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Association Between GSTP1 Ile105Val Polymorphism and Type 2 Diabetes Mellitus Susceptibility in Gezira State, Sudan: Case-Control study.

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Abstract

Background: Glutathione S-transferases (GSTs) are belong to the supergene family of phase II detoxifying enzymes involved in the metabolism and detoxification of reactive oxygen, xenobiotics, and carcinogens. GSTP1 gene, the IIe105Val polymorphism was associated with increased T2DM risk. This case-control study investigated the association between GSTP1 codon 105 (Ile to Val) polymorphism and susceptibility to type 2 diabetes mellitus among population of Gezira State, Sudan.

Objective: To study the individual effect of GSTPi lle105Val in predisposition of T_2DM in Sudanese.

Materials and methods: Eighty-six T2DM patients and ninety-six healthy controls were genotyped using PCR-RFLP method. Genotype frequencies and associations were evaluated using recessive, dominant, co-dominant and over-dominant models of inheritance.

Results: There was no significant difference in genotype distribution between T2DM patients and healthy control groups (P-value = 0.676). All genetic models showed no significant association (P>0.05). However, heterozygote AG genotype showed borderline association with age (P=0.05) in over-dominant model.

Conclusion: The findings indicate lack of association between GSTP1 polymorphism and T2DM risk in this Sudanese population.

Keywords: GSTP1 polymorphism, type 2 diabetes mellitus, Sudan, PCR-RFLP, genetic association

Introduction

One of the biggest global public health problems is type 2 diabetes mellitus (T2DM), a chronic, complicated, multifaceted, and polygenic illness [1]. Diabetes mellitus has been more common during the past 50 years, moving from western nations to those in the western Pacific, Asia, and Africa. About 589 million adults (20-79 years) are living with diabetes worldwide [2], the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. In 2019, about 463 million adults (20–79 years) lived with diabetes worldwide and approximately 4.2 million deaths were directly connected to it [3,4]. Global statistics for the year 2024 reveal a significant burden of diabetes mellitus and related metabolic disorders. An estimated 589 million adults between the ages of 20 and 79 are affected by diabetes worldwide, equals to approximately one in nine individuals in this demographic. Projections indicate a substantial increase, with the prevalence expected to reach 853 million by the year 2050, representing a ratio of one in eight adults [2].

T2DM results from oxidative stress caused by reactive metabolites interactions with body systems [5]. Antioxidant enzymes including Glutathione-S-transferase (GST) play important role in protection against the oxidative stress. It has been observed that functional polymorphisms of these enzymes contribute to pathophysiology of type 2 diabetes [6].

Glutathione S-transferases (GSTs) belong to phase II detoxifying enzymes. GSTs are divided into mu (GSTM), pi (GSTP), theta (GSTT), and alpha (GSTA) classes [7]. GSTM1 and GSTT1 genes have null genotypes due to deletions. GSTP1 has Ile105Val polymorphism at exon 5 codon 105 which reduces enzymatic activity [8].

Previous studies showed mixed results regarding association between GSTPi and T2DM. some studies found GSTP1 the Ile105Val polymorphism was associated with T2DM in some populations [9], while others did not find significant associations [10].

The objective of this study was to investigate the Association between GSTP1 Ile105val polymorphism and Type 2 Diabetes Mellitus susceptibility in Gezira State, Sudan.

Materials and Methods

Study Design and Subjects: A case-control study was conducted to investigate the role of GSTPI variant in the genetic predisposition to type 2 diabetes mellitus among population of Gezira state, Wad Madani City, Sudan. Eighty-six T2DM patients and ninety-six healthy controls participated in this case- control study. The cases group was selected from known T2DM patients who visited the Merits of December Revolution Health Centre for routine follow up and the healthy control group was selected from individuals who visited the National Cancer Institute for HLA investigations prior to kidney donation. T_2DM patients were 77.5% females with mean age 54.93 ± 10.99 years. Controls were 62.1% females with mean age 39.11 ± 11.57 years (P=0.000).

DNA Extraction and Genotyping

Genomic DNA was extracted using standard phenol-chloroform method. GSTP1 codon 105 polymorphism was screened by PCR-RFLP using primers:

Forward: 5'-GTAGTTTGCCCAAAGTCAAG-3'
Reverse: 5'-AGCCACCTGAGGGGTAAG-3'

PCR product (433 bp) was digested with Alw26I enzyme. Digestion patterns: Ile/Ile (328+105 bp), Ile/Val (328+222+106 bp), Val/Val (222+106 bp).

Statistical Analysis

Genotype frequencies tested for Hardy-Weinberg equilibrium. Associations evaluated using χ^2 test and Fisher's exact test across four genetic models. Odds ratios calculated by logistic regression. $P<0.05$ considered significant.

Results

The demographic and laboratory findings are shown in Table 1. Common complications among patients were hypertension, recurrent UTI, cardiac problems and cataract.

