 2010 periods. The age-standardized rates using the 1966 and 2000 World Standard populations were 165.0 and 181.0 per 100,000 populations. Of individuals, 3646 (53.8%) cases were females and 3125 (46.2%) were males. The most widespread major cancer locations in females were breast, leukemia, cervix, ovary, lymphoma, esophagus, and colorectal cancer. In males, the most frequent cancer positions were prostate, leukemia, lymphoma, oral, colorectal, and liver. The most widespread cancer in Khartoum in females are Breast cancer with incidence rate of 25,1 per 100,000 followed by leukemia with incidence rate 10 per 100,000 and among males it was prostate cancer followed by leukemia [7].

The site of geographic distribution of cancer patients includes 19.6% of the patients have come from Khartoum and the same percentage have come from North Kordofan this indicate that these area has a high incidence of cancer diseases. 13.4% from the patients come from Gezira. 7.2% from Northern State and 6.2% from White Nile [8].

Glutathione S-transferase (GSTs) are family of multifunctional enzymes that are involved in the metabolism of many xenobiotics, include environmental carcinogens by catalyzing the conjugation of glutathione to electrophilic compounds [9]. Also, it has a role in modulating the induction of other enzymes and proteins for cellular function, for example DNA repair, and maintaining genomic integrity [9].

Human GSTs are divided into cytoplasmic, mitochondrial and membrane -bound microsomal families. Cytoplasmic GSTs are classified into eight subfamilies: alpha, kappa, mu, omega, pi, sigma, theta, and zeta [10]. Previous studies showed that homozygous deletion or null genotype, at either the *GSTM1* locus or the *GSTT1* locus resulted in enzyme function loss, and thus it was hypothesized to be related to the susceptibility to cancer, resistance to chemotherapy treatment and drug response [9,11].

GSTM1 gene, organized in a gene cluster on chromosome 1p13.3 [12,13]. *GSTT1* gene, located on chromosome 22q11.2 [14,15].

There are two common deletion polymorphisms in *GSTM1* and *GSTT1* genes, which results in virtual absence of enzyme activity [16,17].

A study aimed to test the relation between the GST M1, T1 genes polymorphism in black and white people and the susceptibility for acute leukemia in the United states of America 1997. The results revealed that the double-null genotype for *GSTM1* and *GSTT1* is more common among blacks but not whites with childhood ALL. These data suggest that GST genotype, coupled with unidentified additional risk factors, may play a role in risk of childhood ALL in American black. Another study was made in Brazil in 2008 seeking for Polymorphisms in the glutathione S transferase mu genes and susceptibility to myeloid leukemia and its relation to Acute promyelocytic leukemia. They concluded that, there is no association between Acute promyelocytic leukemia susceptibility and isolated GST M1 genotype [18,19].

According to a study conducted in Turkey, no difference in prevalence of GST M1 and GST T1 null phenotypes between patients and controls, which is mean that there is no association was found between heritable GST polymorphism and the risk of developing childhood ALL [20].

For the same objectives, in India and Jordan a case control study and meta-analysis was made, they found out that the GST M1 did not alter the risk of childhood ALL [21,22]. Whereas, in the French population, researchers found that *GSTM1* null genotype is significant predictors of ALL risk [23].

In Egypt 2007 researchers demonstrated that *GSTM1* null or *GSTT1* null genotypes may be considered as independent risk factors for AML with no impact on prognosis and *GSTP1* * 105 genotype is a prognostic factor, adding independent information to the routine laboratory parameters and cytogenetic and molecular alterations of the tumor cells [24].

A study made to correlate the Glutathione S-transferase M1null Genotype among Sudanese patients with Chronic Lymphoid Leukemia attended at RICK (Radiation Isotope Center-Khartoum) in 2015, the researchers found out that the percentage of *GSTM1* null genotype in CLL patients was significantly higher than in controls but their findings does not suggest that heritable *GSTM1*null may influence the risk of developing CLL. So further studies should be done using a large sample size to validate the results [25].

Another study made in RICK (Radiation Isotope Center-Khartoum) in 2011 - 2012 to search for a relationship between Chronic Myeloid Leukemia (CML) and the Polymorphisms in Glutathione S-Transferees (GST) M1 and S-Transferees (GST) T1 Genes, researchers found out that deletion in *GSTM1* represents approximately 6.67% of AML, 23% of CML and 26.67% of controls. On the other hand for *GSTT1* was found in 73% of AML 76.67% of CML and only 36.67% of controls [26].

