

Original Article

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Role of Glutathione S-transferase (GSTM1, GSTT1) and CYP1A1 (cytochrome p450) Gene Polymorphisms in Susceptibility to Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia (AML) may originate from the combination of genetic susceptibility factors and environmental exposure. The aim of this study was to investigate the association of *GSTM1* and *GSTT1* null genotypes and *CYP1A1**2A allele with susceptibility to AML in an Iranian population.

Method: In this case-control study, 200 patients with AML and 200 normal individuals as controls were included. *GSTM1* and *GSTT1* null genotypes were amplified using multiplex PCR and *CYP1A1**2A polymorphisms were genotyped by PCR-RFLP.

Result: The frequency of *GSTM1* null genotype was significantly higher in the control group compared to the case group. The frequency of *GSTT1* null genotype was significantly lower in the controls. No association was observed between the studied *CYP1A1**2A variant and the risk of acute myeloid leukemia. The combination of *GSTT1* null genotype and *CYP1A1**2A AA and AC alleles further increased the risk of AML.

Conclusion: *GSTT1* null genotype can increase the risk of AML, particularly when combined with *CYP1A1**2A allele. *GSTM1* null genotype can also play a protective role and reduce the risk of AML. However, further studies are required on a larger number of patients.

Keywords: *GSTT1*, *GSTM1*, *CYP1A1*, AML

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Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and the cancer of the myeloid line of blood cells, determined by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.¹ The incidence of AML increases with age, with the median age at diagnosis being 63 years. The French-American-British (FAB) classification system divides AML into eight subtypes, M0 to M7, based on the type of cell from which the leukemia develops and the leukemia's degree of maturity.²

Since this classification system may lack several factors which are important in the treatment and prognosis of the disease such as molecular genetics and therapy related leukemia, WHO has also developed a modern classification of AML.³ For the classification of risk in AML, molecular and cytogenetic findings have been used. A good prognosis is considered for acute promyelocytic leukemia with t(15;17) and inv(16)/t(16;16) or t(8;21) with either NPM1 or biallelic CEBPA mutation. In contrast, deletion of chromosomes 5 or 7, FLT3 ITD changes, monosomal or complex karyotypes, and certain other specific chromosomal rearrangements result in poor prognosis. Normal cytogenetics, isolated +8 and t(9;11) result in intermediate prognosis.⁴

Xenobiotics are foreign chemical substances in the biological system. They include natural compounds, environmental agents, carcinogens, and drugs.⁵ More than 30 different enzymes exist at cellular level, characterized by polymorphic changes modulating their efficacy and inducibility. Any variation in the activity of these enzymes would result in an altered susceptibility to cancer. The association between these polymorphic variations and hematopoietic malignancies has also been examined with contradictory results. The combination of genetic susceptibility and environmental exposure plays a role in the etiology of AML.⁶ DNA damage in the hematopoietic precursor cells is necessary for the development of leukemia, and the body has mechanisms to prevent and repair the DNA damage.⁷ Many

genetic polymorphisms have been reported for *CYP* and *GST* genes, indicating a loss of functional protein or causing either increased or reduced enzyme activity.⁸ These polymorphisms may alter the ability of enzymes to metabolize the chemical carcinogens and mutagens.⁹ Thus, there may be an association between polymorphisms in genes encoding for xenobiotic metabolizing enzymes and susceptibility to cancer.

CYP1A1 belongs to the cytochrome P450 family and is located on chromosome 15q22-24.¹⁰ *CYP1A1* is the phase 1 enzyme involved in the bio activation of several chemical carcinogens, including cytotoxic drugs. *CYP* enzyme variants convert pro carcinogens into DNA-reactive electrophilic forms.¹¹ The T6235C mutation (m1) is located at 1194 bp downstream of exon 7, creating a new MSP1 cleavage site (MSP1 polymorphism in the 3'-flanking region).¹² The A4889G mutation (m2) results in the replacement of Ile by Val at residue 462 in exon 7 (*CYP1A1*2B* allele).¹³ The T5639C mutation (m3) in the 3'-intron region and the C4887A mutation (m4) result in the replacement of Thr by Asn in codon 461, near the site of the A4889G mutation (*CYP1A1*4* allele).¹⁴ Glutathione S-transferases (*GSTs*) belong to the group phase II enzymes, converting the activated chemicals or drugs into non-reactive and water-soluble products.¹⁵ Although polymorphic loci have been identified in each of the four classes of *GST* gene families, most of the attention regarding the possible consequences of *GST* polymorphism has been paid to the polymorphisms at the *GSTM1* gene located on chromosome 1p13.3 and *GSTT1* gene located on chromosome 22q11.2.¹⁶