Table 1. Characteristics of the Study Groups

Characteristic	Patients (Mean ± SD)	Controls (Mean ± SD)	P-value
Age (years)	54.93±10.99	39.11±11.57	0.000*
BMI (kg/m²)	27.35±4.39	27.34±4.12	0.965
FBS (mg/dl)	193.02±76.09	92.20±14.92	0.000*
HbA1c (%)	8.95±2.40	5.87±0.55	0.000*
Triglycerides (mg/dl)	136.92±67.60	81.54±12.65	0.000*

*P<0.05 significant

GSTP1 Genotype Frequencies

In healthy controls, 52 (54.2%) had Ile/Ile (AA), 34 (35.4%) Ile/Val (AG), 10 (10.4%) Val/Val (GG). Among T2DM patients, 34 (49.3%) Ile/Ile, 29 (42%) Ile/Val, 6 (8.7%) Val/Val. Allele frequencies: A allele 72% vs 71%, G allele 28% vs 29% (P=0.676).

Association with T2DM Risk

Table 2. GSTP1 Genotypes and T2DM Across Genetic Models

Model	T2DM n(%)	Controls n(%)	OR (95% CI)	P-value
Recessive GG vs AA+AG				
AA+AG	63 (91.3)	86 (89.6)	0.94 (0.21-4.17)	0.93
GG	6 (8.7)	10 (10.4)		
Dominant AG+GG vs AA				
AA	34 (49.3)	52 (54.2)	1.25 (0.55-2.84)	0.59
AG+GG	35 (50.7)	44 (45.8)		
Co-dominant				
AA	34 (49.3)	52 (54.2)	1.00	0.83
AG	29 (42.0)	34 (35.4)	1.30	
GG	6 (8.7)	10 (10.4)	0.94	

Model	T2DM n(%)	Controls n(%)	OR (95% CI)	P-value
Over-dominant AA+GG vs AG				
AA+GG	40 (58.0)	62 (64.6)	1.30 (0.55-3.04)	0.55
AG	29 (42.0)	34 (35.4)		

No significant associations found across models.

Association with Age

Table 3. GSTP1 Genotypes and Age Distribution

Model	Genotype	Mean Age	P-value
Co-dominant	AA	52.97	0.16
	AG	58.21	
	GG	52.50	
Dominant	AA	52.97	0.12
	AG+GG	57.23	
Over-dominant	AA+GG	52.90	0.05*
	AG	58.21	

*Significant at P=0.05

Discussion

This case-control study investigated the association between GSTP1 Ile105Val polymorphism and predisposition to type 2 diabetes mellitus (T2DM) susceptibility among Gezira State population in Sudan. We found no significant association between GSTP1 genetic variants and T2DM risk across all genetic models tested. These findings are consistent with the meta-analysis conducted by [10] Liu et al. which concluded that GSTP1 polymorphisms are not significantly connected with elevated T2DM risk.

Table 2 findings demonstrate no significant association between GSTP1 polymorphism and T2DM across recessive, dominant, co-dominant, and over-dominant genetic models. This result aligns with comprehensive meta-analytic evidence that GSTP1 alone does not represent

a strong independent risk factor for T2DM [10]. While combined GSTM1, GSTT1, and GSTP1 polymorphisms showed some association with T2DM risk in meta-analyses, the individual GSTP1 Ile105Val variant (rs1695) did not reach statistical significance after adjustments for false-positive probability [10,11]. Studies of GSTM1 and GSTT1 null genotypes provide additional context, showing stronger associations with T2DM risk compared to GSTP1 variants alone [12]. Furthermore, [13] demonstrated that combined GST polymorphisms contribute to T2DM susceptibility through sex-specific and gene-environment interactions. These findings suggest GSTP1 polymorphism lacks significant independent impact on T2DM development, though multi-gene interactions may play a role in specific genetic contexts.

Table 3 shows distribution of GSTP1 genotypes and mean ages across genetic models. While most models showed no significant age differences, the over-dominant model revealed heterozygote GA genotype carriers had higher mean age (58.2 years) compared to combined AA+GG genotypes (52.9 years), approaching statistical significance (p=0.05). This borderline finding suggests potential age-dependent effects of GSTP1 variants. Similar age-related patterns have been observed in other diseases where GSTP1 polymorphisms show stronger effects in older age groups [14]. Although not directly assessing T2DM, these observations support the plausibility of age-modulated GSTP1 effects through oxidative stress pathways [9].

The lack of significant GSTP1-T2DM association in our Sudanese population highlights the polygenic nature of T2DM susceptibility. Individual SNP effects like GSTP1 Ile105Val likely require larger sample sizes or multi-gene approaches for detection. Future studies should investigate combined GST haplotypes alongside gene-environment interactions in African populations

Conclusion

GSTP1 codon 105 polymorphism showed no significant association with T2DM risk in Sudanese population of Gezira State. Heterozygote genotype was associated with older age which may indicate age-dependent effect.

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