Another study looked for a relation between the GST T1 and ploycythemia Vera. They observed that *GSTT1* null genotype was similar among patients as well as control group and they considered *GSTT1* genotype was not related to development of ploycythemia vera [27].

There was a Meta-analysis study of glutathione-S-transferase (*GSTM1*, *GSTP1*, and *GSTT1*) gene polymorphisms and risk of acute myeloid leukemia which is made to investigate the association of glutathione-S-transferase (GST) polymorphisms with the risk of acute myeloid leukemia (AML). A meta-analysis of case-control studies published between 1998 and 2009 was performed. From the limited studies on the association of *GSTP1* with risk of AML, the role of this gene cannot be fully ascertained. But significant association of these three genes with risk of AML must be evaluated further with respect to population, smoking, eating habits, ethnicity, and race [28].

Rationale: According to literature the frequency of Glutathione gene M1 has been previously identified in healthy Sudanese population, showing of 54.4% for *GSTM1* null and 45.6% for *GSTM1* present. As far as we know, very limited work investigated the effect of *GSTM1* null genotype in susceptibility to acute leukemia's among Sudanese patients.

The data analyzed from this study is expected to identify the frequency of *GSTM1* null and assess its influence on the risk of acute leukemia, understanding whether null *GSTM1* gene phenotype is involved in developing acute leukemia. This may additionally help in understanding if it could be participating in resistance to the treatment, and if it could be used as an early genetic marker for the assessment of the risk for the disease. In addition to, the possibility to relate these polymorphisms to patient relapse or further predict of other disease complications.

Objectives of the Study

General objectives

The overall objective of this study is to identify the frequency of *GSTM1* null polymorphism and to assess the risk of association in acute leukemia patients compared to controls.

Specific objectives

1. To determine the frequency of *GSTM1* null in acute leukemia patients and apparently healthy individuals in Sudan.
2. To identify whether *GSTM1* null is associated to the risk of development of acute leukemia.

3. To find out if there is a difference of *GSTM1* null polymorphism in acute lymphoblastic compared to acute myeloblastic leukemia.
4. To correlate between age and frequency of *GSTM1* gene.
5. To correlate between gender and frequency of *GSTM1* gene.

Materials and Methods

Study design

This is a retrospective case control association study conducted to identify the frequency of *GSTM1* gene polymorphism and whether it is associated with acute leukemia in Sudanese patients.

Study area

This study was carried out at Khartoum state, Sudan. Samples were collected from the Radioactive Isotopes Center of Khartoum (RICK).

Study population

Patients included in this study are those diagnosed with acute leukemia based on clinical data and the further laboratory investigations performed. Hospital records, including demographic data were also collected.

Ethical consideration

All patients or patient's relatives were informed about the study by the investigator after approval of the laboratory manager. The study was ethically approved by the ethical committee, Faculty of Medical Laboratory Sciences, University of Khartoum.

Sample size

One hundred blood samples were included in this study. Fifty patients with acute leukemia and 50 apparently healthy controls.

Selection criteria

Inclusion criteria

- **Cases:** Sudanese patients diagnosed with acute leukemia after attending to the Radioactive Isotopes center of Khartoum (RICK) of Flow cytometry private Center in Khartoum.
- **Controls:** include Sudanese blood donors or apparently healthy individuals attended at Soba teaching hospital or Alromy Medical Laboratory, Omdurman.

Exclusion criteria

- Non Sudanese leukemic patients.
- Unable to donate blood.

Method

Blood Sample

2 ml of whole blood taken from each patient in E.D.T.A container for the study of GST M1gene, stored at -20°C until DNA isolation.

Hematological profile

A blood cell counter Sysmex KX-2IN was used for hematological profile.

DNA extraction

After thawing the samples at RT, the red cells lysed out leaving the genomic DNA containing leukocytes which additionally proceeded for the isolation of DNA, using DNA extraction kits of G-spin-Intron Biotechnology).

Molecular analysis

Molecular detection of *GSTM1* gene polymorphisms was performed by polymerase chain reaction, followed the step mentioned below.

DNA amplification by PCR

2 ul of DNA were amplified in total of 25 µl containing 1 µl of forward primer F-5'-GAACTCCCTGAAAAGCTAAAGC-3 and 1 µl of reverse primer R-5'-GTTGGGCTCAAATATACGGTGG-3, 4 µl master mix Maxima PCR Premix Kits (i-StarTaq) and 17 µl sterile distilled water. Beta-globin primers were used in parallel as a housekeeping gene. The cycling condition include initial denaturation at 95c for 5 min; 35 cycle of 94c for 10 sec (denaturation), annealing 59.5°C for 30 sec, and 72c for 45 sec (extension) and final extension at 72°C for 5 minutes.

