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Genetic Polymorphisms of Glutathione S-Transferase and Risk of Acute Myeloid Leukemia: Case-Control Study and Meta-Analysis

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Abstract

Background: Acute myeloid leukemia (AML) is a complex disease that is linked to genetic and environmental factors. The gluthatione S-transferase (GST) is a family of enzymes that play a crucial role in the detoxification of carcinogens. These compounds could cause DNA damage, which might lead to the development of cancer. Interindividual inherited differences caused by the presence of single nucleotide polymorphisms (SNPs) in detoxification enzyme, could play a major role in cancer predisposition. The present study aimed to investigate the association between *GST* gene polymorphisms and AML risk.

Methods: The *GSTP1* genotype was determined by the PCR-RFLP and multiplex PCR for *GSTT1* and *GSTM1*. Meta-analysis was conducted to evaluate the association between *GST* gene and the risk of AML.

Results: We found that *GSTT1* null genotype was significantly associated with the risk of AML. However, *GSTM1* and *GSTP1* polymorphisms did not influence the AML risk. Subjects carrying the *GSTM1* Present, *GSTT1* null and *GSTP1* Ile / Val et Val /Val genotypes had a higher risk of developing AML. The results of meta-analysis showed a positive association between *GSTM1* null, *GSTT1* null and Ile105Val *GSTP1* polymorphisms and AML risk in East Asians, Caucasians, and mixed populations, respectively.

Conclusion: *GST* gene polymorphisms may be risk factors for acute myeloid leukemia.

Keywords: *GSTP1*, *GSTT1*, *GSTM1*, PCR-RFLP, Polymorphism, Acute myeloid leukemia, Susceptibility

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Introduction

Acute myeloid leukemia (AML), the second most prevalent type of leukemia in Morocco, is a very heterogeneous group of disorders characterized by the accumulation of immature white blood cells (blasts) in the bone marrow, leading to the

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Table1. Demographic and biological characteristics of patients and controls

		Cases (N=192)	Controls (N=210)	*P*
Sex N (%)				
	Female	98 (51.0)	122 (58.1)	
	Male	94 (49.0)	88(41.9)	0.66
M:F ratio		0.95	0.72	
Age years (Median±SD)		38±15.09	36±13.19	0.39
	Range	18-78	18-77	
FAB classification N				
(%)		165		
	M0	7 (3.6)		
	M1	36 (18.8)		
	M2	55(28.6)		
	M3	11(5.7)		
	M4	28(14.6)		
	M5	16 (8.3)		
	M6	10 (5.2)		
	M7	2 (1.0)		
	Not classified	27 (14.1)		
Median blasts (%)		83%		
	Range	(22-100)		
Median WBC (G/L)		19.20		
	Range	(0.28-787.0)		
Median platelets (G/L)		36		
	Range	(1-367)		
Median hemoglobin (g/dl)		7.15		
	Range	(2.50-12.80)		
Karyotype N (%)				
	Normal	83 (43.2)		
	Abnormal	97 (50.5)		
	Not done	12(6.3)		

inhibition of normal hematopoiesis process, resulting in anemia, granulocytopenia, and thrombocytopenia. The usual symptoms of AML include fatigue, frequent infections, bleeding, and fever. It is known that the clinical, diagnostic, and therapeutic levels of AML have significantly evolved over the recent years. However, the etiology of this cancer remains obscure. As most cancers, AML is multifactorial caused by the interaction between environmental and genetic factors, such as exposition to carcinogens (benzene, cytotoxic chemotherapy, and ionizing radiation) and individual impaired genetic variation in the ability to eliminate xenobiotics, leading to the development of cancer.[4-7] Therefore, the human body has many enzymes involved in the detoxification of carcinogens such as cytochrome P450 and gluthatione S-transferase (GST). GST is a family of phase II detoxification enzymes that catalyse the conjugation of reduced glutathione (GSH) to a large variety of toxic xenobiotics. Several studies have demonstrated that the GST enzyme activity is reduced in individuals with homozygous deletions or mutations of GST gene. Indeed, the low expression of these enzymes results in diminished ability to eliminate carcinogens and an increased risk of cancer development.[10, 11] The most explored members of this family are *GSTT1*, *GSTM1* and *GSTP1*. The *GSTT1* and *GSTM1* genes are mapped to chromosomes 22q11.23 and 1p13.3, respectively; moreover, the genetic polymorphisms of *GSTT1* and *GSTM1* result in the complete absence of the gene (null allele).[12] Many studies have reported a positive association between the *GSTT1* and *GSTM1* null genotypes and risk of

