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Research Article

GENETIC VARIANTS OF GSTT1 AND GSTM1 AND THEIR POTENTIAL ROLE IN ACUTE MYELOID LEUKEMIA SUSCEPTIBILITY: EVIDENCE FROM A STUDY IN THE SUDANESE POPULATION

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Abstract

Introduction: Leukaemias in general population result from interaction between genetic and environmental factors and time. The interplay of xenobiotics exposure, endogenous physiology, and genetic variability of multiple loci may facilitate knowledge about leukaemia etiology and the identification of individuals who are at increased risk of developing leukaemias .**Objectives :**This is hospital based case control study aimed to determine the genetics polymorphism of GSTT1 and GSTM1 as risk factor to develop acute myeloid leukemia by multiplex PCR in National Cancer Institute, Gezira state, Sudan. **Methods :** The study included 20 diagnosed pediatric patients of acute myeloid leukemia (AML), and 20 healthy volunteers who were selected according to inclusion and exclusion criteria. 2.5 ml of blood was collected in EDTA tubes ,then the complete blood count (CBC) was done by automated hematology analyzer and GST gene, GSTM1 and GSTT1 variants were genotyped by multiplex PCR, . **Results :**The study results showed the frequency of GSTM1 and GSTT1 deletion genotype was 20% and 15%, respectively in AML patient .No statistical significant difference was found with GSTT1 deletion genotype frequency in AML patients as compared to controls, the frequencies of the GSTM1 null genotypes between AML patients and controls and GSTT1 null genotypes frequency in AML patients as compared to controls (value 0.202, 0.189 and 0.582) retrospectively .Also there was no statistical significant among different age groups and genders (p.value0.269 and 0.704) retrospectively .The CBC parameters show highly statistical significant difference between the cases and controls (p.value 0.00) except the WBCs show no statistical significant difference between cases and control (p.value 0. 064). **Conclusion :** GSTT1 and GSTM1 were not consider as risk factor for AML.

Keywords: GSTT1, GSTM1, AML and Risk factor.

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by uncontrolled proliferation and lack of differentiation in myeloid progenitors (Talati and Sweet 2018). Along with acute lymphoblastic leukemia (ALL), the etiology of acute leukemias has remained largely unknown. However, recent genome-wide association studies (GWAS) have shed light on the genetic basis of these diseases. In particular, two chromosomal loci, 7p12.2 and 10q21.2, have been identified as harboring risk variants in study subjects of various ethnicities, including Caucasian, Asian, and African populations (Cao, Yang *et al.,* 2018). These findings provide valuable insights into the genetic factors contributing to the development of acute leukemias. Acute myeloid leukemia (AML) is aggressive diseases with poor outcomes, particularly in developing countries (Van Weelderen, Klein *et al.,* 2021). Identifying genetic alterations is crucial for risk stratification and guiding appropriate treatment decisions (Conneely and Stevens 2021). AML is characterized by symptoms such as fatigue, frequent infections, bleeding, and fever. While significant advancements have been made in the clinical, diagnostic, and therapeutic aspects of AML, its etiology remains elusive. Similar to most cancers, AML is multifactorial, resulting from the interplay between environmental and genetic factors, including exposure to carcinogens such as benzene, cytotoxic chemotherapy, and ionizing radiation, as well as individual genetic variations impairing xenobiotic elimination, ultimately leading to cancer development (Travis, Li *et al.,* 1994; D'Alo, Voso *et al.,* 2004). Despite notable progress in diagnosis and treatment, poor prognosis still persists in AML patients (Butrym, Łacina *et al.,* 2018). Numerous studies have associated AML with multiple genetic mutations, including inherited genetic mutations related to cancer/carcinogen metabolism. One such set of functional and genetic polymorphisms is encoded by the Glutathione-S-transferase (GST) genes, which influence AML susceptibility (Weich, Ferri *et al.,* 2016). Among these genes, GSTM1 and GSTT1 encode homonymous enzymes responsible for detoxifying various potentially harmful substances, including air pollution, drugs, pesticides, and tobacco (Nakanishi, Bertagnolli *et al.,* 2022). The theta class includes GSTT1 and GSTT2, sharing 55% amino acid sequence identity and playing significant roles in human carcinogenesis. Located approximately 50kb apart, the GSTT1 and GSTT2 genes possess similar structures (Cerliani, Pavicic *et al.,* 2016). Glutathione S-transferases (GSTs) form a supergene family of detoxifying enzymes present in virtually all life forms (Hayes, Flanagan *et al.,* 2005). These phase II detoxifying enzymes facilitate the conjugation of reduced glutathione with various electrophilic substrates (Hayes and Pulford 1995). Apart from their role in xenobiotic detoxification, GSTs also exhibit peroxidase and isomerase activities, which can inhibit the c-Jun N-terminal

