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Association of Human GSTM1 and GSTT1 Genes Polymorphisms with Prostate Tumors in Population of the South Provinces of Iraq

Yusra Sebri Abdul Saheb[1], Salwa H.N. AL-Rubai'e[2], Nahi Y. Yaseen[3] and Ahmed Ab. Suleiman[4]

[1]Department of Chemistry, College of Science, Missan University, Missan, Iraq
[2]Department of Chemistry, College of Science, Al-Mustansiriya University, Baghdad, Iraq
[3]Department of Heredity, Iraqi Center for Cancer and Medical Genetics research, Al-Mustansiriya University, Baghdad–Iraq
[4]College of Science, Al-Anbar University, Al-Anbar, Iraq

**Corresponding author*

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A B S T R A C T

The second most common type of cancer in men is prostate cancer (PCa). The incidence of PCa may vary among different ethnic groups and countries. The aim of this study is to evaluate the influence of polymorphisms in glutathione–S–transferases M1 and glutathione–S–transferases T1 genes on the risk of developing prostate cancer and benign prostate hyperplasia in a population of south of Iraq. Several polymorphic genes encoding enzymes involved carcinogenesis were studied as possible risk factor of prostate cancer. Genetic polymorphisms in glutathione–S–transferase M1 and glutathione–S–transferase T1 genes were constantly reported as a critical component on prostate cancer risk due to absence of these enzymes possibly contributed. In this study, ninety five men were participated. Fifty five patients with prostate cancer, the mean age 58.42 ± 6.83 years, forty benign prostate hyperplasia mean age 55.17 ± 5.19 years and fifty healthy control mean age 44.10 ± 9.36 years. Results show there is a highly significant difference in Chi-square levels of presents and deletions in glutathione–S–transferases M1 and glutathione–S–transferases T1 genes in all study groups. Also, Significant associations were observed among *GSTM1*-present + *GSTT1*-present (p= 0.0496) and *GSTM1*-null + *GSTT1*-present (p=0.0136), no significant associations in *GSTM1*-present + *GSTT1*-null (p= 0.207) and *GSTM1*-null + *GSTT1*-null (p=0.094).

Introduction

The second most common type of cancer in men is prostate cancer (PCa). The incidence of PCa may vary among different ethnic groups and countries (de Sa *et al*., 2014).

Benign prostatic hyperplasia (BPH) refers to increase in the number or size of cells, is a benign enlargement or growth of the prostate gland (Chang *et al*., 2012). Since

early detection increases the chance of successful treatment, the prostate-specific antigen (PSA) test and the digital rectal examination should be offered to men annually beginning at age 50 (Sivonova *et al*., 2009). Multiple variables such as, ethnic, origin, environmental, and genetic factor are possibly linked to incidence of PCa especially, the genetic factor may responsible for about 42 % of PCa (Shin *et al*., 2016). Epidemiological data suggested that age, smoking, dietary habits, pollutant exposure, genetics and many other factors may be involved in prostate cancer development. Age plays an important role in the development of prostate cancer and its incidence increases with the increased age (Malik *et al*., 2015).

The biochemical basis for the individual difference in the susceptibility to carcinogens may be attributed to the genetic polymorphisms of genes implicated in the metabolic detoxification of environmental carcinogens (Amankwah *et al*., 2012). Actually, there are various important genes encoding enzymes included in the biotransformation of carcinogens of these enzymes is glutathione–S–transferases (GSTs) (Sharma *et al*., 2004).

GSTs are one of the major phase II detoxification enzymes involved in the xenobiotics metabolism and play an important function in cellular protection against oxidative stress (Zhou *et al*., 2014). The GSTs genes are classified into different classes, including alpha, mu, omega, pi, theta and zeta, that are encoded by the *GSTA, GSTM, GSTO, GSTP, GSTT* and *GSTZ* genes, respectively (Bansal *et al*., 2014; Safarinejad *et al*., 2011). To protect of DNA from damage by detoxifying the carcinogens, the level of GSTs enzymes must be high (Sharma *et al*., 2004). Subsequently, the deficiency in GST enzyme activity may be a risk factor for developing cancer when exposed to some carcinogens (Zhao *et al*., 2015). The expression of GSTs enzymes is mainly affected by the genetic polymorphisms in the GSTs genes (Oakley, 2011). *GSTM1* and *GSTT1* among GSTs genes, are most widely analyzed for its genetic association with several cancers (Bansal *et al*., 2014; Pan *et al*., 2014). The homozygous deletion (null genotype) of the *GSTM1* and *GSTT1* genes result in complete absence of enzyme activities (Safarinejad *et al*., 2011). In the DNA repair pathway, *GSTM1* and *GSTT1* are critical components for it, thus absence of these enzymes possibly contribute to the higher risk of PCa (Cai *et al*., 2013; Liu *et al*., 2013). Many studies were reported regarding the genetic status of *GSTM1* and *GSTT1* polymorphism and PCa development, but the impact of polymorphisms of these two genes on PCa is still unclear because of inconsistent results among different populations (Malik *et al*., 2016; Yang *et al*., 2013).

