

# Increased Risk of Acute Lymphoblastic Leukemia in Adult Patients with GSTM1 Null Genetic Polymorphism

Ezeldine K Abdalhabib<sup>1</sup>, Badr Alzahrani<sup>1</sup>, Fehaid Alanazi<sup>1</sup>, Abdulrahman Algarni<sup>2</sup>, Ibrahim Khider Ibrahim<sup>3</sup>, Hozifa A Mohamed<sup>4,5</sup>, Hassan A Hamali<sup>6</sup>, Abdullah A Mobarki<sup>6</sup>, Gasim Dobie<sup>6</sup>, Muhammad Saboor<sup>6,7</sup>

<sup>1</sup>Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Al-Qurayyat, Saudi Arabia; <sup>2</sup>Department of Medical Laboratory Technology, College of Applied Medical Sciences, Northern Borders University, Arar, Saudi Arabia; <sup>3</sup>Department of Hematology, Faculty of Medical Laboratory Sciences, Al Neelain University, Khartoum, Sudan; <sup>4</sup>Department of Molecular Biology, Faculty of Medical Laboratory Sciences, Al Neelain University, Khartoum, Sudan; <sup>5</sup>Department of Molecular Biology, Faculty of Medical Laboratory Sciences, Sudan International University, Khartoum, Sudan; <sup>6</sup>Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Jazan University, Jazan, Saudi Arabia; <sup>7</sup>Medical Research Center (MRC), Jazan University, Jazan, Saudi Arabia

Correspondence: Muhammad Saboor, Department of Medical Laboratory Technology, Faculty of Applied Medical Science, Jazan University, Jazan, Saudi Arabia, Tel +966 54 495 9029, Email msaboor@jazanu.edu.sa

**Purpose:** Glutathione S-transferases (GSTT1 and GSTM1) detoxify various endogenous and exogenous compounds and provide cytoprotective role against reactive species. This study aimed to assess the frequency of *GSTT1*, and *GSTM1* polymorphisms in newly diagnosed Sudanese adult patients with acute lymphoblastic leukemia (ALL) and to evaluate the association of these polymorphisms with age, gender and type of ALL.

**Patients and Methods:** This case-control study included 128 adult Sudanese, untreated newly diagnosed patients with ALL, aged 18 to 74 years and 128 age-gender matched healthy controls. Deletional polymorphisms of *GSTT1* and *GSTM1* genes were genotyped through a multiplex polymerase chain reaction (PCR) assay using  $\beta$ -globin gene as an internal positive control.

**Results:** The genotypic frequency of *GSTT1* null polymorphism was 22.7% in cases and 14.8% in controls (OR = 1.68, P = 0.111). Statistically significant differences were noted in the frequencies of *GSTM1* null polymorphism in cases and controls (OR = 3.7, P = <0.001). Combined *GSTT1* null and *GSTM1* null gene polymorphisms showed statistically significant difference in patients with ALL as compared to controls (OR = 6.5, CI 95% = 1.42–29.74, P < 0.001).

**Conclusion:** Irrespective of age at diagnosis, gender, and phenotype of ALL, GSTM1 null polymorphism either alone or in combination with GSTT1 null polymorphism poses significantly increased risk of developing ALL in adults.

**Keywords:** GSTT1, GSTM1, polymorphism, acute lymphoblastic leukemia

## Introduction

Acute lymphoblastic leukemia (ALL) is a lymphoproliferative neoplastic disorder characterized by malignant proliferation, impaired differentiation, maturation and accumulation of lymphoid progenitors in the bone marrow and their presence in the blood and/or extramedullary sites.<sup>1</sup> Approximately 80% of ALL cases are reported in children, although relatively uncommon it has devastating effects in adult patients. Because of the relapse, the cure rates range between 40–50% in adult patients with ALL and the 5-year overall survival is just 30–40%.<sup>1,2</sup> Ethnicity has also shown positive association with the incidence and outcome of ALL.<sup>3</sup> Although, the exact etiology of ALL is not well defined, certain genetic disorders (Down syndrome, Fanconi's anemia, Bloom syndrome, ataxia telangiectasia and Nijmegen breakdown syndrome), ionizing radiation, chemicals (pesticides, benzene), and viral infections (Epstein-Barr Virus and Human Immunodeficiency virus) have been proved to be the predisposing factors for the development of ALL. Additionally, somatic chromosomal aberrations including t(12;21) [ETV6-RUNX1], t(1;19) [TCF3-PBX1], t(9;22) [BCR-ABL1] are the hallmark of ALL.<sup>1</sup>