Agarose gel electrophoresis to detect the PCR product

7.5 ul of the PCR product (ready to load) was electrophoresed on 1% Agarose gel, stained with ethidium bromide and then demonstrated by gel documentation system. Gel electrophoresis showed presence of 219 bp bands as *GSTM1* positive or absence of 219 bp band as *GSTM1* null.

Primer sequence	Product size (bp)
Globin-F 5-GAAGAGCCAAGGACAGGTAC-3 Globin-R 3-CAACTTCATCCACGTTACC-5	286
<i>GSTM1</i> -F 5-GAACTCCCTGAAAAGCTAAAGC-3 <i>GSTM1</i> -R 3-GTTGGGCTCAAATATACGGTGG-5	219

Table 1: Primer sequences for *GSTM1* and beta globin.

Data collection

Demographic data were collected from hospital records.

Data management

Graph Pad 6, SPSS version 17 and Microsoft Excel were used for data analysis and preparation of figures. Logistic regression was used to assess the risk of associations between the *GSTM1* null genotype and acute myeloid leukemia was calculated. The odd ratio (OR) and 95% confident interval CI) were calculated. Chi square test was used to compare between cases and controls. A P value of less than 0.05 was considered as statistically significant.

Result

We employed Polymerase Chain reaction to detect a total of one hundred blood samples (50 cases of acute leukemia and 50 apparently healthy controls) for the presence or absence of *GSTM1* gene. Samples were randomly selected from RICK, Soba Teaching Hospital and, Alromy Medical Center. There were a total of 36 females and 64 males; age ranged from 3 - 60 years for the cases and 3 - 50 years for controls.

The overall frequency of deletions of *GSTM1* gene (*GSTM1* Null) among cases was identified in 27 (54%) cases out of 50, while it is less presented in controls as only 19 (38%) controls were expressing the *GSTM1* Null genotype (Table 1). However, statistical analysis of data, using chi square test showed no significant (P = 0.1085) difference in frequency of *GSTM1* between patients and controls, the percentage of *GSTM1* null genotype was obviously greater (Odds Ratio (OR) = 1.915) in cases than in controls (95% confidence interval 0.8629 to 4.251 (Figure 1).

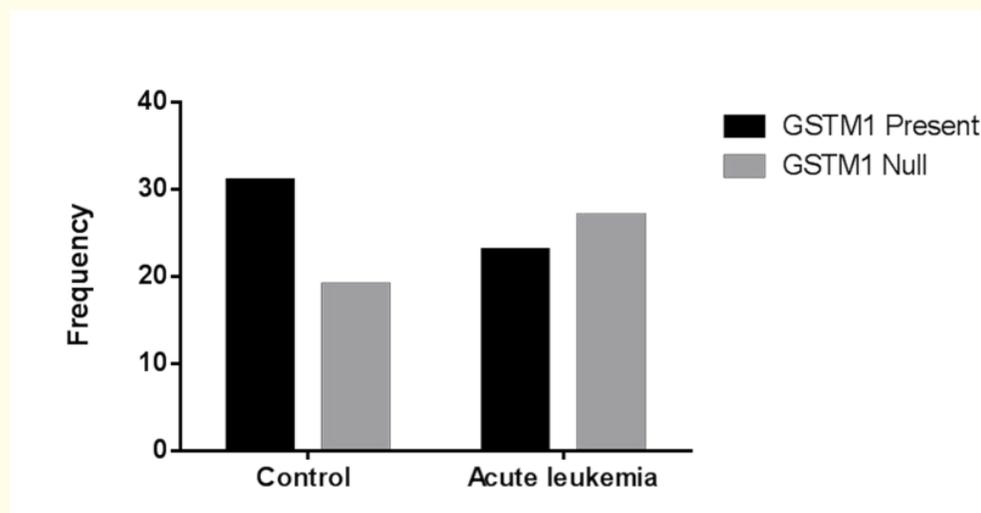


Figure 1: *GSTM1* polymorphism in Acute Leukemia compared to control. The presence or absence of *GSTM1* gene in cases compared to apparently healthy controls, using PCR technique for gene amplification. *GSTM1* null genotype is 1.915 fold greater in cases compared to controls without statistical significance ($P = 0.1085$, 95% CI 0.8629 to 4.251).

Regarding, the *GSTM1* frequency in relation to gender, our results showed insignificant difference between males and females ($P = 0.150$, Figure 2). The alteration in *GSTM1* frequency among different age groups was statistically insignificant ($P = 0.698$) in both cases and controls (Figure 2).