Although a few studies have shown the significant association of the *GST* and *CYP1A1*2A* polymorphisms with acute myeloid leukemia, others have shown conflicting results.^{11,17,18} This could be due to the differences in population size, genetic susceptibility, environmental exposures, ethnicity, diet, gender and the statistical tests used for analyses.¹⁹

Homozygous deletions in *GSTT1* and *GSTM1* that result in null genotypes and a complete loss were found to be associated with an increased

risk of acute leukemia,^{20,21} particularly when *GSTT1* homozygous deletions is accompanied with polymorphisms of phase I reaction enzymes and prolonged exposure to external carcinogens.

Due to the controversy in different studies, the present study was conducted to investigate the association of *GSTM1* and *GSTT1* null genotypes and *CYP1A1*2A* allele with the susceptibility to AML in an Iranian population.

Materials and Methods

Cases and Controls

In this case-control study, our study population consisted of 200 patients diagnosed with AML (102 females, 98 males, with a mean age of 30.04±10.09 years) diagnosed in the Division of Hematology-Oncology of Shariati Hospital, Tehran, Iran. The diagnosis was based on the criteria of FAB and WHO based on the clinical picture, cell morphology and cytochemical and molecular studies as well as immunophenotypic analysis. In terms of therapy, in general, AML is divided into M3 and non-M3 AML. In this study, FAB classification was employed to easily interpret the results obtained for the above-mentioned gene polymorphisms, and the association between the results and AML subtypes.

The control group consisted of 200 age- and sex-matched unrelated healthy volunteers without a medical history of cancer or other chronic diseases (94 females, 106 males, with a mean age of 32.91± 10.75 years). The Ethical Committee of Zanjan University of Medical Sciences

approved the study (Ethics code: A-11-190-1), and written informed consent was obtained from all the patients and controls, all of whom were Iranian.

DNA isolation

5 mL venous blood samples were collected from all the patients and controls in EDTA anticoagulant tubes. Genomic DNA was extracted from whole blood using BIORAN AccuPrep Genomic DNA Extraction kit (Germany). Isolated DNA was stored at -20 °C until use.

GSTM1 and *GSTT1* polymorphisms

The polymorphic deletion of the *GSTM1* and *GSTT1* genes were genotyped using the multiplex PCR. The primers used for *GSTT1* and *GSTM1* amplification were: F-5'- GAA CTC CCT GAA AAG CTA AAG C -3', R-5'- GTT GGG CTC AAA TAT ACG GTG G -3' and F-5'- TTC CTT ACT GGT CCT CAC ATC TC -3', and R-5'- TCA CCG GAT CAT GGC CAG CA -3', respectively. A part of the b-globin gene was amplified as internal control by use of primers F-5'- GAA GAG CCA AGG ACA GGT AC -3' and R-5'- CCA CTT CAT CCA CGT TCA CC -3'.¹⁸ PCR was performed in 25 µL containing 100 ng of genomic DNA, 1 µL of each primer, 12/5 µL of RedMix (Taq DNA polymerase), and 4/5 µL of dH₂O. In the thermo cycling procedure, initial denaturation at 94 °C for 4 minutes was followed by 35 cycles of 1 minute at 94 °C, 45 seconds at 58 °C, 1 minute at 72 °C, and the final

