The Variant Allele Frequency of *Gstp1 Rs1695* (313a>G) Polymorphism With Leukemia Susceptibility in the Saudi Arabian Population and Other Ethnic Groups

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ABSTRACT

Introduction: single nucleotide polymorphisms (SNPs) in exon 5 of the Glutathione-S-transferase Pi 1 (*GSTP1*) gene are directly associated with the progression and onset of leukemias. SNPs are common prognostic biomarkers for predicting and early onset of leukemia risk. The variant frequency of *GSTP1 rs1695* (313 A>G) polymorphisms may affect various ethnic groups differently. In this study, the allelic frequency distribution of *rs1695* (313 A>G) polymorphisms was assessed in the Saudi Arabian population and compared with other world populations.

Material and Methods: Data were extracted from case-control studies in several ethnic groups using PubMed (Medline) and similar web databases.

Results: The frequency of *GSTP1 rs16955* (313 A>G) variant allele (G) was observed at 29.5% and different frequencies were significantly found in Egypt ($p = 0.001$), and India ($p = 0.002$). The prevalence of the frequency of *GSTP1 rs16955* in the Saudi Arabian population was compared to that of other populations. The observed findings reveal a distinct pattern of *GSTP1 rs1695* (313 A>G) polymorphism variant allele in the populations of Saudi Arabia, possibly due to differences in race.

Conclusion: The observed findings can help assess the risk for the population harboring the risk allele of *rs1695* (313 A>G) SNP and their subsequent susceptibility to leukemia.

Keywords:GSTP1, rs1695, 313 A >G, Single nucleotide polymorphism, Leukemia.

INTRODUCTION

Leukemia is a malignant clonal hematological disease caused by the excess leucocytes found in the bone marrow[1], and is a multifactorial genetic disease and a malignant tumor of the hematopoietic cells [2]. Based on the origin of the affected blood cell, leukemia was mainly classified into two subtypes, myeloid and lymphoid leukemia. Additionally, based on the onset of the disease, it can be classified into acute and chronic leukemia [3].

Among leukemias, AML is one of the heterogeneous disorders having various molecular pathways, which have characteristics of uncontrolled proliferation and undifferentiation of progenitors of myelocytic cells [4]. It is mostly found in adults, specifically in elderly people [5]. Among various cancers, AML is reported as the 6th leading cause of mortalities [6].

ALL is a lymphoproliferative neoplastic disease that has characteristics of malignant proliferation, impaired differentiation, and maturation, leading to the accumulation of progenitors of lymphoid tissue in the bone marrow, also found in the blood and extramedullary region [7]. About 80% of ALL cases are reported in children and are rarely found in the cases of adults.

CML is a myeloproliferative disease, and the carcinogenic mechanism of this disorder is not well defined [8]. The environmental exposure of the cytotoxic and genotoxic agents that are derivatives of benzene can be associated with increasing CML risks [9]. The genetic variations in metabolizing enzymes of xenobiotics are directly associated with the development of cancer, this metabolism provides a crucial role in defense against several other carcinogenic agents [10].

It is evident from earlier studies that there is an association of GSTs with leukemogenesis, and this gene polymorphism affects leukemia treatments, as GSTs play an important role in the detoxification of active metabolites used as chemotherapeutic agents for killing cancerous cells [11, 12]. Leukemia progression has been widely studied over the last decades, although their mechanisms progression is not well-known. Various risk factors can result in leukemia progressions, such as genetic variations in the pathways of DNA damage response [13, 14].

The *GSTP1* gene spans about 2.8 kbs and is found on chromosome 11q13.2 has seven exons and is one of the members of the *GSTs* superfamilies. The polymorphism of *GSTP1 rs1695* (313 A>G, Ile105Val) is broadly studied, in the coding region guanine (G) replaces adenine (A) at 313 bases of exon 5, corresponding towards valine (Val) substituted for isoleucine (Ile) at 105 [15].