Hematopoietic precursor cells' DNA damages are instrumental for the development of leukemia. Amongst others, reactive species produced either endogenously or exogenously by environmentally encountered carcinogens can damage the DNA of hematopoietic progenitors.<sup>4</sup> Glutathione S-transferases (GTs) are oxidative stress Phase II detoxification enzymes, encoded by eight highly polymorphic genes. In addition to several functions, GTs play an instrumental role in the detoxification of various endogenous and exogenous compounds (carcinogens, chemotherapeutic drugs, and environmental pollutants) by catalyzing conjugation of glutathione (GSH) and protects the tissues from the toxic effects of reactive electrophiles.<sup>5–7</sup> Polymorphisms of the GTs genes including *GSTT1*, located on chromosome 1q13.3, and *GSTM1*, on chromosome 22q11.2, might encode loss-of-function enzymes compromising the activity of GTs leading to several types of malignancies including hematological neoplasms.<sup>4, 8–12</sup> Furthermore, administration of chemotherapeutic drugs in patients with malignancies could also develop secondary neoplasia due to the impaired detoxification process of GTs.<sup>12,13</sup>

Literature shows conflicting results of *GSTT1* and *GSTM1* polymorphisms and their association with the risk for developing ALL.<sup>4, 14–25</sup> *GSTM1* polymorphism has shown increased risk of developing ALL in children while *GSTT1* was found not to predispose to childhood ALL.<sup>26</sup> Additionally, patients with combined genotype (*GSTT1* null and *GSTM1* null) were found to be at slight increased risk of relapse.<sup>27</sup> In a meta-analysis of 30 published case control studies, significantly increased risk of ALL showed association with *GSTM1* and *GSTT1* null genotypes {pooled ORs 1.24 (95% CI 1.17–1.31) and 1.30 (95% CI 1.06–1.60), respectively}.<sup>28</sup> Several studies have evaluated the association of *GSTT1* and *GSTM1* polymorphisms as predisposing genetic risk factors for the development of chronic myeloid leukemia in Sudanese population.<sup>5,29,30</sup> However, data about these polymorphisms in patients with ALL is scarce in Sudanese. This study aimed to investigate *GSTT1*, and *GSTM1* polymorphisms in newly untreated diagnosed Sudanese adult patients with ALL and to evaluate the association of these polymorphisms with age, gender and phenotype of ALL.

## Materials and Methods

All study participants in this case–control study were Sudanese, and included 128 adult patients diagnosed with ALL, aged 18 to 74 years (75 males and 53 females) and 128 normal healthy controls (88 males and 40 females). Patients were recruited from the Radiation and Isotope Center in Khartoum (RICK) during December 2019 and June 2021, before starting the treatment. This study was approved by the ethical committee at Al-Neelain University in Khartoum, Sudan. In accordance with the Declaration of Helsinki, each participant provided written informed consent. There was no previous history or diagnosis of other malignancies among the patients enrolled in the study. All patients were diagnosed by hemato–oncologists through complete blood count, bone marrow examination, and flow cytometry. To represent the same age range and ethnic background as the patients, controls from the same geographic area were selected with no prior history or evidence of malignancy. A structured questionnaire was used to record clinical and demographic data. A total of three mL of EDTA anticoagulated venous blood samples was collected from the subjects for PCR analysis after establishing the diagnosis of ALL.

## DNA Extraction

Using a commercially available kit (QIAamp® DNA Mini kit; Qiagen GmbH, Hilden, Germany), DNA was isolated from peripheral blood samples according to the manufacturer's protocol. The quantity and quality of extracted DNA was verified using gene quant device (Amersham Biosciences – Biochrom LTD, Cambridge CB4, England). Until analysis, aliquots of the extracted DNA samples were stored at –20°C.

## Molecular Analysis

The genomic DNA was used for the analysis of *GSTT1* and *GSTM1* gene polymorphisms through multiplex polymerase chain reaction (PCR) assay using  $\beta$ -Globin gene as an internal positive control. PCR reaction was carried out utilizing a total volume of 25  $\mu$ L which was prepared by adding 100–150 ng of genomic DNA in a 10x PCR buffer mixture containing 0.5 units of Taq polymerase, 1.5  $\mu$ M MgCl<sub>2</sub>, and 200  $\mu$ M dNTPs. The specific primers used and PCR conditions were similar to those described by Agrawal et al.<sup>31</sup> An agarose gel electrophoresis was used to examine the banding patterns of the amplified products. A PCR product with 268 bp indicated successful amplification. Based on the

presence or absence of a band at 480 bp and 215 bp, *GSTT1* and *GSTM1* genotypes were identified respectively. This method does not distinguish heterozygous and homozygous null (*GSTT1* and *GSTM1*) genotypes.