Table 2. Allelic and genotypic distribution of *GSTM1*, *GSTT1* and Ile105Val *GSTP1* polymorphisms among AML patients and controls

Genotype	Patients N (%)	Controls N (%)	OR (95% CI)	*P*
GSTM1				
Present	101 (52.6)	105 (50.0)	**Ref.**	
Null	91(47.4)	105(50.0)	0.9 (0.60-1.33)	*0.60*
GSTT1				
Present	119 (62.0)	163 (77.6)	**Ref.**	
Null	73 (38.0)	47 (22.4)	2.12 (1.37-3.29)	***0.0007***
GSTP1				
Ile/Ile	71(37.0)	93 (44.3)	**Ref.**	
Ile/Val	101(52.6)	96 (45.7)	1.37 (0.90-2.09)	0.13
Val/Val	20 (10.4)	21 (10.0)	1.24 (0.62-2.47)	0.52
Ile/Val & Val/Val	121(63.0)	117 (55.7)	1.35 (0.90-2.02)	0.13

prostate, lung, and head and neck cancers.[13-15]

The *GSTP1* gene is located on chromosome 11q13,[16] and is overexpressed in many cancers, including esophageal, stomach, pancreatic, colon, brain, cervical, rectal, testicular cancers, and leukemia,[17-19] hence considered as a tumor biomarker.[20] Two polymorphisms have been identified in the *GSTP1* active site region: a C to T substitution causing alanine 114 to valine transition, and an A to G substitution generating isoleucine 105 to valine transition; it has further been reported that homozygous individuals for the mutant allele have less GSTP1 enzyme activity compared to those who are of heterozygous or homozygous wild-type.[21] The decrease in the detoxification ability of *GST* gene for carcinogens linked to genetic variation might play a crucial role in the leukemogenesis of AML. Accordingly, the aim of the current study was to investigate the relationship between *GST* polymorphisms and susceptibility to AML in a Moroccan population.

Patients and Methods

This case-control study was approved by the Ethical Committee of Hassan II University, School of Medicine and Pharmacy, Casablanca, Morocco, N°02/19. A written informed consent was obtained from all participants before entering the study. The study population consisted of 192 patients diagnosed with AML and 210 healthy controls without any history of cancer. The patients were classified according to the World Health Organization 2008 (WHO) classification system. Subjects were recruited from the department of Onco-Hematology of the Ibn Rochd University Hospital in Casablanca, Morocco from May 2014 to February 2017. Demographic and biological data were obtained from the medical record file of each patient. Control subjects were recruited during the same period, comprising students from the faculty of medicine and other volunteers working at the same faculty or in the Ibn Rochd University Hospital. Four milliliters of peripheral blood were collected in an EDTA tube.

DNA extraction and genotyping

Genomic DNA was isolated from white blood cells using salting-out method.[22] DNA was quantified using Nanovue Plus spectrophotometer. The *GSTM1* and *GSTT1* genotypes were determined using multiplex polymerase reaction, where the *BCL2* gene was used as an internal control. Forward and reverse primers as well as detailed technical aspects have been previously described by Boujmia et al.[23]

The *GSTP1* Ile 105 Val genotype analysis was determined by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method as previously described by Harries et al. The forward and reverse primers used were: 5′-ACC-CCA-GGG-CTC-TAT-GGG-AA-3′ and 5′-TGA-GGG-CAC-AAG-AAG-CCC-CT-3′.The reaction mixture was composed of 100 ng of genomic DNA, 1X of 5X GoTaq Flexi Buffer (Promega), 1.5 mM of MgCl2, 0.2

Table 3. Combination effect of *GST*s polymorphisms and AML risk

GSTT1	*GSTM1*	*GSTP1*	Patients N (%)	Controls N (%)	OR(95% CI)	*P*
Present	Present	Ile/Ile	23(12.0)	48(23.0)	**Ref.**	
Present	Present	Ile/Val & Val/Val	36(18.7)	41(20.0)	1.83 (0.94-3.57)	*0.076*
Present	Null	Ile/Ile	22(11.4)	24(11.0)	1.91 (0.89-4.10)	*0.095*
Present	Null	Ile/Val & Val/Val	38(20.0)	50(24.0)	1.58 (0.82-3.04)	*0.165*
Null	Present	Ile/Ile	15(7.8)	7(3.0)	**4.47(1.60-12.47)**	***0.004***
Null	Present	Ile/Val & Val/Val	27(14.0)	9(4.0)	**6.26(2.53-15.45)**	***0.0001***
Null	Null	Ile/Ile	11(5.7)	14(7.0)	1.63(0,64-4,16)	*0.29*
Null	Null	Ile/Val & Val/Val	20(10.4)	17(8.0)	**2.45 (1.08- 5.54)**	***0.03***