The phase II detoxifying enzyme GSTs is involved in cellular protection against carcinogenic agents, xenobiotics, and oxidative stresses [16]. The GSTs are non-enzymatic proteins that can mediate signaling pathways, control proliferation of cells, differentiation, cell death, and process DNA damage [17]. The functional polymorphisms of *GSTM1* and *GSTT1* genes because of their complete deletion and substitution

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of a single nucleotide in GSTP1 c.313A>G, are commonly found in the populations, and distributions of their genotypes show remarkable differences between different ethnicities [18, 19].

The identified polymorphism found in exon 5 of the *GSTP1* gene at nucleotide 313 is A>G leading to amino acid substitutions of isoleucine (IE) by valine (Val) at position 105 amino acid (Ile 105 Val). This polymorphism may perform important functions in leukemogenesis, by altering protein functions, diminishing its detoxifying abilities for certain mutagenic and carcinogenic agents, leading to increased DNA damage and mutations, and a higher risk of cancer progression [20].

Various epidemiological studies were conducted for the investigation of the association of *GSTP1 rs1695* (313A>G) polymorphism and its role in leukemia progression. However, functional effects of *rs1695* 313A>G polymorphism in the Saudi Arabian population in any type of leukemia have yet to be elucidated. Thus, the current study sought to determine the frequency distribution of *GSTP1 rs1695* 313A>G polymorphisms among the healthy normal population of Saudi Arabia compared to some other ethnicities.

MATERIAL AND METHODS

Gene variants search criteria: The databases were searched from PubMed, CGEMS, Web of Science, Embase, and EBSC for articles having keywords "*GSTP1*" "*rs1695*" "313 A>G" and "polymorphisms". The search criteria covered all subjects were written in any language. The studies having the frequencies of genotypes of control groups were included. However, those studies having allele frequencies only and not having genotype frequencies were excluded.

The first author name, publication years, nationality of subjects, type of research, number of controls, inclusions and exclusions criteria, alleles, and genotype frequencies of the subjects were abstracted for each study that qualified those criteria. If multiple reports were found from the same race, the most recently published data were included. Data on the population of Saudi Arabia was included in the most recent reports.

Table 1. Analysis of *GSTP1 rs1695* (313A>G) gene variant in different populations

S No.	Study	Country/ Ethnicity	Race	Disease/ Cancer types	Total no. of subjects (n)
1.	Farasani., 2019	Saudi Arabia	Arab	AML	100
2.	Idris et al., 2020	Sudan	North African	CML	100
3.	Rostami et al., 2019	Iran	Persian	CML	104
4.	Hamed et al., 2016	Egypt	North African	CML	30
5.	Nasr et al., 2015	Egypt	North African	AML	50
6.	Weich et al., 2016	Argentina	Hispanic	AL	133
7.	Dunna et al., 2012	India	Asian	AL	248
8.	Ibrahim et al., 2012	Egypt	North African	NHL	50
9.	Kim et al., 2009	Korea	Asian	NHL	1696
10.	Stanulla et al., 2000	Germany	Caucasian	ALL	64

AML (Acute myeloid leukemia); CML (Chronic myeloid leukemia); AL (Acute leukemia); NHL (Non-Hodgkin lymphoma); ALL (Acute lymphoblastic leukemia)

Table 2. Observed and expected genotypic frequencies *of GSTP1 rs1695* (313A>G) polymorphism in the control group

Study	Observed Genotype (n)			Expected Genotype (n)			MAF	*p*-value (HWE)
	AA	AG	GG	AA	AG	GG		
Farasani., 2019	46	49	05	50	40	10	0.300	0.03 (Chi^2 4.85)

Table 3. *GSTP1 rs1695* (313A>G) gene variant genotype and allele frequency distribution in different populations and *p*-values in contrast to the Saudi Arabian population