## Statistical Analysis

The statistical analysis including descriptive statistics of mean, standard deviation, odds ratio (OR) with a confidence interval (CI) of 95% were performed using statistical package for social sciences (SPSS) for Windows (Chicago, IL, USA) version 23. The genotype distributions of patients and controls were compared using Pearson's chi-square tests. In addition, quantitative variables were also tested using an independent *t*-test. Statistical significance was determined by a *P* value less than 0.05.

## Results

This study evaluated the association of *GSTT1* and *GSTM1* genetic polymorphisms in newly diagnosed patients with ALL and normal healthy individuals. Demographic data ie, gender, age and type of ALL are depicted in Table 1. Male patients were 58.6% while female patients with ALL were 41.4%. Mean age of the patients and controls did not exhibit any statistically significance. A total of 80.5% patients had B-ALL while the rest had T-ALL.

Findings of this study show that *GSTT1* gene was present in 85.2% of the normal controls and 77.3% of the patients as shown in Table 2. The genotypic frequency of *GSTT1* null polymorphism was 22.7% in cases and 14.8% in controls (OR= 1.68, *P* = 0.111). Statistically significant differences were noted in the frequencies of *GSTM1* null polymorphism in cases and controls (OR= 3.7, *P* = <0.001) (Table 2).

Combination analysis of *GSTT1* and *GSTM1* polymorphisms showed statistically significant association with ALL. In healthy controls, the frequencies of the simultaneous presence of *GSTT1* and *GSTM1* genes were higher as compared to patients with ALL (*p*<0.001) as shown in Table 2. Additionally, significant difference was observed in controls as compared to patients with ALL in the frequencies when *GSTT1* gene was present and *GSTM1* was absent (OR= 2.9, *P* <0.001). Contrary to this finding, statistically no significant difference was observed when *GSTM1* gene was present and *GSTT1* was absent in controls as compared to patient group. Furthermore, both *GSTT1* null and *GSTM1* null genes polymorphisms showed statistically significant difference in patients with ALL as compared to controls (OR= 6.5, CI 95%= 1.42–29.74, *P* <0.001) (Table 2).

Table 3 shows the genotypic distribution of *GSTT1* and *GSTM1* polymorphisms in B-ALL. *GSTT1* polymorphism did not exhibit any association with B-ALL while *GSTM1* null genetic polymorphism showed positive association with B-ALL as shown in Table 3. Similarly, the combination analysis showed statistically significant association of *GSTT1* null and *GSTM1* null polymorphisms with B-ALL as compared to controls (Table 3).

**Table 1** Demographic Characteristics of the Studied Subjects

| Category         | Cases (n=128) | Controls (n=128) | (P-value) |
|------------------|---------------|------------------|-----------|
| Gender           |               |                  |           |
| Male n (%)       | 75 (58.6%)    | 88 (68.8%)       | 0.091     |
| Female n (%)     | 53 (41.4%)    | 40 (31.3%)       |           |
| Age              |               |                  |           |
| Mean ±SD (year)  | 45.05±14.1    | 44.37±9.7        | 0.651     |
| Range (year)     | 18 –74        | 24–58            |           |
| < mean age n (%) | 61 (47.7%)    | 53 (41.4%)       | 0.314     |
| > mean age n (%) | 67 (52.3%)    | 75 (58.6%)       |           |
| Immunophenotype  |               |                  |           |
| B-ALL n (%)      | 103 (80.5%)   | -                | -         |
| T-ALL n (%)      | 25 (19.5%)    | -                | -         |

**Table 2** Genotypes Distribution in the ALL Cases and Control Groups

| SNP                  | Genotype | ALL (N = 128) | Controls (N = 128) | Odds Ratio (95% CI)     | P-value |
|----------------------|----------|---------------|--------------------|-------------------------|---------|
| GSTT1                | Present  | 99 (77.3%)    | 109 (85.2%)        | 1.68 (0.8867 to 3.1848) | 0.111   |
|                      | Null     | 29 (22.7%)    | 19 (14.8%)         |                         |         |
| GSTM1                | Present  | 69 (53.9%)    | 104 (81.3%)        | 3.7 (2.1086 to 6.5110)  | <0.001  |
|                      | Null     | 59 (46.1%)    | 24 (18.8%)         |                         |         |
| Combination analysis |          |               |                    |                         |         |
| GSTT1                | GSTM1    |               |                    |                         |         |
| Present              | Present  | 53 (41.4%)    | 85 (66.4%)         | 2.8 (1.6828 to 4.6498)  | < 0.001 |
| Present              | Null     | 46 (35.9%)    | 22 (17.2%)         | 2.9 (1.6151 to 5.1745)  | < 0.001 |
| Null                 | Present  | 16 (12.5%)    | 16 (12.5%)         | 1.0 (0.4767 to 2.0976)  | 1.00    |
| Null                 | Null     | 13 (10.2%)    | 2 (1.7%)           | 6.5 (1.4282 to 29.7409) | 0.016   |