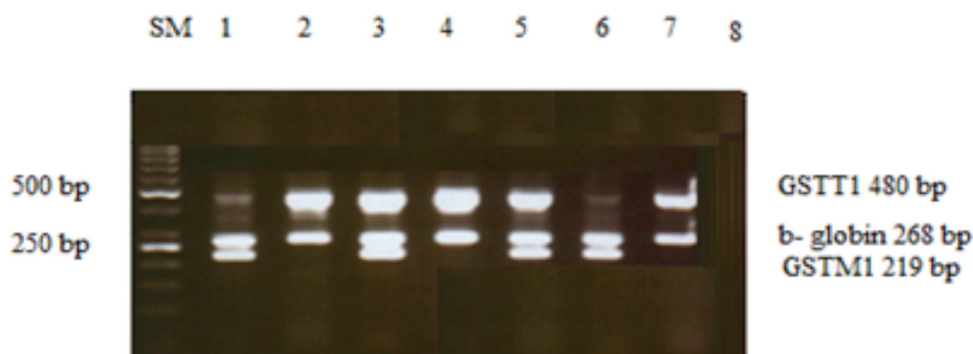


Figure 1. *GSTT1* and *GSTM1* gene polymorphism in AML and control group.

SM: molecular marker (100 bp ladder)

Lane 1, 6: represent the *GSTT1* null genotype

Table 1. Distribution of age and sex in AML and Controls

Variable	AML	Control	OR(95%CI)	P-value
Age	30/04±10/09	32/91±10/75	(0.955-0.993)	0.008
Sex	n(%)	(%)n		
Male	98(49%)	106(53%)	(0.623-1.366)	0.689
Female	102(51%)	94(47%)		

extension was 5 minutes at 72 °C. Genotyping of the genes (null genotypes) was revealed by the absence of the 480 bp in *GSTT1* and 219 bp in *GSTM1* PCR products, respectively, using the b-globin amplification (268 bp) as an internal control. PCR products related to the genotyping of polymorphisms were visualized by 2% agarose gel electrophoresis with GelRed. The absence of b-globin amplification indicated a failure of the PCR reaction.

*CYP1A1*2A* polymorphism

The *CYP1A1*2A* mutation was characterized by the PCR-RFLP approach. The employed primer pairs were F-5'- GGCTGAGCAATCTGACCCTA -3' R-5'-TAGGAGTCTTGTCTCATGCCT-3'.¹⁸ The PCR conditions for *CYP1A1*2A* polymorphism were: initial denaturation at 94 °C for 3 minutes, followed by 35 cycles of 45 seconds at 94 °C, 1 minute at 63 °C, 1 minute at 72 °C and a final extension of 5 minutes at 72 °C.

The 899-bp PCR product was digested with 1

U of *MspI* (MBI Fermentas) for 3 hr at 37°C, resulting in smaller fragments (693 and 206 bp) in case of mutation.²⁷ The *MspI* restriction site polymorphism resulted in three genotypes: a predominant homozygous m1 allele without the *MspI* site (type A, TT), the heterozygote (type B, TC) and a homozygous rare with the *MspI* site (type C, CC).²¹ Genotypes were analyzed by electrophoresis on a 2% agarose gel.

Statistical Analysis

The statistical significance of the differences in the frequency of genotypes was assessed using a two-sided Fisher's exact test ($P < 0.05$ was assumed to be statistically significant), and odds ratios (ORs) were calculated along with their 95% confidence intervals (CI) on the SPSS statistical package (version 16.0).

Results

The age and sex distribution of AML patients

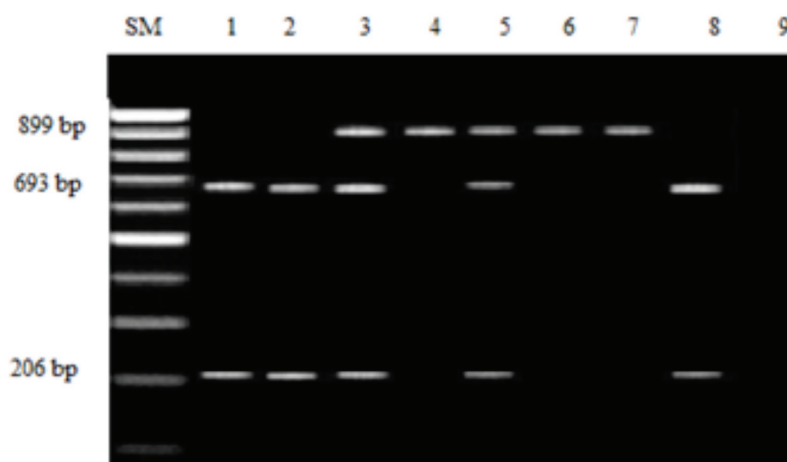


Figure 2. *CYP1A1*A2* gene polymorphism in AML and control groups.