mM deoxyribonucleoside triphosphate, 10 pM of each primer and 0.5 U of GoTaq polymerase (Promega) completed to 25 µL with molecular grade water. The samples were amplified using a thermal cycler with an initial denaturation at 94°C for 5 min followed by 35 cycles of 94°C for 1 min, 57°C for 30 s, 72°C for 1 min and a final extension at 72°C for 7 min. PCR products were cleaved with restriction enzyme BsmA I at 55°C for 1 hour. The digested PCR products were resolved on a 3% agarose gel and stained with ethidium bromide. The presence of a single fragment of 176 pb indicated the wild-type genotype (Ile/Ile), while the 85 and 91 pb fragments indicated the homozygous polymorphic genotype (Val/Val); heterozygote was detected by the presence of all three fragments.

Meta-Analysis

Search strategy

Published studies were identified by searching in PubMed and Google Scholar before August 2017, using the following keywords: *GSTP1*, *GSTT1*, *GSTM1* polymorphism, acute myeloid leukemia or AML, and susceptibility.

Inclusion and exclusion criteria

The inclusion criteria were 1) case-control studies investigating the association between the 105 *GSTP1*, *GSTM1* and *GSTT1* polymorphisms and AML risk, and 2) studies with sufficient data to calculate allele frequencies, odds ratios (OR) and 95% confidence intervals (CIs) of patients and controls. Studies and review articles that were not case-control, duplicate publications, and studies with insufficient data were excluded from the meta-analysis.

Genetic model

For the *GSTP1*gene polymorphism, the meta-analysis was conducted under the allele contrast model (Val versus Ile) and the subgroup analysis was performed according to the ethnicity.

Statistical analysis

Data were analyzed by the statistical package SPSS version 16 (SPSS Inc., Chicago, IL, USA). Differences between patients and controls were assessed by Mann-Whitney U test for continuous variables. Difference in the distribution of genotypes between these groups was assessed by chi-squared test (X2) or Fisher's exact test. Crude odds ratios (OR) with confidence interval (CI) at 95% was calculated to evaluate the association between *GST* gene polymorphisms and AML risk. The Hardy-Weinberg equilibrium was tested by X2 analysis and the meta-analysis was performed by MedCalc Statistical Software version 11.6.1.0.

Results

The current study enrolled 192 cases of AML and 210 healthy controls. Among the patients, 94 (49.0%) were males and 98 (51.0%) were females, with a median age of 38±15.09 years at diagnosis. Among controls, 122 (58.1%) were females and 88 (41.9%) were males, whose median age was 34.2±12.51 years. The *GSTP1* polymorphism did not deviate from Hardy-Weinberg equilibrium in cases and controls (*P* were 0.07 and 0.6, respectively). Demographic, clinical and biological characteristics of AML cases and the controls are summarized in table

Table 4. Genotypic frequencies of *GSTM1, GSTT1* and Ile105Val *GSTP1* polymorphisms in patients with AML according to clinical parameters

		GSTP1		*P*	GSTT1		*P*	GSTM1		*P*
	N	Ile/Ile	Ile/Val+Val/Val		Present	Null		Present	Null	
Age	192									
≤35	87	38	49	**0.045**	54	33	0.610	50	37.	0.249
36-60	93	32	61		56	37		47	46	
>60	12	1	11		9	3		4	8	
Sex	192									
Woman	98	35	63	0.710	64	34	0.332	53	45	0.675
Man	94	36	58		55	39		48	46	
FAB classification										
M0- M1	43	1	31	0.776	29	14	0.298	29	14	0.406
M2	55	22	33		29	26		29	26	
M3	11	3	8		9	2		5	6	
M4	28	9	19		14	14		14	14	
M5	16	7	9		11	5		7	9	
M6-M7	12	4	8		7	5		5	7	
Karyotype	**180**									
Normal	83	34	49	0.268	52	31	0.801	49	34	0.090
Abnormal	97	32	65		59	38		45	52	

1. There were no statistically significant differences between the two groups in terms of sex (*P*=0.66) and age (*P*=0.39). M2 was observed to be the most common subtype (28.6%) followed by M1 subtype (18.8%) and LAM4 (14.1%), while the unclassified cases represented 14.1% according to the French-American-British (FAB) classification.