**Table 3** Genotypes Distribution in the B-ALL/T-ALL Cases and Control Groups

| SNP                  | Genotype | B-ALL<br>(N = 103) | Controls<br>(N = 128) | Odds Ratio<br>(95% CI)     | P-value | T-ALL<br>(N = 25) | Controls<br>(N = 128) | Odds Ratio<br>(95% CI)      | P-value |
|----------------------|----------|--------------------|-----------------------|----------------------------|---------|-------------------|-----------------------|-----------------------------|---------|
| GSTT1                | Present  | 80 (77.7%)         | 109 (85.2%)           | 1.6 (0.8417<br>to 3.2318)  | 0.145   | 19 (76%)          | 109 (85.2%)           | 1.8 (0.6409 to<br>5.1213)   | 0.262   |
|                      | Null     | 23 (22.3%)         | 19 (14.8%)            |                            |         | 6 (24%)           | 19 (14.8%)            |                             |         |
| GSTM1                | Present  | 59 (57.3%)         | 104 (81.3%)           | 3.2 (1.7894<br>to 5.8364)  | <0.001  | 10 (40%)          | 104 (81.3%)           | 6.5 (2.6033 to<br>16.2295)  | <0.001  |
|                      | Null     | 44 (42.7%)         | 24 (18.8%)            |                            |         | 15 (60%)          | 24 (18.8%)            |                             |         |
| Combination analysis |          |                    |                       |                            |         |                   |                       |                             |         |
| GSTT1                | GSTM1    |                    |                       |                            |         |                   |                       |                             |         |
| Present              | Present  | 45 (44.7%)         | 85 (66.4%)            | 2.5 (1.4923<br>to 4.3499)  | < 0.001 | 8 (32%)           | 85 (66.4%)            | 4.2 (1.6792 to<br>10.5079)  | 0.002   |
| Present              | Null     | 36 (35.9%)         | 22 (17.2%)            | 2.6 (1.4034<br>to 4.7756)  | 0.002   | 10 (40%)          | 22 (17.2%)            | 3.2 (1.2768 to<br>8.0808)   | 0.013   |
| Null                 | Present  | 14 (13.6%)         | 16 (12.5%)            | 1.1 (0.5101<br>to 2.3767)  | 0.806   | 2 (8%)            | 16 (12.5%)            | 0.61 (0.1309<br>to 2.8307)  | 0.527   |
| Null                 | Null     | 8 (7.8%)           | 2 (1.7%)              | 5.3 (1.1013<br>to 25.5576) | 0.038   | 5 (20%)           | 2 (1.7%)              | 15.8 (2.8590<br>to 86.7654) | 0.001   |

*GSTM1* null polymorphism was more prevalent in patients with T-ALL as compared to normal control (60% vs 18.8% respectively) while *GSTT1* did not show any difference in T-ALL and controls as shown in Table 3. Similar to B-ALL, T-ALL also showed statistically significant difference in *GSTT1/GSTM1* (present), *GSTT1* present/*GSTM1* null polymorphism and *GSTT1* null/*GSTM1* null polymorphisms in controls and patient group (Table 3). However, when *GSTM1* gene was present and *GSTT1* was absent (*GSTT1* null) no association was observed in patient group as compared to controls (OR= 0.61, CI 95%= 0.13–2.83, P=0.527). Further analysis of the results showed that there was no association between the *GSTT1* and *GSTM1* polymorphisms with age (less than mean Vs more than mean), gender and phenotype of ALL as shown in Table 4.