SM: molecular marker (100 bp ladder)
Lane 1, 2, 8: represent the CC genotype

Table 2. FAB subtypes and frequency of the *GSTM1*

Subtypes	null genotype	present genotype
M0,1,3,5,6	8 (10.5%)	15 (12.2%)
M2	20 (26.3%)	30 (24.2%)
M4	14 (18.4%)	20 (16.1%)
*AML	34 (44.7%)	59 (47.5%)

P=0.93, *unclassified FAB AML

and normal people is shown in table 1. There was a significant statistical difference in the age distribution between normal controls and AML patients, but the sex distribution was not statistically significant.

Data of FAB subtypes were available for only 107 of the AML patients. Based on FAB classification, 1M0 (0.5%), 3M1 (1.5%), 50M2 (25%), 6M3 (3%), 34M4 (17%), 7M5 (3.5%), 6M6 (3%), 0M7 were included in this study. As shown in table 2, we analyzed the frequency of *GSTM1* null genotype and FAB classification. We placed M0, M1, M3, M5 and M6 in one group, because these subtypes were present in few patients. The frequencies of the *GSTM1* null genotype and the present genotype were respectively 10.5% and 12.2% in M0, M1, M3, M5 and M6 subtypes, 26.3% and 24.2% in M2 subtype, and 18.4% and 16.1% in M4 subtype. In unclassified AML, the frequency of the *GSTM1* null genotype and present genotype were 44.7% and 47.6%, respectively. No significant statistical difference was observed between distribution frequency *GSTM1* null genotype and FAB classification (*P*=0.93).

The frequency of *GSTT1* null genotype and FAB classification is shown in table 3. The frequencies of the *GSTT1* null genotype and the present genotype were respectively 8.4% and 13.7% in M0, 1, 3, 5, 6 subtypes, 30.1% and 21.4% in M2 subtype, and 16.9% and 17.1% in M4 subtype. In unclassified AML, the frequency

Table 3. FAB subtypes and frequency of the *GSTT1*

Subtypes	null genotype	present genotype
M0,1,3,5,6	8 (10.5%)	15 (12.2%)
M2	20 (26.3%)	30 (24.2%)
M4	14 (18.4%)	20 (16.1%)
*AML	34 (44.7%)	59 (47.5%)

P=0.43, *unclassified FAB AML

of the *GSTT1* null genotype and the present genotype were 44.6% and 47.9%, respectively. No significant statistical difference was observed between distribution frequency *GSTT1* null genotype and FAB classification (*P*=0.43).

150 patient DNAs were analyzed for *CYP1A1*2A* gene. The results of the analysis between the polymorphism *CYP1A1*2A* and FAB subtypes are shown in table 4. The FAB subtype was not known in 65 of patients (46.5%). In the rest of the patients, the rate was as follows: 0 M0 (0%), 2M1 (1.3%), 50M2 (25.3%), 6M3 (4%), 34M4 (19.3%), 5M5 (3.3%), 5M6 (3.3%). The frequency of the *CYP1A1*2A* homozygous mutants (TT) was 11.3% in M0, M1, M3 and M6 subtypes, but 28%, 18%, and 42% in M2, M4 and unclassified AML, respectively. The frequency of the *CYP1A1*2A* heterozygous mutants (TC) was 12.6% in M0, 1, 3, 5, 6 subtypes, and 18.2%, 23.7%, and 45.5% in M2, M4 and unclassified AML, respectively. Homozygous absence (CC) was 16.7%, 50%, 0%, and 33.3% in M0, 1, 3, 5, 6 subtypes, M2, M4 and unclassified AML respectively; no significant statistical difference was observed (*P*=0.78).