As shown in table 2, the distribution of the *GSTM1* null genotype was comparable between AML patients (47.4%) and controls (50.0%). Interestingly, the frequency of *GSTT1* null genotype was significantly higher among AML cases (38.0%) compared with the controls (22.4%), with a 2.12-fold increase in individuals with the *GSTT1* null genotype compared with the *GSTT1* present (95% CI: 1.37-3.29, *P*=0.0007).

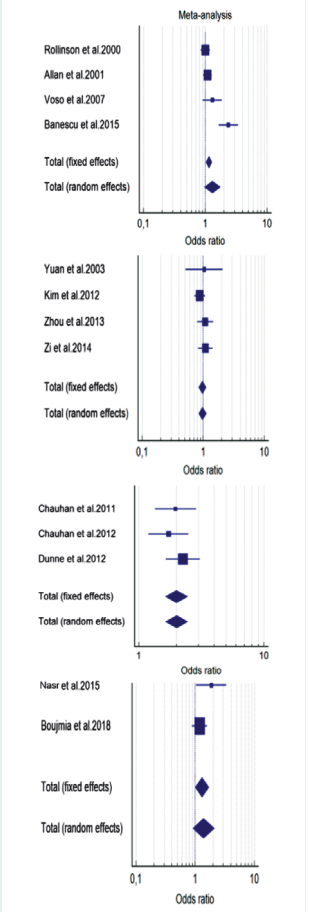
The genotype distribution of *GSTP1* gene is shown in table 2. No statistically significant differences in allele and genotype frequencies were found between AML patients and controls (*P*> 0.05). In the cases, 71 (37.0%) were homozygous for the wild type (Ile/Ile), 101 (52.6%) were heterozygous, and 20 (10.4%) were homozygous for Val/ Val. The distribution and frequencies of the *GSTP1* in controls were 93 (44.3) Ile/Ile, 96(45.7) Ile/ Val, and 21 (10.0) Val/Val. Compared with the subjects having a wild genotype (Ile/Ile), the odds ratios for (Ile/Val), (Val/Val) and dominant model were (1.37, 95% CI 0.90–2.09, *P*=0.13), (1.24, 95% CI 0.62-2.47, *P*=0.52) and (1.35, 95% CI 0.90-2.02, *P*=0.13), which showed no statistically significant association either.

Table 3 examines the risk associated with the combinations of the three genotypes *GSTT1*, *GSTM1,* and *GSTP1*. The reference group consisted of subjects carrying the wild-type genotypes of these three polymorphisms. The presence of at least one mutant genotype was associated with an increased risk of AML; a strong significant association was found between the combined genotypes *GSTT1* null, *GSTM1* present and *GSTP1* (Ile/Val & Val/Val) (OR: 6.26, 95% CI: 2.53-15.45, *P*=0.0001), and AML risk. Furthermore, the interaction between the null *GSTM1*, null *GSTT1* and *GSTP1* (Ile/Val&Val/Va) polymorphisms was found to be associated with an increased AML risk (OR 2.45, CI: 1.08–5.54, *P*= 0.03).

To determine whether the GST polymorphisms modulate the severity of the AML, the associations between the genotype and clinical features were further examined. No significant correlations were

Table 5. Pooled analysis of studies investigating the association between Ile105Val *GSTP1* polymorphisms and AML risk under the allele contrast