S N	Study	Disease/ tumor type	Total no. of subjects (n)	Genotype			Allele		Total Alleles	A Allele frequency	G Allele frequency	*p*-value	MAF
				AA	AG	GG	A	G					
1.	Farasani., 2019	AML	100	46	49	05	141	59	200	0.705	0.295	**Ref. 0.03***	29.5
2.	Idris et al., 2020	CML	100	62	36	02	160	40	200	0.800	0.200	0.21	20.0
3.	Rostami et al., 2019	CML	104	66	33	05	165	43	208	0.794	0.206	0.59	20.6
4.	Hamed et al., 2016	CML	30	21	08	01	50	10	60	0.833	0.167	1.00	16.7
5.	Nasr et al., 2015	AML	50	32	08	10	72	28	100	0.72	0.28	**0.001***	28.0
6.	Weich et al., 2015	AL	133	53	65	15	171	95	266	0.642	0.358	0.45	35.8
7.	Dunna et al., 2012	AL	248	140	105	03	385	111	496	0.776	0.223	**0.002***	22.3
8.	Ibrahim et al., 2012	NHL	50	10	32	08	52	48	100	0.52	0.48	**0.04***	48.0
9.	Kim et al., 2009	NHL	1696	1077	558	61	2712	680	3392	0.800	0.200	0.29	20.0
10.	Stanulla et al., 2000	ALL	64	32	22	10	86	42	128	0.671	0.329	0.09	32.9

AML (Acute myeloid leukemia); CML (Chronic myeloid leukemia); AL (Acute leukemia); NHL (Non-Hodgkin lymphoma); ALL (Acute lymphoblastic leukemia)

* significant

In this study, the prevalence rate of *GSTP1 rs1695* 313A>G polymorphisms was extracted from ten studies [20-28] (as shown in Table 1) that the gene variants of *GSTP1 rs1695* (313A>G) were analyzed in different populations and matched with the population of Saudi Arabia [21] (as shown in Table 2).

Statistical Analysis: For the comparison of the allelic and genotypic frequencies, Pearson's $\chi 2$ test was applied to different populations by utilizing the statistical software program SPSS. The Hardy-Weinberg Equilibrium (HWE) was applied in this study using the Court Lab (a software program based on the web). In the analysis, if the *p*-value was found $p \leq 0.05$ is considered statistically significant.

RESULTS

According to the distribution of genotype, minor allele frequency (MAF) of *GSTP1 rs1695* 313 A>G polymorphisms was found to be 29.50% in the population of Saudi Arabia, which was found consistent with the HWE accordingly as shown in Table 2. The different MAF was found in the genotypes (AA, AG, and GG), and the distribution of allelic frequencies of polymorphisms studied in several populations is shown in Table 3.

The *GSTP1 rs1695* 313 A>G polymorphisms were significantly different MAFs for Egyptian ($p = 0.001$), Indian ($p = 0.002$), and Egyptian ($p = 0.04$) ethical groups compared to that observed in the Saudi Arabian population that were matched with other population groups *(*$p = 0.03$).
In the population of Saudi Arabia, the distribution frequency of *GSTP1* genotypes- AA was 46%, of -AG was 49%, and -GG was 5% in the case of AML, whereas the frequency of A and G alleles in AML was found to be 70.5%and 29.5%, respectively.

However, another MAF was not observed significantly for the ethnicity of Sudan ($p = 0.21$), Iran ($p = 0.59$), Egypt ($p = 1.00$), Argentina ($p = 0.45$), Korea ($p = 0.29$), and Germany ($p = 0.09$).

DISCUSSION

GSTs play an essential role in the maintenance of cellular homeostasis by providing cryoprotection from toxins, drugs, and byproducts of oxidative stress [29]. The non–enzymatic functions of GTs include post-translational modifications, cell signaling, proliferation, apoptosis, inhibition of DNA damage, and resistance to chemotherapeutic drugs [30, 31].

An association between the *GSTP1* gene polymorphisms and the susceptibilities to various types of cancers, including lung [32], breast (Hashemi et al., 2012) and ovarian cancers [33] have been reported. Likewise, the association of *GSTs* with leukemias was documented [20, 22, 25, 34]. Additionally, the contribution of *GSTP1* mutant allele to the vulnerability to CML was reported [23].

Various studies have shown the association between *GST* polymorphisms and ALs [20, 35]. However, limited information was found about *GST* polymorphisms in CML progression. A study by Taspinar et al., (2008)[36] showed *GSTM1* and *GSTT1* polymorphisms, while other studies reported *GSTP1* (*Ile105Val*) gene polymorphisms in CML patients [37, 38].