The present study was, therefore, undertaken to Examine the relative impact of the genetic polymorphisms at the gene loci *GSTT1* and *GSTM1* on susceptibility to PCa and to investigate the implications of the null genotypes in South Iraqi PCa patients in relation to the BPH and normal controls by using multiplex PCR analysis. The aim of this study is to evaluate the influence of polymorphisms in *GSTT1* and *GSTM1* genes on the risk of developing prostate cancer and Benign Prostate Hyperplasia in a population of the south of Iraq.

Materials and Methods

Sampling

Two groups of patients (PCa and BPH) were included in this study, they were diagnosed

with prostate tumor, confirmed by histological examination, and treated at the Oncology centre in Al–Basra Hospital during the period from July 2014–September 2015. Fifty five of PCa patients between 40–69 years of age (mean 58.42 ± 6.83), forty of BPH patients between 40–69 years of age (mean 55.17 ± 5.19). The distribution of PCa patients were consist of 40 and 15 from AL–Basra and Thi Qar provinces respectively, while the distribution of BPH patients were 30 of AL–Basra and 10 of Thi Qar provinces. The 50 healthy volunteers as control group were from the same provinces (mean 44.10 ± 9.36 years). Five milliliters of blood sample were collected from patients and control, 3 mL were placed into plain tubes and centrifugation at 1500 × g for 5 min, the serum were removed and refrigerated at -20°C until analysis of PSA. Erythrocytes were washed three times with cold saline to determine GST activity. The remaining blood placed into EDTA tubes. The information on age, marital status, smoking habit, alcohol consumption, family history of cancer, geographical location, and ethnicity, were collected by questionnaire of patients and control groups.

DNA extraction

Total genomic DNA extracted from the whole blood collected in EDTA anticoagulant tubes was applied using genomic DNA purification kits (geneaid) south Korea, in order to perform genotyping analysis. Multiplex Polymerase Chain Reaction (PCR) from Agilent Technologies/ USA for *GSTM1* and *GSTT1*genotypig was don using specific primer synthesized at Bioneer/south korea Company as a lyophilized product as shown in Table 1. Multiplex PCR was performed in a 20µL total volume, Primer forward1µL (20PM for each one), Primer reverse 1µL (20 PM for each one), Template DNA 5 µL (50–100 ng), completed with specific master mix. The PCR amplification was conducted in PCR system under the conditions: 94 ºC for 5 min, followed by 35 cycles of 94 ºC for 1 min, 58 ºC for 1 min and 72 ºC for 1 min, then a final extension at 72 ºC for 10 min. Each PCR products were analyzed by electrophoresis on 2 % agarose gel. The length of PCR products were 230 bp for individuals with one or more *GSTM1* alleles, 459 bp for individuals with one or more *GSTT1* alleles and 350 bp for albumin as internal control, as seen in Fig. 1.

Laboratory assessments

All chemicals and reagents of analytical grade were purchased from Fluka unless indicated otherwise. The GST activity was assayed spectrophotometrically at 23C, using a Shimadzu UV160U (Shimadzu Corp., Columbia, Md.) to measure the rate of conjugation of GSH to Chloro-2,4-dinitrobenzene (CDNB) at 340 nm (Carrmagnole *et al*., 1981). Serum of PSA levels was measured by mini–VIDIS assay (Bio Merieux, France) using kit supplied by Bio Merieux – France.