	Cases (events/total)	Controls. (events/total)	Odds ratio	95% CI
Caucasians				
Rollinson et al. 2000[33]	308/944	537/1646	1	0.843 to 1.186
Allan et al. 2001[27]	345/1006	658/2030	1.088	0.927 to 1.277
Voso et al. 2007[47]	91/310	76/314	1.301	0.912 to 1.857
Banescu et al. 2016[31]	69/204	108/606	2.357	1.649 to 3.368
Subtotal	**Q=19.01**	**I2=84.22**		
Heterogeneity	**df= 3**	**Z=2.44**	**1.14**	**1.027 to 1.268**
	(*P*=0.0003)	**(*P*=0.014)**		
East Asians				
Yuan et al. 2003[48]	14/80	29/170	1.031	0.511 to 2.080
Kim et al. 2012[41]	146/812	680/3392	0.874	0.717 to 1.066
Zhou et al. 2013[42]	121/326	144/406	1.074	0.793 to 1.454
Zi et al. 2014[43]	161/412	172/462	1.081	0.823 to 1.422
Subtotal	**Q=2,13**	**I2=00 %**		
Heterogeneity	**df= 3**	**Z= 0.42**		
	(*P*=0.54)	**(*P*=0.67)**	**0.971**	**0.845 to 1.115**
Mixed				
Chauhan et al. 2011[28]	70/240	70/404	1.965	0.404 to 1.167
Chauhan et al. 2012[29]	75/262	75/398	1.727	0.492 to 1.434
Dunna et al. 2013[59]	118/286	118/496	2.25	2.258 to 5.884
Subtotal	**Q=1.16**	**I2=00 %**		
Heterogeneity	**df= 2**	**Z= 6.72**		
	(*P*= 0.55)	**(*P*<0.001)**	2	1.634 to 2.446
Africans				
Nasr et al. 2016[45]	42/100	28/100	1.862	1.032 to 3.360
Boujmia et al. 2020	141/384	138/420		
Subtotal	**Q=1.80**	**I2=44.70 %**	1.186	0.887 to 1.586
Heterogeneity	**df= 1**	**Z=1.953**		
	(*P*= 0.178)	**(*P*=0.051)**	**1,296**	**0.999 to 1.681**
Total (fixed effects)	**1701/5366**	**2908/10844**	**1.136**	**1.055 to 1.222**
(random effects)	**1701/5366**	**2908/10844**	**1.232**	**1.043 to 1.455**



Test for heterogeneity: Q =51.86; DF =12; *I*2 = 76.86 % *P* < 0.0001 Z= 3,389 *(P* =0.001).

observed with gender, FAB subtype, and cytogenetic (*P*>0.05). However, the *GSTP1* genotype frequencies between age-classified patients were different (*P*=0.045) (Table 4).

For the *GSTP1* meta-analysis, we included a total of 13 studies with 2644 cases of AML and 5398 controls, which explored the relationship between *GSTP1* Ile105Val polymorphism and AML risk. The association between *GSTP1* Ile105Val polymorphism and AML under the allele contrast model among the 13 studies is shown in table 5, where a high level of between-study heterogeneity is observed in the overall meta-analysis. To explain the source of this heterogeneity, the subgroup analysis was performed.

The subgroup analysis based on ethnicity showed a significant association between the *GSTP1* Ile105Val polymorphism and AML risk in the mixed population (OR=2.25, 95% CI=2.26 to 5.88, *P*<0.001). The funnel plots did not provide any evidence of publication bias.

Regarding the meta-analysis of *GSTT1*, 28 studies with a total of 4951 patients and 8126 controls were included. As shown in table 6, the statistical heterogeneity was higher among the 27 studies, hence the subgroup analysis. The ethnicity subgroup showed that *GSTT1* was

Table 6. Pooled analysis of studies investigating the association between *GSTT1*polymorphisms and AML risk