## Discussion

Glutathione S-transferases are pivotal in maintaining cellular homeostasis by providing cytoprotection from environmental carcinogens, toxins, byproducts of oxidative stress and drugs. Additionally, cell signaling, post-translational

**Table 4** Distribution of the Studied Polymorphisms Among ALL Patients According to Age Group, Gender, and Origin of Disease

| Parameter            | Category     | GSTT1         |      | GSTM1         |      |
|----------------------|--------------|---------------|------|---------------|------|
|                      |              | Present       | Null | Present       | Null |
| Age groups           | < mean years | 47            | 14   | 37            | 24   |
|                      | > mean years | 52            | 15   | 32            | 35   |
| Chi square (P-value) |              | 0.006 (0.939) |      | 2.14 (0.144)  |      |
| Gender               | Male         | 61            | 14   | 40            | 35   |
|                      | Female       | 38            | 15   | 29            | 24   |
| Chi square (P-value) |              | 1.65 (0.199)  |      | 0.024 (0.877) |      |
| Origin               | B-ALL        | 80            | 23   | 59            | 44   |
|                      | T-ALL        | 19            | 6    | 10            | 15   |
| Chi square (P-value) |              | 0.032 (0.857) |      | 2.42 (0.119)  |      |

modifications, cell proliferation, differentiation, cellular apoptosis, anti-inflammatory, proinflammatory, prevention of DNA damages, and resistance to chemotherapeutic drugs are other non-enzymatic function of GTs.<sup>12,32</sup> *GSTT1* and *GSTM1* genetic polymorphisms are associated with loss-of-function mutations that leads to the complete loss of activities of these enzymes.<sup>16</sup> In the present study, *GSTT1* and *GSTM1* genetic polymorphisms were investigated in newly diagnosed adult patients with ALL in Sudanese population. Several studies have investigated the association of *GSTT1* and *GSTM1* deletions in patients with acute leukemia with conflicting results. This risk has been evaluated in a limited number of studies in adult ALL patients, and largely focused on children with ALL due to a higher incidence occurring in children as compared to adults.

In this study, the most prevalent type of ALL was B-ALL (80.5% of the cases) which is similar to the reported rates.<sup>3</sup> In the current study, although the frequency of *GSTT1* null polymorphism was higher in patients as compared with controls (22.7% Vs 14.8%); this difference was statistically insignificant ( $p > 0.05$ ). Furthermore, no association between *GSTT1* polymorphism and ALL susceptibility was found. In comparison to *GSTT1* polymorphism, *GSTM1* null polymorphism was highly prevalent in patients with ALL as compared to controls (46.1% vs 18.8%). It is evident that patients with *GSTM1* null polymorphism were at 3.7-folds increased risk of developing ALL. Literature shows contradictory reports regarding the frequency of *GSTT1* null and *GSTM1* null phenotypes and its association with ALL; for a quick review please refer to Table 5. A study conducted in Pakistan on adults reports no association of either *GSTM1*

**Table 5** Association of *GSTT1* and *GSTM1* Polymorphisms in Patients with ALL Reported in Different Studies

| Association of GTs Polymorphism(s) with ALL |                   |                                                  | Reference |
|---------------------------------------------|-------------------|--------------------------------------------------|-----------|
| <i>GSTT1</i> Null                           | <i>GSTM1</i> Null | Combined <i>GSTT1</i> Null and <i>GSTM1</i> Null |           |
| No                                          | No                | No                                               | [32]      |
| No                                          | No                | Yes                                              | [20]      |
| No                                          | Yes               | Not analyzed                                     | [18]      |
| No                                          | Yes               | Not analyzed                                     | [35]      |
| Yes                                         | No                | Yes                                              | [16]      |
| Yes                                         | Yes               | Yes                                              | [24]      |
| Yes                                         | Yes               | Yes                                              | [25]      |

null polymorphism or *GSTT1* gene deletion and ALL susceptibility among adult patients.<sup>33</sup> Another study on children with ALL reported low risk for leukemia in *GSTM1* null polymorphism while *GSTT1* polymorphism did not exhibit any increased risk of ALL. This was presumed that these differences in the susceptibility to ALL and *GSTT1* and *GSTM1* null phenotypes could be attributed to ethnic differences, age, treatment and follow up duration.<sup>34</sup>