Results and Discussions

This study focused on polymorphism of *GSTM1* and *GSTT1* genes among patients with prostate tumors (PCa and BPH) and healthy subjects as control group of the two southern provinces (Al–Basra, and Thi Qar) of Iraq. Table 2 illustrates the distribution state of the three study groups. The mostly distribution percentage was in Al–Basra (72.73 %), followed by Thi–Qar (27.27 %).

The results in this study showed that the mean levels of GST activity decreased in PCa (0.078 ± 0.02 U/Hb) and BPH patients (0.109 ± 0.02 U/Hb), in comparison with

control group (0.852 ± 0.04 U/Hb). In addition, there was a highly significant decreased (P=0.001) in the serum level of enzyme activity in PCa patients when compared with those of BPH patients or control group. In cellular metabolism, the progressive changes occurring over years could play a substantial role within the initiation, and improvement of cancer. Insufficiency in the antioxidant defense system or increasing of ROS levels could cause oxidative stress leading to progress of cancers as well as PCa (Tefik *et al*., 2013).

The results revealed that PSA levels were significantly increased (P=0.001) in PCa (24.413± 6.306 ng/mL) and BPH patients (4.917± 1.655 ng/mL) in comparison to control group (0.490± 0.186 ng/mL). PSA is used as serum marker for prostate cancer due to its high specificity for prostate tissue, (Alva *et al*., 2016). In regards of the genotyping analysis of *GSTT1* and *GSTM1* genes in tumor prostate patients and control group, the results showed a highly significant difference of presents and deletions in *GSTM1* and *GSTT1* genes in all study groups using Chi-square analysis. In the current study, 32(58%) patients with PCa had present *GSTM1* amplification 41 (75%), 26 (67%) patients with BPH had 29 (73%) present *GSTM1* while 38 (76%) of control subjects had 43 (87.5%) present *GSTT1* amplification. On the other hand deletion *GSTM1* amplification was 23(42%), 14(33%) and 12 (24%) for PCa, BPH patients and control subjects respectively. Furthermore, deletion *GSTT1* amplification was 14(25%) of PCa patients, 11 (27%) and 7 (12.5%) of BPH and control groups respectively as seen in Table 3.

Table.1 Primer sequences used multiplex PCR amplification of GSTM1, GSTT1 and Albumin genes

Primer	Primer sequences (5-3)	L	Tm˚C
Albumin	F-5-GCC CTC TGC TAA CAA GTC CTA C-3	22	53.7
	R-5-GCC CTA AAA AGA AAA TCG CCA ATC-3	24	60.0
GSTM1	F-5-CGCCATCTTGTGCTACATTGCCCG -3	24	75.0
	R-5-TTCTGGATTGTAGCAGATCA -3	20	56.0
GSTT1	F-5-TTCCTTACTGGTCCTCACATCTC -3	23	68.0
	R-5-TCACCGGATCATGGCCAGCA -3	20	64.0

Tm: Melting Temperature , F: Forward Primer ,R: Reverse Primer.

Table.2 The percentage distribution of prostate patients and control groups in southern provinces of Iraq

Province	PCa		BPH		Control	
	N	(%)	N	(%)	N	(%)
Basra	40	72.73	30	75	30	60
Thi–Qar	15	27.27	10	25	20	40
Total number	55		40		50	

Table.3 Distribution of genotype for GSTT1 and GSTM1 genes in tumor prostate patients and control group

Type	Genotype	PCa N(%), N=55	BPH N(%), N=40	Control N(%),N=50	Chi-square-χ2
GSTM	**Present**	32 (58)	26 (67)	38 (76)	8.155 **
	Deletion	23 (42)	14(33)	12 (24)	8.155 **
Chi-square-χ^2		6.522 **	9.305 **	11.728 **	---
GSTT	**Present**	41 (75)	29(73)	43 (87.5)	7.026 **
	Deletion	14 (25)	11 (27)	7 (12.5)	7.026 **
Chi-square-χ^2		10.063 **	12.866 **	14.053 **	---

Table.4 Combined genotype frequencies of the GSTM1 and GSTT1 polymorphisms in the PCa patients and control group