The results showed that the frequency of *GSTM1* null genotype was significantly higher in the control groups compared to the case group (48% vs. 38%), and the *GSTM1* null genotype was associated with decreased risk of AML (OR=1.50, %95 CI: 1.01- 2.24, *P*= 0.044). On the other hand, the frequency of *GSTT1* null

Table 4. FAB subtypes and frequency of the *CYP1A1*2A*

Subtypes	TT	TC	CC
M0,1,3,5,6	10 (11.3%)	7 (12.6%)	1 (16.7%)
M2	25 (28%)	10 (18.2%)	3 (50%)
M4	16 (18%)	13 (23.7%)	0 (0%)
*AML	38 (42.7%)	25 (45.5%)	2 (33.3%)

P=0.78, *unclassified FAB AML

Table 5. Distribution of *CYP1A1*, *GSTM1*, and *GSTT1* genotypes in AML and controls

Polymorphism	Genotype	Case	Control	OR	P-value
<i>GSTM1</i>	Present	124(62%)	104(52%)	1.5 (1.01-2.24)	0.044
	Null	76(38%)	96(48%)	0.24 (0.14-0.38)	
<i>GSTT1</i>	Present	117(58.5%)	171(85.5%)	1.056 (0.67-1.66)	0.0001
	Null	83(41.5%)	29(14.5%)	1.089 (0.68-1.73)	0.81
<i>CYP1A1*2A</i>	TT	85 (56.7%)	83 (55.3%)	0.56 (0.21-1.47)	0.72
	TC	58 (38.7%)	55 (36.7%)		0.23
	CC	7 (4.7%)	12 (8%)		

Statistically significant data are shown in bold.

genotype was significantly lower in the controls(14.5% vs. 41.5%), hence the association between *GSTT1* null genotype and increased risk of susceptibility to AML (OR= 0.24, %95 CI: 0.14- 0.38, P= 0.0001). Therefore, the most significant factor associated with the increased risk of AML was the *GSTT1* null genotype (Table 5, Figure 1). There was no significant difference regarding the prevalence of the *CYP1A1* *2A allele between AML patients and controls (Table 5, Figure 2).

We investigated whether this risk was more increased when both genotypes were combined. A significantly increased AML risk was observed in patients with the combined *GSTT1* null genotype and the *CYP1A1* *2A AA allele (OR=12.76, P=0. 000) or *GSTT1* null genotype and *CYP1A1* *2A AC allele (OR=3. 43, P= 0. 002) (Table 6). Therefore, the combination of the three genotypes *CYP1A1**2A (AA, AC) and *GSTT1* null genotype showed an increased cancer risk when compared with no-risk genotypes. On the contrary, there was no significant difference between the combination of the *CYP1A1**2A (AA, AC) and the *GSTM1* null genotype (OR=1 (95%CI: 0.56-1.77), OR= 0.73 (95%CI: 0.4-1.3), respectively).

Discussion

Multiple studies have demonstrated that susceptibility to cancer is caused by a deficiency in xenobiotic-metabolism genes (*CYP1A1* and

GSTT1), which may cause the accumulation of high levels of hydrophobic DNA adducts in cells. The increase in DNA adducts causes various kinds of mutations in tumor suppressor genes and oncogenes, and may influence the susceptibility to developing into acute myeloid and acute lymphoblastic leukemia.^{20,22-27}

This is the first report on the role of *GSTM1*, *GSTT1* and *CYP1A1* (cytochrome p450) gene polymorphisms in susceptibility to AML in an Iranian population.

This study showed that the frequency of *GSTM1* null genotype was significantly greater in the control groups, and *GSTM1* null genotype was associated with the decreased risk of AML. *GSTM1* null genotype may play a protective role and reduce the risk of AML in the Iranian population.

The frequency of *GSTT1* null genotype was observed to be higher in the case group compared with the controls; hence, there is an association between *GSTT1* null genotype and a high risk of AML.

Several studies have indicated that the risk of carcinogenesis might be increased by *CYP1A1**2A genetic variations.²⁸⁻³⁰ However, insignificant relationships have been observed between polymorphic *CYP1A1**2A and diseases such as gastric, colorectal, esophageal and breast cancers.³¹⁻³⁴ Thus, the polymorphism of *CYP1A1* MspI might have various roles in different cancers.