	Cases (events/total)	Controls (events/total)	Odds ratio	95% CI
Caucasians				
Allan et al. 2001[27]	98/506	140/1019	1.508	1.136 to 2.003
Aydin-Sayitoglu et al. 2006[48]	21/94	29/140	1.101	0.584 to 2.077
Bolufer et al. 2007[49]	74/289	61/455	2.223	1.524 to 3.243
D'Alo et al. 2004[7]	56/193	52/273	1.737	1.126 to 2.680
Eyada et al. 2007[50]	9//19	5//11	1.08	0.243 to 4.791
Gra et al.2008[54]	21/71	94/490	1.769	1.014 to 3.089
Haase et al. 2002[52]	49/213	38/239	1.58	0.987 to 2.532
Muller al. 2008[34]	25/136	44/217	0.886	0.513 to 1.528
Ouerhani et al. 2011[38]	14/47	88/309	1.065	0.544 to 2.087
Rollinson et al. 2000[33]	89/475	125/826	1.293	0.959 to 1.743
Banescu et al. 2016[31]	24/102	63/303	1.172	0.686 to 2.002
Subtotal	**Q=12.26**	**I2=18.48%**	**1.45**	**1.273_1.66**
Heterogeneity	**df= 10 (*P*=0.26)**	**Z=1.273 (*P*<0.001)**		
East Asians				
Kim et al. 2012[41]	197/411	859/1700	1.139	0.915 to 1.417
Naoe et al. 2000[54]	214/398	81/150	0.784	0.539 to 1.141
Sasai et al. 1999[55]	21/38	13/36	2.186	0.859 to 5.559
Yang et al. 2005[37]	110/228	108/241	1.148	0.798 to 1.651
Zhou et al. 2013[42]	61/163	55/204	1.62	1.040 to 2.523
Zou et al. 2004[56]	14/25	89/183	1.344	0.580 to 3.118
Zi et al. 2014[43]	73/206	55/231	1.756	1.158 to 2.663
Subtotal	**Q=11.86**	**I2=49.41%**	**1.2**	**1.043_1.38**
Heterogeneity	**df= 6 (*P*=0.065)**	**Z= 2.54 (*P*=0.011)**		
Mixed				
Arruda et al. 2001[57]	13/38	44/276	2.742	1.303 to 5.768
Chauhan et al. 2011[28]	26/120	58/202	0.687	0.404 to 1.167
Chauhan et al. 2012[29]	27/131	47/199	0.84	0.492 to 1.434
Crump et al. 2000[58]	48/297	26/152	0.934	0.554 to 1.576
Dunna et al. 2013[59]	57/142	39/251	3.645	2.258 to 5.884
Majumdar et al. 2008[39]	16/110	11/137	1.95	0.865 to 4.395
Subtotal	**Q=31.87**	**I2=84.31**	**1.38**	**1.100_1.735**
Heterogeneity	**df= 5 (*P*<0.001)**	**Z= 2.77 (*P*=0.005)**		
Africans				
Nasr et al. 2016[45]	30/50	4//50	17.25	5.365 to 55.464
Boujmia et al. 2016[23]	52/129	25/129	2.809	1.604 to 4.922
Swellam et al. 2017[35]	48/88	24/90	3.3	1.761 to 6.184
Boujmia et al. 2020	73/192	47/210	2.127	1.375 to 3.291
Subtotal	**Q=11.12**	**I2=73.02 %**		
Heterogeneity	**df= 3 (*P* = 0.0111)**	**Z=7.47 (*P*<0.001)**	**2.98**	**2.238 to 3.968**
Total (fixed effects)	**1560/4911**	**2324/8723**	**1.441**	**1.323 to 1.568**
(random effects)	**1560/4911**	**2324/8723**	**1.441**	**1.292 to 1.828**

Test for heterogeneity: Q =51.86; DF =12; *I2* = 76.86 %*P* < 0.0001 Z= 3,389 (*P* =0.001).

associated with AML in Caucasians (1.45, 95%CI 1.27–1.66, *P*<0,001), and the funnel plot showed no evidence of publication bias.

30 case-control studies comprised of 5400

Table 7. Pooled analysis of studies investigating the association between *GSTM1*polymorphisms and AML risk

	Cases (events/total)	Controls (events/total)	Odds ratio	95% CI
Caucasians				
Allan et al. 2001[27]	278/506	496/1019	1.286	1.038 to 1.592
Aydin-Sayitoglu et al. 2006[48]	64/94	77/140	1.745	1.010 to 3.016
Bolufer et al. 2007[49]	143/295	232/451	0.888	0.662 to 1.191
D'Alo et al. 2004[7]	82/193	128/273	0.837	0.577 to 1.213
Gra et al. 2008[54]	28/71	238/490	0.689	0.415 to 1.146
Haase et al. 2002[52]	106/213	122/239	0.95	0.657 to 1.375
Lemos et al. 1999[34]	10//18	74/128	0.912	0.338 to 2.464
Muller et al. 2008[53]	70/136	119/217	0.873	0.568 to 1.342
Ouerhani et al. 2011[38]	23/47	163/309	0.858	0.465 to 1.586
Rollinson et al. 2000[33]	258/475	407/826	1.224	0.976 to 1.535
Seedhouse et al. 2004[34]	120/242	78/177	1.248	0.846 to 1.843
Banescu et al. 2016[31]	59/102	178/303	0.964	0.611 to 1.518
Subtotal	**Q=16.01**	**I2=31.33**		
Heterogeneity	**df= 11**	**Z=1.385**	**1.075**	**0.970_1.190**
	(*P*=0.14)	**(*P*=0.166)**		
East Asians				
Kim et al. 2012[41]	230/398	923/1700	1.152	0.924 to 1.437
Naoe et al. 2000[54]	227/411	77/150	1.17	0.804 to 1.701
Sasai et al. 1999[55]	21/38	23/36	0.698	0.275 to 1.776
Yang et al. 2005[37]	142/228	127/241	1.482	1.025 to 2.142
Zhou et al. 2013[42]	86/163	97/204	1.232	0.816 to 1.861
Zou et al. 2004[56]	17/25	99/183	1.803	0.741 to 4.387
Zi et al. 2014[43]	114/206	107/231	1.436	0.985 to 2.094
Subtotal	**Q=4,13**	**I2=0.00 %**		
Heterogeneity	**df= 6**	**Z= 3.04**	**1.24**	
	(*P*=0.65)	**(*P*=0.002)**		
Mixed				
Arruda et al. 2001[57]	28/38	102/276	4.776	2.229 to 10.237
Bhatla et al. 2008[60]	218/461	299/639	1.02	0.803 to 1.297
Chauhan et al. 2011[28]	45/120	97/202	0.649	0.409 to 1.030
Chauhan et al. 2012[29]	50/131	95/199	0.676	0.431 to 1.059
Crump et al. 2000[58]	159/297	75/152	1.183	0.800 to 1.749
Dunna et al. 2013[59]	90/142	94/251	2.891	1.887 to 4.428
Majumdar et al. 2008[39]	57/110	34/137	3.258	1.901 to 5.583
Subtotal	**Q= 56.66**	**I2=89.41 %**		
Heterogeneity	**df= 6**	**Z= 3.17**	**1.26**	**1.095_1.468**
	(*P*<0.001)	**(*P*=0.002)**		
Africans				
Nasr et al. 2016[45]	24/50	7//50	5.67	2.144 to 14.997
Boujmia et al. 2016[23]	68/129	63/129	1.168	0.717 to 1.903
Swellam et al. 2017[35]	20/88	44/90	0.307	0.161 to 0.588
Boujmia et al. 2020	91/192	105/210	0.901	0.609 to 1.333
Subtotal	**Q= 25.36**	**I2=88.7**		
Heterogeneity		**Z=-0.24**	**0.94**	**0.73_1.22**
	(*P*=0.67)			
Total (fixed effects)	**2928/5619**	**4780/9652**	**1.145**	**1.068 to 1.227**
(random effects)	**2928/5619**	**4780/9652**	**1.157**	**1.000 to 1.338**