Genotypes of GST	PCa n (%) N= 55	Controls n (%) N=50	OR with 95% CI	Chi-square (χ^2)	p-value
		GSTM1			
Present	32(57.5)	38 (75)	0.671 (0.66-1.26)	4.619 *	0.0466
Deletion	23(42.5)	12 (25)	0.671 (0.66-1.26)	4.619 *	0.0466
		GSTT1			
Present	39(70)	44 (87.5)	0.849 (0.68-1.03)	6.256 **	0.0148
Deletion	16(30)	6(12.5)	0.849 (0.68-1.03)	6.256 **	0.0148

* p<0.05, ** p<0.01. The Chi square and P value using Bonfferoni correction for multiple testing, OR adjusted in multivariate logistic regression models including age and GST genotypes

Table.5 The combinations of GSTM1 and GSTT1 genes polymorphisms in the PCa patients and control group

Combinations of *GSTM1* and *GSTTT1*	PCa n (%) N= 55	Controls n (%) N=50	OR with 95% CI	Chi-square (χ^2)	p- value
+/+	17(31)	20(40)	0.369 (0.47-0.97)	4.027 *	0.0496
+/-	6(11)	7 (14)	0.073 (0.36-0.89)	0.227 NS	0.207
- /+	29(52.7)	16 (32)	0.702 (0.68-1.03)	7.249 **	0.0136
- /-	3 (5.3)	7 (14)	0.264 (0.52-0.83)	2.681 NS	0.094

* p<0.05, ** p<0.01. The Chi square and P value, using Bonfferoni correction for multiple testing, OR adjusted in multivariate logistic regression models including age and GST genotypes.

Table.6 The distribution of ages, family history, ethnicity and smoking in PCa patients

Factors		*GSTM1* Present N(%)	*GSTM1* Deletion N(%)	*GSTT1* Present N(%)	*GSTT1* Deletion N(%)
Age	**40 – 49, N=10**	7 (70)	3 (30)	8 (80)	2 (20)
	50 – 59, N=30	25 (83.3)	5 (16.4)	27 (90)	3 (10)
	60 – 69, N=15	10 (66.6)	5 (33.4)	12 (80)	3 (20)
P value		<0.01		<0.01	
Ethnicity	**Basra, N=40**	28 (70)	12 (30)	30 (75)	10 (25)
	Thi Qar, N=15	11 (73.3)	4 (26.7)	11 (73.3)	4 (26.7)
P value		<0.01		<0.01	
Family history	**Yes, N=7**	4(57)	3 (43)	5 (71)	2 (29)
	No, N=48	36 (75)	12 (25)	40 (83.3)	8(16.7)
P value		<0.01		<0.01	
Smoking	**Yes, N=12**	8 (66.6)	4 (33.4)	10 (83.3)	2 (16.7)
	No, N=43	32 (74.4)	11 (25.6)	35 (81.4)	8 (18.6)
Factors		*GSTM1* Present N(%)	*GSTM1* Deletion N(%)	*GSTT1* Present N(%)	*GSTT1* Deletion N(%)
Age	**40 – 49, N=10**	7 (70)	3 (30)	8 (80)	2 (20)
	50 – 59, N=30	25 (83.3)	5 (16.4)	27 (90)	3 (10)
	60 – 69, N=15	10 (66.6)	5 (33.4)	12 (80)	3 (20)
P value		<0.01		<0.01	
Ethnicity	**Basra, N=40**	28 (70)	12 (30)	30 (75)	10 (25)
	Thi Qar, N=15	11 (73.3)	4 (26.7)	11 (73.3)	4 (26.7)
P value		<0.01		<0.01	
Family history	**Yes, N=7**	4(57)	3 (43)	5 (71)	2 (29)
	No, N=48	36 (75)	12 (25)	40 (83.3)	8(16.7)
P value		<0.01		<0.01	
Smoking	**Yes, N=12**	8 (66.6)	4 (33.4)	10 (83.3)	2 (16.7)
	No, N=43	32 (74.4)	11 (25.6)	35 (81.4)	8 (18.6)

Fig.1 PCR product for GSTT1&GSTM1 polymorphisms on 2% agarose gel. Lane M:100bp DNA marker. Lane (1,5): represent present GSTM1/deletion GSTT1 genotypes, lane (2,8,9,10): represent present GSTM1/ present GSTT1 genotypes, Lane (3,4,6,11,12): represent deletion GSTM1/ present GSTT1 genotypes. Lane (7): represents deletion GSTM1/ deletion GSTT1 genotypes.