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kinase (JNK) (Zhang, Meng *et al.,* 2023). Additionally, GSTs can non-catalytically bind to a wide range of endogenous and exogenous ligands (Zhang, Meng *et al.,* 2023). In humans, GST enzymes consist of several cytosolic, mitochondrial, and microsomal proteins, with the cytosolic family comprising eight distinct classes: alpha (A), kappa (K), mu (M), omega (O), pi (P), sigma (S), theta (T), and zeta (Z) (Strange, Spiteri *et al.,* 2001; Hayes, Flanagan *et al.,* 2005). Polymorphisms within GST genes have been associated with susceptibility to both nonmalignant and malignant human diseases (Wilson, Grant *et al.,* 2000; Dusinska, Staruchova *et al.,* 2012). Previous studies have suggested a link between GSTs and leukemogenesis, and polymorphisms in these genes may impact leukemia treatment due to the involvement of GSTs in detoxifying active metabolites of cytotoxic chemotherapeutic agents used for tumor cell eradication (Guven, Unal *et al.,* 2015; Rollinson, Roddam *et al.,* 2000). Given the limited information on GSTT1, GSTM1, and GSTP1 polymorphisms and their association with AML susceptibility in the Sudanese population, we initiated this study to investigate the potential relationship between GSTT1 and gene polymorphisms as risk factors for AML in Sudan.

MATERIALS AND METHODS

Study setting and population

It case-control prospective inpatient study was planned to investigate the relationship between the GSTT1 gene polymorphism and its role as an AML risk factor. There were 40 individuals in this study; 20 were cases and 20 were controls. 2.5 ml of venous blood from each subject was drawn into a K3EDTA container for DNA extraction and CBC analysis.

DNA extraction

Upon admission, venous blood samples were taken in test tubes containing EDTA. Whole genome amplification and DNA extraction followed.Plasma was separated within two hours of collection, and pellets were frozen at 20°C. Leucocytes from peripheral blood were used to extract genomic DNA using the G-spinTM complete DNA Extraction Kit. Gene quant used to measure the DNA and found that it was within permitted limits.

Molecular analysis of GSTT1 and GSTM1 genes polymorphism

PCR amplification was performed on of genomic DNA, in a reaction mixture with the total volume of 20 mL that contained 2mM MgCl2 and 12.5 pM each of the forward and reverse GSTT1, GSTM1, and IL-4 primers. The reaction was carried out, using 30 cycles of 94°C for 1 min, 62°C for 1 min, and 72°C for 1 min. The PCR product was run in 1.5% (w/v) agarose gel and the bands were visualized with UV light. DNA from patients with positive GSTM1, GSTT1 219 bp, 480 bp products, respectively. The absence of GSTM1 or GSTT1 (in the presence of IL-4 PCR product) indicates the respective null genotype for each. Samples positive for all three PCR products were considered (wild type). Co-amplification of human IL-4 served as a positive control, to ensure that a null genotype was attributed to the absence of the respective gene and not because of a PCR failure. PCR products was checked on 2.% agarose gel and was visualized by gel documentation system.

Primer sequences for GST multiplex PCR

Gene	Nucleotide sequences of primers
GSTM1	F-GAA CTC CCT GAA AAG CTA AAG G
	R-GTT GGG CTC AAA TAT ACG GTG G
GSTT1	F-TTC CTT ACT GGT CCT CAC ATC TC
	R-TCA CCG AT CAT GGC CAG CA

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, New York, United States). Significance was observed with P value < 0.05.

RESULTS

In this study, a total of 40 participants were included. Among them, 50% (n=50) were case subjects, and the remaining 50 were control subjects. Among the participants, 70% were males, while 30% were females. All participants had no history of acute myeloid leukemia (AML). The study population was characterized into different age groups. Among the participants, 25% (n=10) were aged less than 5 years, 42.5% (n=17) were aged between 5-10 years, and 32.5% (n=13) were aged more than 10 years. According to the French-American-British (FAB) classification, the distribution of AML subtypes was as follows: 50% (n=25) were classified as M2, 20% (n=10) as M3, 10% (n=5) as M4, and 5% (n=2) as M0, M5, and M7, respectively. In terms of genetic polymorphisms, the study found that 55% (n=11) of participants had a null genotype, 15% (n=3) had GSTT1 deletion, 20% (n=4) had GSTM1 deletion, and 10% (n=2) had a wild-type genotype. Among the male participants (n=12), 58.3% (n=7) had a null genotype, 8.3% (n=1) had GSTT1 deletion, 25% (n=3) had GSTM1 deletion, and 8.3% (n=1) had a wild-type genotype. Among the female participants (n=8), 50% (n=4) had a null genotype, 25% (n=2) had GSTT1 deletion, 12.5% (n=1) had GSTM1 deletion, and 12.5% (n=1) had a wild-type genotype. Statistical analysis revealed no significant differences in GSTT1 and GSTM1 polymorphisms among different age groups (p-value=0.269). Similarly, there were no statistically significant differences in the distribution of GSTT1 and GSTM1 polymorphisms between the case and control groups (p-value=0.202).