The combined effect of *GSTT1* and *GSTM1* genetic polymorphisms was evaluated with a presumption that it may have significant association with the risk of ALL as compared to single genetic variant. When combination analysis was carried out it was noted that the frequencies of *GSTT1* and *GSTM1* genes were markedly lower in the patient group as compared to controls (OR= 2.8). This finding signifies the pathognomonic role of these genes in neoplastic disorders. It is interesting to note that when *GSTM1* null polymorphisms was detected either alone or along with *GSTT1* null polymorphisms, significant association was observed with ALL susceptibility. Patients with *GSTT1* null and *GSTM1* null polymorphisms were 6.5 times more likely to develop ALL as compared to normal individuals (Table 2). Similar findings were also noted when the prevalence of *GSTT1* and *GSTM1* was analyzed in the subtype of ALL ie, B – and T – cell type. *GSTT1* null phenotype did not show any statistical difference in cases as compared to controls while patients with B–ALL were more prone (3.2 times) to develop ALL with *GSTM1* null polymorphism. Furthermore, in B-ALL patients with combined *GSTT1* null and *GSTM1* null polymorphisms were 5.3 times risk of development of ALL. In T–ALL, identical findings were noted (Table 3). As the role of GTs in the detoxification process is well-established, the null polymorphisms of *GSTT1* and *GSTM1* could be linked with increased risk of leukemogenesis due to lack of the enzymatic activity of both these genes disposing DNA to oxidative damages. Significantly more than 3–times increased risk of ALL in patients has been reported in *GSTT1* null and *GSTM1* null genotypes.<sup>11,16,24</sup> Similarly, more than 4–folds increased risk of ALL with combined *GSTT1* null and *GSTM1* null polymorphisms has also been reported by Baba et al.<sup>16</sup>

Additionally, association of *GSTT1* and *GSTM1* polymorphisms with age, gender and subtype of ALL was also assessed in the current study. Patients with more than mean age (45.05±14.1) presented no risk of ALL with *GSTT1* and *GSTM1* polymorphisms (p =0.939) as compared to patients with age less than the mean. Similarly, insignificant difference was also observed in relation to gender (p=0.199) and subtype of ALL (p=0.857) and *GSTT1* and *GSTM1* polymorphisms. These findings are similar to other reports.<sup>17,24,35</sup> A study by Dunna et al<sup>24</sup> also reported no association of gender with increased risk of ALL, as with age. Furthermore, another study has also reported no association of increased risk of ALL with age at diagnosis, gender, total leukocyte count, B– or T– cell type, cytogenetic abducts, or treatment outcome.<sup>22</sup>

It is a well-known fact that GTs demonstrate tissue specificity in humans, ie, GSTA are exclusively expressed in liver and kidneys, GSTM are found in brain, lymphocytes, muscles and testes, and GSTP are expressed in spleen, kidneys hepatic ducts, and placenta. It has been found that GSTM1 are found in predominantly in lymphoblasts while GSTT1 are expressed in erythroid precursors.<sup>36</sup> This could be the possible explanation of the increased risk for the development of ALL in individuals with *GSTM1* null polymorphism.

In conclusion, irrespective of age at diagnosis, gender, and phenotype of ALL; *GSTM1* null polymorphism either alone or in combination with *GSTT1* null polymorphism significantly increases the probability of developing ALL in adult.

## Acknowledgments

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this work through the grant number “375213500”. The authors would like to extend their sincere appreciation to the central Laboratory at Jouf University for support this study.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J.* 2017;7(6):e577. doi:10.1038/bcj.2017.53