Test for heterogeneity: Q =108.74; DF = 29; *I2* = 73.33 % *P*<0.0001 Z= 3.830 (*P* <0.001)

AML cases and 9679 controls were included in the meta-analysis of *GSTM1* polymorphism. As seen in table 7, the results showed a high level of heterogeneity in the overall analysis; hence, the ethnicity-based subgroup analyses which showed that the *GSTM1* polymorphism was associated with risk of AML in East Asians (1.24, 95% CI 1.8–1.43, *P*=0.02). The funnel plot showed no evidence of publication bias.

Discussion

The GST is a family of enzymes involved in the detoxification of many xenobiotics, through which GST protects cells against the negative effects of carcinogens. However, the polymorphisms in *GST*s reduce carcinogens detoxification caused by the decreased enzyme activity. Therefore, polymorphisms in the *GST* could modulate the susceptibility to developing cancers such as AML. In our previous study, both *GSTT1* null and *GST* double-null genotypes (*GSTT1*null/*GSTM1* null) were associated with an increased risk of AML.[23] The aim of the present case-control study was to evaluate the influence of *GSTT1*, *GSTM1* and Ile105Val *GSTP1* polymorphisms on susceptibility to AML. The genotype frequencies of the Ile 105 Val *GSTP1* and null genotype of *GSTM1* and *GSTT1* polymorphisms were determined in 210 control individuals.

The frequency of the null genotype of *GSTM1* in our control group was 50.0%, which is consistent with those reported in Caucasian, North Tunisian (50.2%), Japanese (51.3%), Chinese (50.4%), and white American (52%) populations. The frequency of *GSTT1* null genotype was 22.0%, similar to that reported by Garcia-Closas et al. in a Spanish population.

The frequencies of homozygous wild-type (Ile/Ile), heterozygous (Ile/Val), and homozygous (Val/Val) were 0.44, 0.46, and 0.10, respectively, which is in agreement with other African populations (0.45, 0.41,0.14) and European populations (0.47, 0.43, 0.10), yet quite different from Asiatic (0.61, 0.34, 0.05) and Indian (0.50, 0.44, 0.06) populations. Our results showed that the distribution of *GST* polymorphisms in our control population is similar to that of African populations, both of which could be grouped into a case-control study large enough to explore the relationship between these polymorphisms and the risk of cancers such as AML.