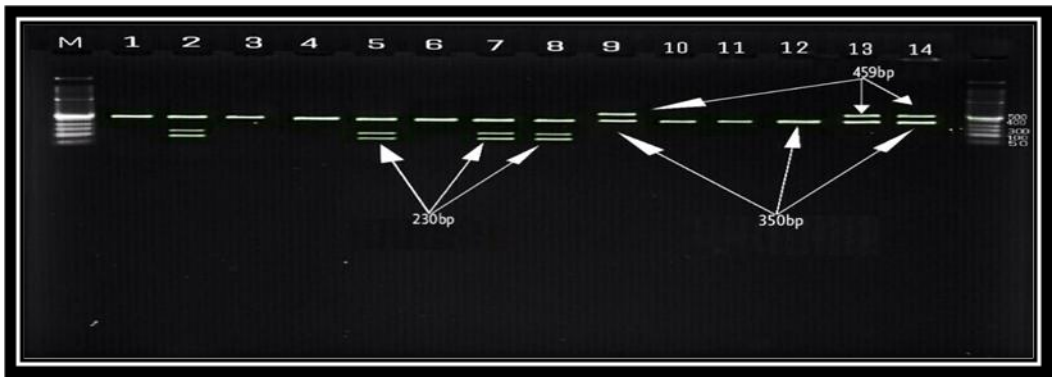

Table 4 shows the analyzed frequencies of combined *GSTM1* and *GSTT1* genotypes. Significant associations were observed among *GSTM1*-present + *GSTT1*-present (p= 0.0496) and *GSTM1*-null + *GSTT1*-present (p=0.0136), no significant associations was observed in *GSTM1*-present + *GSTT1*-null (p= 0.207) and *GSTM1*-null + *GSTT1*-null (p=0.094).

Glutathione–S–transferase genes are organized in chromosomal clusters, and most of these genes are polymorphic, mainly due to single nucleotide substitutions or variations. Genetic variations can be classified as synonymous or nonsynonymous (Hollman *et al*., 2016). The molecular epidemiologic studies suggested that allelic (deletion or null) variants of *GSTM1* genes are associated with failure to express GST proteins, which may lead to less effective detoxification of potential carcinogens and increased capability to cancer (Spurdle *et al*., 2001). Mavis *et al*., (2009) examined GST gene expression and GST promoter DNA methylation in normal murine prostates and transgenic adenocarcinoma of mouse prostate tumors, and demonstrated that reduced GST gene expression is a common event in primary tumors arising in the secondary model, reminiscent of human PCa. In accordance with our findings, the meta – analysis of 2172 PCa cases and 3258 controls from 18 case–control studies provides evidence that the *GSTM1* null genotype is associated with a increase in the risk of PCa in Asian population (Zheng–Hui Hu *et al*., 2013).

On the other hand, *GSTT1* enzyme is reported to be involved in metabolism of potentially carcinogenic dichloromethane, ethylene oxide, and acrolien, a compound found in tobacco and associated with lung cancer (Kumar *et al*.,2011). Since *GSTM1*and *GSTT1* genes are reported to be deleted causing a loss in enzymatic activity of these isoenzymes deletion of both genes concomitantly might lead to more susceptibility for various cancers as well as that of prostate. Hence, GST polymorphisms are reported to be associated with higher risk of PCa (Agalliu *et al*., 2006). Mittal *et al*., (2009) demonstrated a risk of BPH due to GSTs genes polymorphism. Table 6 shows the distribution of ages, family history, ethnicity and smoking in PCa patients. These risk factors increases significantly (P<0.01) in the patients with PCa. Family history can be accessed from a relatively early age like to be offering the chance for earlier involvement for men at increased risk

of PCa by enhanced surveillance and, in the future, strategies were decreased by active risk if they become accessible (Madersbacher *et al*., 2010). Nemesure *et al*., (2012) reported the relationship between cancer grade and PCa risk among men with a family history of disease may be confounded by age, as younger men may have better recall than those who are older.

In conclusion, this is the first study was done in south of Iraq after the 2003 war and it's support a significant association between GSTM1, GSTT1 null genotype and risk of PCa in South Iraqi population. We have a study not published until now is related to another GSTs genes in Iraqi Marshlands, So larger and more rigorous analytical studies will be required to generate a more robust result in the future of genomics data in Iraq.

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