2. Paul S, Kantarjian H, Jabbour EJ. Adult acute lymphoblastic leukemia. *Mayo Clin Proc.* 2016;91(11):1645–1666. doi:10.1016/j.mayocp.2016.09.010
3. Xu K, Feng Q, Wiemels JL, de Smith AJ. Disparities in acute lymphoblastic leukemia risk and survival across the lifespan in the United States of America. *J Transl Genet Genomics.* 2021;218–239. doi:10.20517/jtgg.2021.20
4. Suneetha KJ, Nancy KN, Rajalekshmy KR, Sagar TG, Rajkumar T. Role of GSTM1 (Present/Null) and GSTP1 (Ile105Val) polymorphisms in susceptibility to acute lymphoblastic leukemia among the South Indian population. *Asian Pacific J Cancer Prev.* 2008;9(4):733–736.
5. Idris HME, Elderderly AY, Khalil HB, Mills J. Genetic polymorphism of GSTP1, GSTM1 and GSTT1 genes and susceptibility to chronic myeloid leukaemia. *Asian Pacific J Cancer Prev.* 2020;21(2):499–503. doi:10.31557/APJCP.2020.21.2.499
6. Cummins I, Dixon DP, Freitag-Pohl S, Skipsey M, Edwards R. Multiple roles for plant glutathione transferases in xenobiotic detoxification. *Drug Metab Rev.* 2011;43(2):266–280. doi:10.3109/03602532.2011.552910
7. Board PG, Menon D. Structure, function and disease relevance of Omega-class glutathione transferases. *Arch Toxicol.* 2016;90(5):1049–1067. doi:10.1007/s00204-016-1691-1
8. Louie SM, Grossman EA, Crawford LA, et al. GSTP1 is a driver of triple-negative breast cancer cell metabolism and pathogenicity. *Cell Chem Biol.* 2016;23(5):567–578. doi:10.1016/j.chembiol.2016.03.017
9. Duvoix A, Delhalle S, Blasius R, et al. Effect of chemopreventive agents on glutathione S-transferase P1-1 gene expression mechanisms via activating protein 1 and nuclear factor kappaB inhibition. *Biochem Pharmacol.* 2004;68(6):1101–1111. doi:10.1016/j.bcp.2004.05.032
10. Tang ZH, Zhang C, Cheng P, et al. Glutathione-S-transferase polymorphisms (GSTM1, GSTT1 and GSTP1) and acute leukemia risk in Asians: a meta-analysis. *Asian Pacific J Cancer Prev.* 2014;15(5):2075–2081. doi:10.7314/APJCP.2014.15.5.2075
11. Moulik NR, Parveen F, Kumar A, Agrawal S. Glutathione-S-transferase polymorphism and acute lymphoblastic leukemia (ALL) in north Indian children: a case-control study and meta-analysis. *J Hum Genet.* 2014;59(9):529–535. doi:10.1038/jhg.2014.66
12. Cerliani MB, Pavicic W, Gili JA, Klein G, Saba S, Richard S. Cigarette smoking, dietary habits and genetic polymorphisms in GSTT1, GSTM1 and CYP1A1 metabolic genes: a case-control study in oncohematological diseases. *World J Clin Oncol.* 2016;7(5):395–405. doi:10.5306/wjco.v7.i5.395
13. Mossallam GI, Abdel Hamid TM, Samra MA. Glutathione S-transferase GSTM1 and GSTT1 polymorphisms in adult acute myeloid leukemia; its impact on toxicity and response to chemotherapy. *J Egypt Natl Canc Inst.* 2006;18(3):264–273.
14. Alves S, Amorim A, Ferreira F, Norton L, Prata MJ. The GSTM1 and GSTT1 genetic polymorphisms and susceptibility to acute lymphoblastic leukemia in children from north Portugal. *Leukemia.* 2002;16(8):1565–1567. doi:10.1038/sj.leu.2402543
15. Joseph T, Kusumakumary P, Chacko P, Abraham A, Pillai MR. Genetic polymorphism of CYP1A1, CYP2D6, GSTM1 and GSTT1 and susceptibility to acute lymphoblastic leukaemia in Indian children. *Pediatr Blood Cancer.* 2004;43(5):560–567. doi:10.1002/pbc.20074
16. Baba SM, Pandith AA, Shah ZA, et al. GSTT1null and rs156697 polymorphism in GSTO2 influence the risk and therapeutic outcome of B-acute lymphoblastic leukemia patients. *Front Oncol.* 2021;11:1–10. doi:10.3389/fonc.2021.714421
17. Bolufer P, Collado M, Barragán E, et al. The potential effect of gender in combination with common genetic polymorphisms of drug-metabolizing enzymes on the risk of developing acute leukemia. *Haematologica.* 2007;92(3):308–314. doi:10.3324/haematol.10752
18. Suneetha KJ, Nirmala Nancy K, Rajalekshmy KR, Rama R, Sagar TG, Rajkumar T. Role of glutathione-s-transferase and CYP1A1FNx012A polymorphisms in the therapy outcome of south Indian acute lymphoblastic leukemia patients. *Indian J Med Paediatr Oncol.* 2011;32(1):25–29. doi:10.4103/0971-5851.81886
19. Krajcinovic M, Labuda D, Richer C, Karimi S, Sinnett D. Susceptibility to childhood acute lymphoblastic leukemia: influence of CYP1A1, CYP2D6, GSTM1, and GSTT1 genetic polymorphisms. *Blood.* 1999;93(5):1496–1501. doi:10.1182/blood.V93.5.1496
20. Chen HC, Hu WX, Liu QX, et al. Genetic polymorphisms of metabolic enzymes CYP1A1, CYP2D6, GSTM1 and GSTT1 and leukemia susceptibility. *Eur J Cancer Prev.* 2008;17(3):251–258. doi:10.1097/CEJ.0b013e3282b72093
21. Pakakasama S, Mukda E, Sasanakul W, et al. Polymorphisms of drug-metabolizing enzymes and risk of childhood acute lymphoblastic leukemia. *Am J Hematol.* 2005;79(3):202–205. doi:10.1002/ajh.20404
22. Davies SM, Bhatia S, Ross JA, et al. Glutathione S-transferase genotypes, genetic susceptibility, and outcome of therapy in childhood acute lymphoblastic leukemia. *Blood.* 2002;100(1):67–71. doi:10.1182/blood.v100.1.67
23. Haranatha RP, Kaiser J. Polymorphisms in the GST (M1 and T1) gene and their possible association with susceptibility to childhood acute lymphocytic leukemia in Indian population. *African J Biotechnol.* 2006;5(16):1454–1456. doi:10.4314/ajb.v5i16.43138
24. Dunna NR, Vure S, Sailaja K, et al. Deletion of GSTM1 and T1 genes as a risk factor for development of acute leukemia. *Asian Pacific J Cancer Prev.* 2013;14(4):2221–2224. doi:10.7314/APJCP.2013.14.4.2221
25. Rollinson S, Roddam P, Kane E, et al. Polymorphic variation within the glutathione S-transferase genes and risk of adult acute leukaemia. *Carcinogenesis.* 2000;21(1):43–47. doi:10.1093/carcin/21.1.43
26. Kampouraki E, Goulielmos GN, Stiakaki E. Understanding the role of genetics in childhood acute lymphoblastic leukemia (Review). *World Acad Sci J.* 2020;2(5):1–10. doi:10.3892/wasj.2020.54
27. Leonardi DB, Abbate M, Riccheri MC, et al. Improving risk stratification of patients with childhood acute lymphoblastic leukemia: glutathione-S-Transferases polymorphisms are associated with increased risk of relapse. *Oncotarget.* 2017;8(1):110–117. doi:10.18632/oncotarget.8606
28. Ye Z, Song H. Glutathione s-transferase polymorphisms (GSTM1, GSTP1 and GSTT1) and the risk of acute leukaemia: a systematic review and meta-analysis. *Eur J Cancer.* 2005;41(7):980–989. doi:10.1016/j.ejca.2005.01.014
29. Muddathir ARM, Abdallah EI, Khabour OF, Abdelgader RE, Elgari MM. Age- and gender-independent association of glutathione S-transferase null polymorphisms with chronic myeloid leukemia. *Bosn J Basic Med Sci.* 2019;19(4):350–354. doi:10.17305/bjbm.2019.4176
30. Abdalhabib EK, Jackson DE, Alzahrani B, et al. Combined GSTT1 null, GSTM1 null and XPD Lys/Lys genetic polymorphisms and their association with increased risk of chronic myeloid leukemia. *Pharmgenomics Pers Med.* 2021;14:1661–1667. doi:10.2147/PGPM.S342625
31. Agrawal D, Gupta S, Agarwal D, Gupta OP, Agarwal M. Role of GSTM1 and GSTT1 polymorphism: susceptibility to oral submucous fibrosis in the north Indian population. *Oncology.* 2011;79(3–4):181–186. doi:10.1159/000318533
32. Singh RR, Reindl KM. Glutathione S-transferases in cancer. *Antioxidants.* 2021;10(701):1–25. doi:10.3390/antiox10050701
33. Zehra A, Zehra S, Ismail M, Azhar A. Glutathione S-transferase M1 and T1 gene deletions and susceptibility to Acute Lymphoblastic Leukemia (All) in adults. *Pakistan J Med Sci.* 2018;34(3):666–670. doi:10.12669/pjms.343.14911