With respect to FAB classification, the most frequent FAB subtype observed in our study was M2, confirming the findings of our previous study,[23] and in line with other similar studies. No correlation was found between clinical and demographic (age and sex) parameters and *GSTT1* and *GSTM1* polymorphisms, which is similar to Voso et al. and Banescu et al. who reported no association between the *GST* genotypes and karyotype or FAB subtypes.However, a positive correlation was found between the *GSTP1* distribution and age, consistent with Dunne et al. who reported a positive correlation between sex, age, biological parameters (WBC count and LDH levels) and Val/Val genotype in an Indian population.[32] In contrast, Rollinson et al. reported no relationship between the *GSTP1* distribution and cytogenetic classification, age and FAB types.[33]

In the current study, the *GSTM1* null genotype did not show any statistically significant association with the risk of AML. Lemos et al. and Swellam et al. reported similar results. However, Seedhouse et al. found a significantly higher risk of AML development in patients with the *GSTM1* null genotype.[36] Yang et al. also showed a significantly higher frequency of the *GSTM1* null genotype in AML patients compared to controls.[37] Strikingly, we found that the *GSTT1* null genotype was significantly associated with increased risk of AML. Ouerhani et al. found no association between the *GSTT1* null genotype and AML risk in Tunisia.[38] Swellam et al. and Majumdar et al. reported a similar result, but several studies have reported a positive association between *GSTT1* null genotype and AML risk.[33, 40, 41]

Regarding the effect of Ile105 Val *GSTP1* polymorphism on AML risk, Ile/Val and Val/Val genotypes were slightly higher in patients (52.6%; 10.4%) than in controls (45.7%; 10.0%) in the present research, which also showed that these genotypes were not significantly associated with

the risk of AML. In our study, the combined variant genotypes Ile/Val and Val/Val of Ile105Val were not significantly correlated with AML risk as the Ile/ Ile genotype. These findings are in line with many case-control studies which reported no statistically significant association between this polymorphism and risk of AML.,[30] Similarly, in a meta-analysis of 5 studies (852 cases and 2339 controls), He et al. concluded that there was no association between the polymorphism and risk of AML in the homologous contrast, recessive and dominant genetic models. On the contrary, a study from Egypt posited that heterozygous genotype and mutant G allele (AG+GG) was significantly higher among AML patients than controls, respectively.[45] Banescu et al. and Dunne et al. also observed a significantly higher risk of AML development in patients with homozygous mutant genotype Val/Val. Similarly, Xi et al. showed subjects with Ile/Val and Val/Val genotypes had a 2.214-fold increased risk of developing AML compared to those with the wild genotype Ile/Ile.[46]

We further analyzed the combined effect of *GSTT1*, *GSTM1* and *GSTP1* polymorphisms, and noticed a statistically significant association between the combination of *GSTM1*, *GSTT1* null and Ile/Val+val/val regarding *GSTP1* and AML risk. Subjects carrying the *GSTM1* Present, *GSTT1* null and *GSTP1* Ile / Val et Val /Val genotypes had a higher risk of developing AML, partially confirming the hypothesis of the absence of an association between the *GSTM1* null genotype and AML. A similar finding was reported by Zhou et al.[42] The difference between studies concerning the relationship between *GST* polymorphisms and AML risk could be explained by factors such as sample size, genotyping method, and selection of control groups, and lifestyle, geographic and ethnic differences.

In our meta-analysis, the ethnicity stratification showed a significant association between *GSTM1* null genotype and AML risk in East Asians. Likewise, genotype *GSTT1* null was associated with AML among Caucasians. These results are in agreement with the previous meta-analysis of He et al.[44] However, the meta-analysis by Das et al. showed that only the *GSTM1* polymorphism was associated with risk of AML.[40] The subgroup analysis also showed a significant association between the Ile105Val *GSTP1* polymorphism and risk of AML under the contrast model in mixed populations.

There are some limitations in the current meta-analysis: First, the small number of published studies on the relationship between Ile105Val polymorphism and risk of AML might influence the evaluation of this association. Second, some studies included in this meta-analysis might have a sample size insufficient to explore the relationship between this polymorphism and AML risk. Third, the studies published with languages other than English were excluded from this meta-analysis. Fourth, AML remains a multifactorial complex disorder associated with genetic and environmental factors, yet the present study did not include the analysis of environmental factors (such as benzene, pesticides), life-style and gene-gene interactions. Therefore, the results of this meta-analysis should be treated with caution and further studies are required to confirm our findings.

Conclusion

The present case-control study indicated that the GST gene polymorphisms may be involved in susceptibility to AML in Moroccan adult populations. The meta-analysis suggests that the *GSTM1*-null genotype is a risk factor for AML in East Asians, *GSTT1*-null genotype among Caucasians and *GSTP1* Ile 105 Val polymorphisms in mixed population. Further studies are needed to confirm these results.

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Conflicts of Interest

None declared.

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