With regard to leukemia subtype, out of the 50 cases of acute leukemia, there were 26 cases of AML and 24 cases of ALL. The frequency of *GSTM1* Null genotype was approximately expressed in 77% of AML cases and in 29% of the ALL. The difference was of statistical significance ($P = 0.0015$, OR = 0.124, 95% CI = 0.0348 to 0.439 (Figure 3).

Discussion

Glutathione s-transferase are family of phase II drug metabolize enzyme, involved in the metabolism of many xenobiotic, including environmental carcinogen and also play a role in modulating the induction of other enzyme and protein for cellular function.

GSTM1 in number of population has been reported to be associated with acute leukemia susceptibility. As known that the GST null genotype causes accumulation of DNA that may result in mutations in oncogenes or tumor suppressor gene that may increase susceptibility to cancer development as in case of leukemia.

In our study we concluded that the *GSTM1* null genotype is not significantly associated with acute leukemia ($P = 0.108$ (Figure 1). However, the frequency of *GSTM1* Null was approximately 2- fold to that of control (OR 1.92). No statistical differences were found, with regard to gender or different age groups (Figure 2 and 3).

Our findings are in agree with other studies in India, Turkey, and Jordan, which showed no significance association with acute leukemia, other studies in white American results showed no relation between childhood ALL and *GSTM1* null. Moreover, a study in Egypt demonstrated that *GSTM1* null may be considered as independent risk factors for AML.

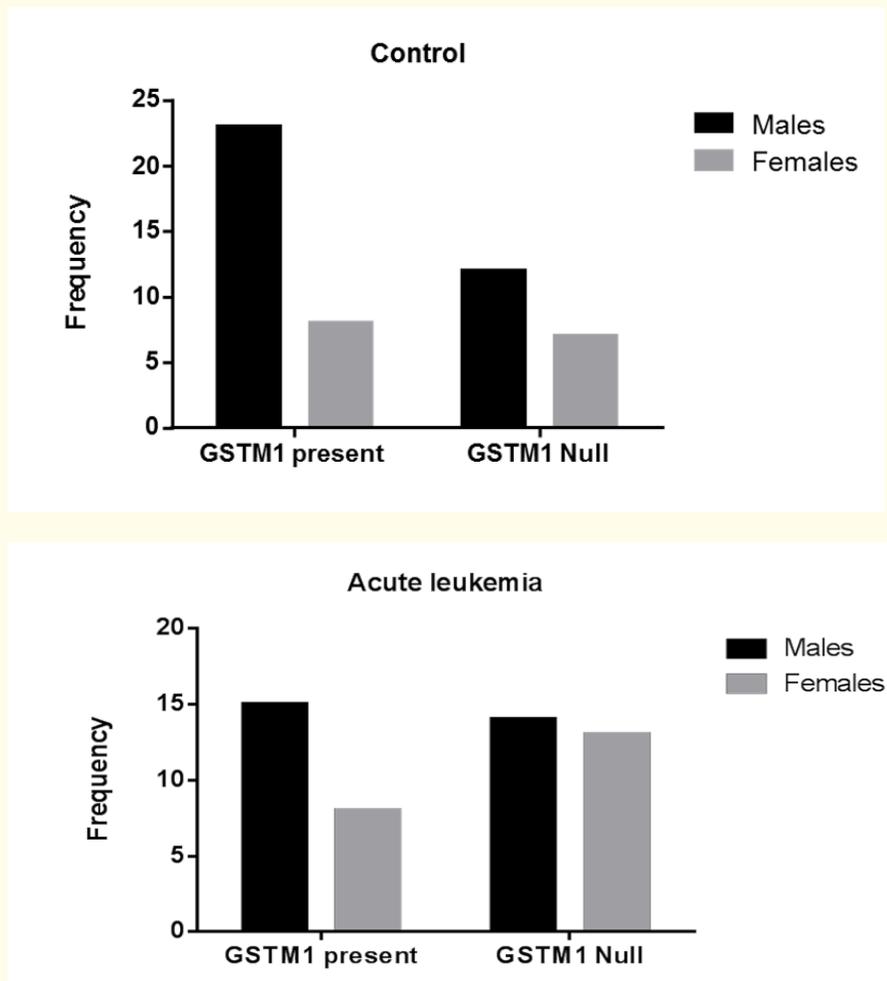


Figure 2: *GSTM1* polymorphism in males and females for cases and controls. The *GSTM1* Null is more frequent in females (13(62%)) in cases of acute leukemia, while less presented by in controls (7(47%)).