Table 1. Characterization of the study population

Factor		Frequency
Study population	Cases	20 (50%)
	Controls	20 (50%)
Gender	Male	28 (70%)
	Female	12 (30%)
Family history	Yes	0 (0.0%)
	No	20 (100%)

Table 2. Distribution of the type of AML according to FAB classification

AML according to FAB classification	Frequency	Percent
M0	1	5
M1	0	0
M2	10	50
M3	4	20
M4	2	10
M5	1	5
M6	1	5
M7	1	5
Total	20	100

Table 3. The frequency and percentage between GSTT1 and GSTM1 polymorphism and study population

		Null	GSTT1 deletion	GSTM1 deletion	Wide type	Total
Study population	Case	11(55%)	3(15%)	4(20%)	2(10%)	20(100%
	Control	6(30)	9(45%)	3(15%)	2(10%)	20(100%)

Table 4. The association between GSTT1 and GSTM1polymorphism and study population

	Value	df	P.value
Pearson Chi-Square	4.613[a]	3	.202
Likelihood Ratio	4.775	3	.189
Linear-by-Linear Association	.391	1	.532
N of Valid Cases	40		

Table 5. The association between GSTT1, GSTM1polymorphism, and age

Age group (Age/years)		GSTT1 and GSTM1polymorphism				Total	2 sided
		Null	GSTT1 deletion	GSTM1 deletion	Wide type		
Less than 5 years	Count	4	3	2	1	10	
	%	40.0%	30.0%	20.0%	10.0%	100.0%	0.269
5 - 10 years	Count	5	8	2	2	17	0.243
	%	29.4%	47.1%	11.8%	11.8%	100.0%	
More than 10 years	Count	8	1	3	1	13	0.949
	%	61.5%	7.7%	23.1%	7.7%	100.0%	
Total	Count	17	12	7	4	40	
	%	42.5%	30.0%	17.5%	10.0%	100.0%	

Table 6. Frequencies of GSTT1 and GSTM1polymorphism according to the gender

			GSTT1 and GSTM1polymorphism				Total
			Null	GSTT1 deletion	GSTM1 deletion	Wide type	
Gender	Male	Count	7	1	3	1	12
		%	58.3%	8.3%	25.0%	8.3%	100.0%
	Female	Count	4	2	1	1	8
		%	50.0%	25.0%	12.5%	12.5%	100.0%
Total		Count	11	3	4	2	20
		%	55.0%	15.0%	20.0%	10.0%	100.0%

Table 7. Comparison between CBC parameter of cases and controls

CBC parameters	Study population	N	Mean	Std. Deviation	P.value
RBCs /**106***ul	Case	20	2.4150	91954.	0.000
	Control	20	3.8200	71200.	
Hb g/dl	Case	20	7.2250	2.41266	0.000
	Control	20	10.4300	1.98497	
PCV**%**	Case	20	21.4250	7.60505	0.000
	Control	20	31.8500	6.31018	
MCV /fl	Case	20	86.3100	8.06878	0.15
	Control	20	79.1850	9.48474	
MCH/ pg	Case	20	29.4500	3.21436	0.26
	Control	20	27.0100	3.45724	
MCHC/ g/dl	Case	20	34.2750	2.41069	0.000
	Control	20	30.8550	2.78615	
Platelet count / **103***ul	Case	20	60.5000	102.37418	0.000
	Control	20	3.5060E2	141.73675	
WBCs /**103***ul	Case	20	44.2950	77.80318	0.064
	Control	20	10.6850	12.09425	
Neutrophil**%**	Case	20	21.2500	12.85905	0.000
	Control	20	48.3500	11.39841	
Lymphocyte**%**	Case	20	20.9000	14.64276	0.000
	Control	20	42.3500	11.71268	
Monocyte**%**	Case	20	3.0500	3.20321	0.01
	Control	20	6.3500	2.68083	
Eosinophil**%**	Case	20	2.2500	5.83884	0.513
	Control	20	3.1500	1.72520	
Basophil**%**	Case	20	0500.	22361.	0.313
	Control	20	0000.	00000.	
Blast**%**	Case	20	50.3000	20.34984	0.000
	Control	19	3.6842	16.05910	
Other Immature WBC**%**	Case	20	4.1500	8.54262	0.34
	Control	20	0000.	00000.	