34. Weich N, Nuñez MC, Galimberti G, et al. Polymorphic variants of gstm1, gstt1, and gstp1 genes in childhood acute leukemias: a preliminary study in Argentina. *Hematology*. 2015;20(9):511–516. doi:10.1179/1607845415Y.0000000007
35. Bolufer P, Barragan E, Collado M, Cervera J, López JA, Sanz MA. Influence of genetic polymorphisms on the risk of developing leukemia and on disease progression. *Leuk Res*. 2006;30(12):1471–1491. doi:10.1016/j.leukres.2006.01.016
36. Wang L, Groves MJ, Hepburn MD, Bowen DT. Glutathione S-transferase enzyme expression in hematopoietic cell lines implies a differential protective role for T1 and A1 isoenzymes in erythroid and for M1 in lymphoid lineages. *Haematologica*. 2000;85(6):573–579.

## Pharmacogenomics and Personalized Medicine

Dovepress

### Publish your work in this journal

Pharmacogenomics and Personalized Medicine is an international, peer-reviewed, open access journal characterizing the influence of genotype on pharmacology leading to the development of personalized treatment programs and individualized drug selection for improved safety, efficacy and sustainability. This journal is indexed on the American Chemical Society's Chemical Abstracts Service (CAS). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/pharmacogenomics-and-personalized-medicine-journal>