With regard to expression of *GSTM1* Null in different subtypes of acute leukemia, our data revealed that AML subtypes is more associated with the absence of the *GSTM1* compared to ALL subtype (Figure 4). These findings are in contrary with some authors who suggested that ALL subtype is more associated with GST polymorphisms.

Our findings are also inconsistent with the studies done in black Americans. Their findings have showed significant association between the *GSTM1* and acute lymphoblastic leukemia. In contrast, our current study which demonstrated a higher frequency of *GSTM1* null genotype expressed by the AML subtype.

The current study is supported by the research done by Zehra A., *et al.* which revealed that homozygous null polymorphism of *GSTM1* and *GSTT1* genes does not influence ALL susceptibility among adult patients. Cancer susceptibility associated with *GST* polymorphism varies with ethnic and geographic differences [29].

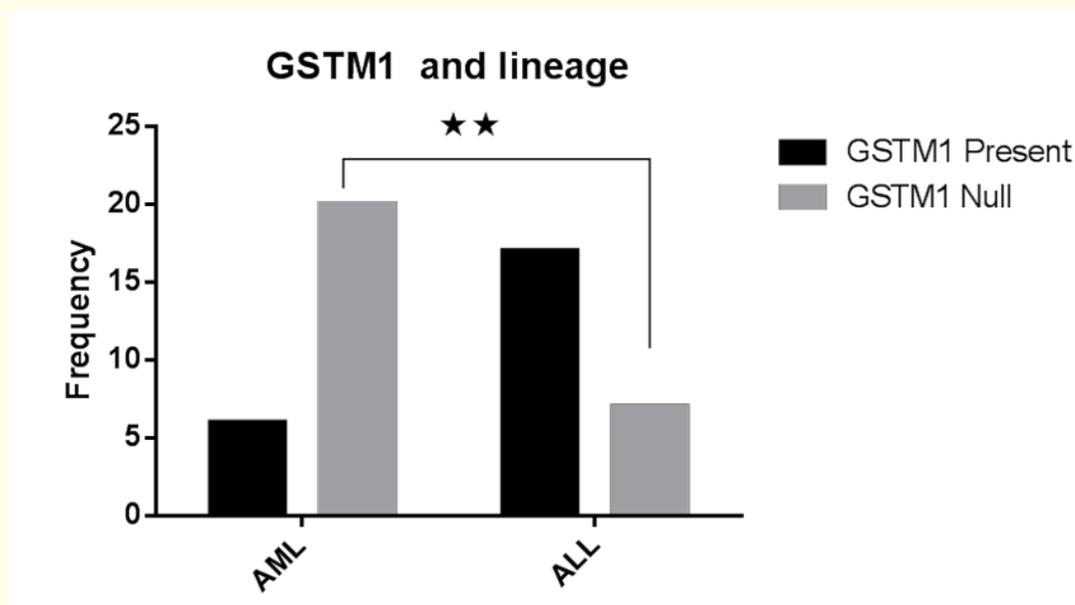


Figure 3: *GSTM1* genotype and leukemia lineage: The frequency of *GSTM1* Null and *GSTM1* present among ALL and ALL leukemia subtypes. *GSTM1* Null genotype is significantly higher in AML compared to ALL subtype ($P = 0.0015$, $OR = 0.124$, $95\%CI = 0.0348$ to 0.439).

Also our findings is supported by outcomes of the study done by Cheng H et.al; showed that EPHX1 expression is obviously associated with recurrence rate of acute myeloid leukemia and chemoresistance-promoting role of EPHX1, and the potential of targeting EPHX1 was proposed to counteract drug resistance in leukemia treatment [30].

This could be due to disease heterogeneity between different populations or because of the small sample size. The therefore further study with a larger sample size is needed for validation.

We also recommend to study the GST family members in different ethnic groups in Sudan and to include a larger sample size of acute leukemia. In addition, meta-analysis on relatively similar population may help to interpret and assess the statistical significance. So, the limitation of our study was the smaller sample size so we recommend conducting the same work with a greater sample size and include at least other GST family member such as *GSTT1* and *GSTP1*.

Conclusion

Our findings suggest that heritable *GSTM1* null might influence the risk of developing acute leukemia in Sudanese due to Both GST M1 (*GSTM1*) and GST theta 1 (*GSTT1*) genes have a "null" variant allele, in which the entire gene is absent.

Recommendation

Further studies with a larger sample size, to investigate diverse GST polymorphism in Sudanese patients with different types of leukemia.

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