DISCUSSION

This hospital-based case-control study aimed to investigate the genetic polymorphisms of GSTT1 and GSTM1 as risk factors for developing acute myeloid leukemia (AML) at the National Cancer Institute in Gezira state,Sudan. The study employed multiplex PCR to determine the null genotype frequency of GSTT1 and GSTM1 genes in AML patients. The study included 40 participants, with 20 cases and 20 controls, comprising 29% females and 71% males, ranging in age from 1 to 16 years. The results revealed that all 20 cases (100%) had no family history of AML. The study population was divided into different age groups, with 10 participants (25%) aged less than 5 years, 17 participants (42.5%) aged between 5-10 years, and 13 participants (32.5%) aged over 10 years. According to the FAB classification, 50% of the cases were classified as M2. The frequency of GSTM1 deletion genotype in the patients was 20%, which did not show a statistically significant difference from the controls. This frequency was lower than the 42% reported in AML cases by Voso *et al.,* (2002) and lower than the 44% reported in the normal Egyptian population by Awar *et al.,* (1996), which may be attributed to differences in sample size and ethnic origin. Thus, GSTM1 polymorphism may not be a probable risk factor for AML development in Sudan. Conversely, the frequency of GSTT1 deletion genotype in our study was 15%, which also did not show a statistically significant difference from the controls. This finding was consistent with a previous study conducted in the Saudi population (Farasani, 2019), indicating no evidence of an association between GSTT1 polymorphism and AML risk in our series. Several other studies have investigated the association between GST polymorphisms and AML risk. Crump *et al.,* (2000) conducted a case-control study in the United States, reporting no support for the hypothesis that GSTT1 gene deletion is associated with AML risk. Similarly, Liu *et al.,* (2005) reported no association between variation in GSTT1 genotype and AML susceptibility in a Chinese population. In contrast, other studies, such as those conducted in Egypt and Iran, have reported conflicting results (Nasr *et al.,* 2015; Mortazavi *et al.,* 2020).

The discrepancies observed in these studies could be attributed to differences in population size, genetic susceptibility, environmental exposures, ethnicity, diet, gender, and the statistical tests used for analysis (Board *et al.,* 1997). While a few studies have shown a significant association between GST polymorphisms and AML, others have yielded conflicting results (Nebert *et al.,* 1996; Ingelman-Sundberg, 2001; Krajinovic *et al.,* 1999). In our study, the frequency of GSTT1 and GSTM1 null genotypes in the cases was 55%, which showed no significant difference compared to the controls. This frequency was higher than that reported in the Egyptian population by Anwar *et al.,* (1996) (8.8%) and higher than that reported by Voso *et al.,* (2002) in adult AML (17.9%), possibly due to differences in ethnic origin and sample size. In conclusion, this case-control study in Sudan did not find a significant association between GSTT1 and GSTM1 null genotypes and the risk of developing AML. These findings are consistent with some previous studies (Crump *et al.,* 2000; Liu *et al.,* 2005) but contradict others (Nasr *et al.,* 2015; Mortazavi *et al.,* 2020). The observed discrepancies may be attributed to various factors, including population characteristics, genetic variations, environmental exposures, and methodological differences. Further research with larger sample sizes and diverse populations is warranted to elucidate the role of GST polymorphisms in AML development. The complete blood count (CBC) parameters showed highly significant differences between the cases and controls, which could be attributed to chemotherapy, bone marrow infiltration, or suppression. However, no clinical significance was observed for white blood cell counts (WBC) between the cases and controls, likely due to the effects of chemotherapy.

Conclusion

The study found no discernible difference between AML cases and controls in the null genotype frequency of GSTT1 and GSTM1. Furthermore, neither age groups nor gender were significantly associated with these gene polymorphisms. According to the research, there may not be a significant risk of AML formation in the Sudanese population due to GSTT1 and GSTM1 gene polymorphisms. For these findings to be confirmed and other potential genetic factors influencing AML susceptibility to be explored, additional research with bigger sample sizes and various populations is required. Understanding the genetic underpinnings of AML can offer important insights into the disease's development and help direct future personalised treatment approaches.

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