The association of *CYP1A1**2A and AML in

Table 6. Relative risk of AML for combined *CYP1A1*, *GSTM1*, and *GSTT1* genotypes

Combined <i>CYP1A1</i> * <i>2A</i> and <i>GST</i> genotypes	AML patient (n= 150)	Control (n= 150)	OR (95%CI)	P-value
<i>CC</i> and <i>GSTT1</i>	3	2	1.5 (0.25-9.2)	1
Null	4	10	0.4 (0.12-1.25)	0.17
<i>CA</i> and <i>GSTT1</i>	31	36	0.8 (0.5-1.4)	0.6
Null	27	9	3.4 (1.5-7.6)	0.002
<i>AA</i> and <i>GSTT1</i>	54	80	0.5 (0.3-0.8)	0.004
Null	31	3	12.76 (3.8-42.8)	0.001
<i>CC</i> and <i>GSTM1</i>	3	0	0.98 (0.95-1)	0.24
Null	4	12	0.31 (0.01-1)	0.07
<i>CA</i> and <i>GSTM1</i>	34	24	1.53 (0.86-2.74)	0.18
Null	24	31	0.73	0.37
<i>AA</i> and <i>GSTM1</i>	56	54	1.06 (0.66-1.7)	0.9
Null	29	29	1 (0.56-1.77)	1

Statistically significant data are shown in bold.

our case-control study was not statistically significant.

Francesco D’alo et al. reported a higher frequency of *GSTT1* null genotype in AML patients, but the frequency of *CYP1A1***2A* allele in AML patients was not statistically different from the controls.³⁵

A meta-analysis of case-control studies indicated a higher frequency of *GSTM1* polymorphisms in patients with AML, while borderline significance was seen with *GSTT1* null genotypes.³⁶

Aydin Sayitoglu and et al.²⁰ showed that the increased homozygous *CYP1A1***2A* genotype frequency in AML patients was not statistically different from the controls. Also, the association between *GSTT1* gene deletion and AML was not statistically significant.

Significantly more frequency in the *GSTM1* deletions have been reported in AML patients compared to the control group.¹⁸

Balta and et al. found statistically lower homozygous *CYP1A1***2A* genotypes in ALL patients compared to the controls.²⁷ Zhuo et al. in a meta-analysis on a total of ten case- control studies reported that AML risk in Asians was more significant than in Caucasians or mixed

racers. Also, in the analysis age groups, no associations were seen in either the childhood AML or the adult AML subgroups.³⁷

Zhou et al. reported that individuals with a null *GSTT1* genotype compared to a non-null genotype, had a high risk of AML; moreover, those carrying combinations of null genotypes of *GSTM1*, *GSTT1* and *GSTP1* Val allele genotypes had higher risks compared to those carrying wild genotypes.³⁸ Several recent studies have shown that *GSTT1* null and *GSTM1* null genotypes may be potential risk factors for AML.³⁹⁻⁴¹

Farasani et al. in a Saudi population observed no statistical association of the genotypes and alleles in *GSTM1*, *GSTT1* with AML.⁴² In our study, the combination of the genotypes *CYP1A1* *AA*, *AC* and *GSTT1* null genotype increased AML risk when compared to no-risk genotypes (*CYP1A1***2A* *CC* genotype and *GSTT1* present genotype).

Krajinovic et al. reported that the presence of both *CYP1A1***2A* allele and the *GSTM1* null-genotype increased the risk of ALL on the carriers.¹⁸

Francesco et al. reported that the combination of *GSTT1* null genotype and *CYP1A1* **2B* and

*4 alleles augmented the risk of AML.³⁵

This is the first study evaluating susceptibility to AML in individuals with polymorphic variants in phases I and II of enzyme genes.

No significant statistical association was observed between the FAB classification and the frequency of *GSST1*, *GSTM1* null genotypes and *CYP1A1**2A variant.

Conflicting data have been reported in other epidemiological studies possibly due to several agents such as ethnicity, a different pattern of carcinogen exposure, combination of susceptibility variants, or the number of patients. Further studies with a boundary range of detoxification enzymes in different ethnic groups are recommended.

Acknowledgements

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Conflict of Interest

None declared.

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