Several mechanisms have evolved for the protection of DNA integrity from endogenous and exogenous damage. The involvement of GSTs in the metabolism of carcinogenic agents and pollutants of the environment suggests that polymorphisms located at *GST* act as candidate genes for leukemia predispositions [12]. The regulation of GSTP1 activities by various cellular proteins through the formation of protein: protein interactions [39].

The modulation of GSTs affects signaling pathways and non-enzymatic proteins, controlling proliferation and differentiation, leading to cell apoptosis [25]. In the case of the *GSTP1* gene, the G allele lowers the enzymatic activities, reduces antioxidant properties, and enhances oxidative stresses, leading to cellular damage [21]. Polymorphisms result in decreased enzymatic activities and are associated with increasing hydrophobic levels of DNA adducts [40, 41]. The relationship between genetic variants of *GSTs* and AML was observed in earlier studies carried out in adult AML patients in Saudi Arabia.

The *SNP rs1695* (313 A>G) is linked to a high risk associated with different types of leukeimas. Other several studies have connected the *rs1695* gene to various forms of leukemias such as AL, AML, ALL, NHL; CML [20-22, 24-26, 28, 42].

Nasr et al., (2015)[24] found that the effect of *GST* polymorphisms and its polymorphic variants account for susceptibility and make a difference in patients' outcome with AML by applying chemotherapy. It was observed that wild genotype (AA) was significantly high in control groups, although the frequency of hetero mutant genotype (AG) and mutant G allele (AG + GG) was significantly high in patient groups [24].

In a study carried out by Dunna et al., (2012)[20], a significantly high frequency of *GSTP1 GG* genotypes was observed in both the patients of ALL and AML when compared with controls, showing that such genotypes may confer a risk of developing AL. Various studies showed a significant correlation between the valine (G) allele and susceptibilities to tumor development of the breast, bladder, lungs, and multiple myelomas [43-45]. Earlier studies reported the *GSTP1 105 Val* (GG) genotype is correlated with a favorable prognosis followed by chemotherapies in various types of malignancies, including breast and colon cancers, and pediatric ALL [28, 46, 47].

A study was carried out by Ibrahim et al., (2012)[26], on the metabolism of carcinogenic agents exogenously in humans producing active metabolites, that bind and damage nuclear and mitochondrial DNA. The exposure of cytotoxic chemicals causing oxidative stresses contributes to the development of many diseases and cancers. Also, it was found that the relationship of *GSTP1 rs1695 313* A>G polymorphisms with NHL risks is associated with smoking tobacco. It is evident that the association between *GSTP1* 313 A>G polymorphism and diffuse large B-cell lymphoma (DLBCL), showed that AG and GG genotypes of GSTP1, and the G allele are associated with lower risks for DLBCL [26].

The discrepancies among various studies are attributed to factors such as the assessed populations being of different ethnic groups; various methods of genotypes may affect the results; several studies have deviated from the HWE; and methods of study design for each study were different, resulting in reduced in consistency. However, leukemias and other disorders have different inheritance patterns.

The disease progressions and their consequential effects on genetic and epigenetic alterations, copy number variation, and influences of various environmental factors. The different prevalence of the *rs1695* (313 A>G) SNP among populations suggests that vulnerability factors have various effects on different population groups.

In this analysis, the frequencies of allele and genotypes studied do not show the overall ranges of variants at the same location. However, these types of studies provide insight into the developmental process of clinical and epidemiological databases for prospects. It was observed by

genome-wide association studies (GWAS) and association of genetic studies that common types of alleles and their frequencies contribute to the hereditary component of most prevalent complex diseases.

The association of various genetic model tests is needed for the identification of essential genes and their corresponding SNPs participating in the progression and early development of therapeutic preventions of the disease progression leading to the possible treatments.

However, there are many shortcomings, including statistical and computational analysis, and the reproducibility factors, that must be considered for essential genetic markers applied in the associations of the gene-disease research that could be identified [48].

CONCLUSION

The allelic variants of *rs1695* (313 A>G) polymorphism in the population of Saudi Arabia substantially vary from those in different populations worldwide. The findings can be applied for screening leukemias, as well as in assessing and predisposing disease progression significantly, which could be used as a potential biomarker in the progression of leukemias.

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